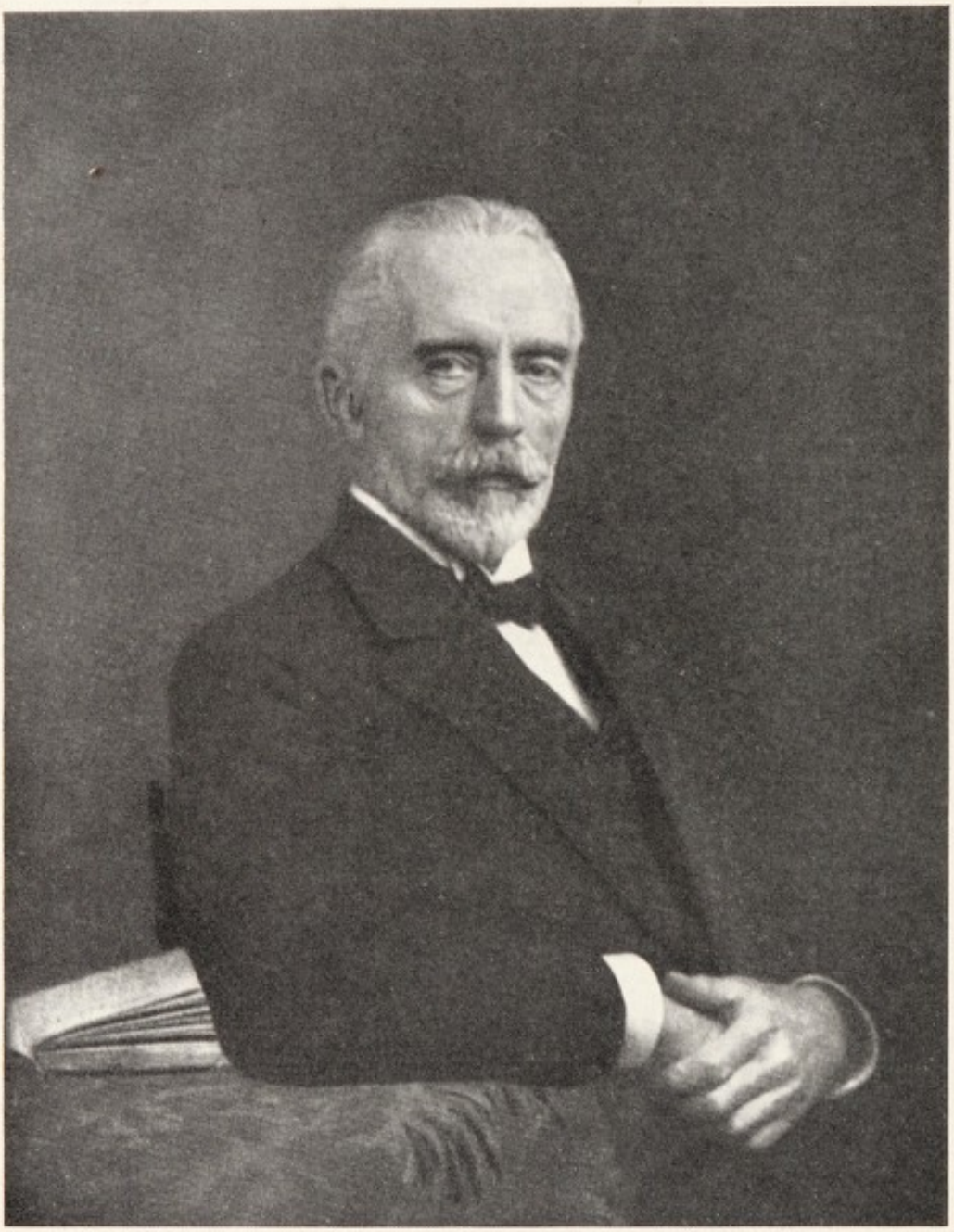
Diagnosis and treatment of diseases of thyroid gland / by George Crile and associates.



Sincerely

Theodor Kocher

DIAGNOSIS and TREATMENT of DISEASES of the THYROID GLAND

By

GEORGE CRILE and ASSOCIATES

●

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PREFACE

THIS volume is not a formal treatise on the thyroid gland; it is rather an account of the experience of the Staff of the Cleveland Clinic in the treatment of diseases of that organ. Chapters on the rôle of iodine in the organism and on the biochemistry of iodine are included but the greater part of the book is devoted to an interpretation of clinical experience in the diagnosis and treatment of simple goiter, of hyperthyroidism and of malignant tumors of the thyroid gland and to discussions by various specialists of certain disorders of other organs which may be associated with hyperthyroidism.

Beyond a review of the literature pertaining to the rôle of iodine, no attempt has been made to review the massive current literature pertaining to the manifold phases of diseases of the thyroid gland, but the authors wish to express their appreciation of the valuable contributions of the investigators in this field, the work of many of whom is cited in the various chapters of this book.

No volume which deals with the treatment of diseases of the thyroid gland would be complete without a statement regarding our obligation to Theodor Kocher. Because of his contribution to our knowledge of the physiology and pathology of the thyroid gland, to the clinical picture of hypo- and hyperthyroidism and to the prevention of goiter, and because of his skill as a surgeon and his sound reasoning as a scientific physician as to the nature, diagnosis, and treatment of every form of goiter, to Theodor Kocher, as to no other man, is due the credit for writing the chapter on goiter in the history of medicine.

CLEVELAND, OHIO,
September, 1932.

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INTRODUCTION

GEORGE CRILE

IN the prevention of goiter and in the diagnosis and treatment of hyper- and hypothyroidism and of the benign and malignant tumors of the thyroid gland, most of the science and the practice of medicine with all of its specialties is involved.

Thus in the presence of disorders of the thyroid gland the biochemist finds many changes in the blood, in the urine, in the activity of the stomach and of the intestines, and in the consumption of oxygen and the elimination of carbon dioxide. The biophysicist finds many changes in the conductivity, the capacity, and the potential of the cells and organs of the body. In hyperthyroidism the physiologist sees all the normal functions exalted—as if viewed through a physiologic microscope. The pathologist is puzzled by the ever-changing cells of the acini—which change in winter as well as in summer, as the result of infection, of pregnancy, of emotion, of fatigue, of age, of tumors, of the swiftly moving cycles of hyperthyroidism, of the use of iodine, of rest, and of ligation of the thyroid arteries. Graham has shown that in the same gland every morphological picture may be found—a puzzle picture that has baffled dogma.

The dermatologist copes with the loss of hair and with many skin lesions such as furuncles, leukoplakia and rashes; the dentist searches for focal infection and finds the structure of the teeth altered. The oculist is perplexed by the mechanism which produces exophthalmos and the weakness of the ocular muscles, etc. The laryngologist has the difficult task of deciding the relation of infected tonsils to hyperthyroidism and of overcoming the problem of disturbed innervation of the vocal cord muscles. The cardiologist must cope with myocardial

failure, with auriculofibrillation, and general anasarca. In both hyper- and hypothyroidism the orthopedist finds changes in the joints. The gynecologist and the obstetrician find menstrual disorders and sterility, and at times must deal with the complication of pregnancy. The gastro-enterologist finds duodenal ulcer, hypermotility, diarrhea, and gastric disturbances associated with hyperthyroidism. In the diabetic division are seen many cases in which glycosuria and diabetes are associated with hyperthyroidism. The psychiatrist in some degree finds almost the entire gamut of his specialty in the psychoses associated with hyperthyroidism. The roentgenologist identifies intrathoracic goiters and the deformities and displacements of the trachea and changes in the structure of the joints. The internist often finds difficulty in differentiating mild forms of hyperthyroidism from psychoneuroses, incipient tuberculosis, neurocirculatory asthenia, chronic fatigue, and endocarditis. The surgeon finds his judgment, his technical skill, and his hospital organization taxed to the utmost in the treatment of hyperthyroidism. Thus with one or another phase of hyperthyroidism or hypothyroidism the entire clinic is concerned, and in these pages there will appear an account of the activities of the various departments of the Cleveland Clinic in their relation to the many problems presented by diseases of the thyroid gland.

The primary reason why the thyroid gland in health and disease involves all of the science and the practice of medicine is that the thyroid gland is the principal agency for controlling the metabolism. The thyroid gland controls the permeability of every cell of the organism and it is the state of permeability of the cells that governs functional activity. Therefore, the work of the thyroid gland is essential to the maintenance of normal activity of all of the cells of the body. This body-wide influence of the thyroid is solely through the effect of an organic iodine; that is to say, the element, iodine, is responsible for the evolution of the thyroid, or more properly, the iodine gland. Attention will therefore be focussed upon the function of the thyroid gland as a controller of energy transformation in the organism as a whole, for thus only can we arrive at a proper understanding of the problems presented by diseases of the thyroid gland and their treatment.

CHAPTER I

IODINE AND THE THYROID GLAND

REVIEW OF THE LITERATURE

GEORGE CRILE, JR.

I. EARLY STUDIES

ALTHOUGH the thyroid gland has been recognized anatomically for a number of centuries, it is only during comparatively recent years that its functions have been studied. Starting with the idea that its rôle was to fill up space because "nature abhors a vacuum," many theories regarding its function have evolved. Prominent among these were Wharton's theory that it was a cosmetic organ to round the neck; and Boerhaave's, that it was a cushion serving to modulate the voice, and that as a result of its position in relation to the carotid arteries, it was an automatic regulator of the cerebral circulation.

The first real progress in the study of thyroid function came from Sir Astley Cooper who in 1840 noticed a peculiar symptom-complex in animals following thyroidectomy and concluded that the thyroid gland played some rôle in metabolic activities. This line of thought was carried on by Kocher and Reverdin who in 1874 practically simultaneously recognized the clinical entity of myxedema and interpreted it correctly. All the evidence indicates that priority in this discovery must, despite the controversy, be given to Kocher. Horsley, Wagner, Schiff, and others continued to work on thyroidectomized animals and satisfied themselves that the gland was essential to the normal metabolic activities of the animal and especially of the young animal, but it remained for Gley, Vassale, and Generali to separate the functions of the thyroid and parathyroid glands and assign to each its proper rôle. Finally in 1896 Halsted published his fundamental work on the compensatory hypertrophy of the remaining thyroid tissue after removal of a large part of the gland.

How the thyroid accomplished its function was, of course, totally unsuspected until 1869 when Brown-Séquard proposed his theory

regarding internal secretions. This work, at least as far as the thyroid is concerned, was soon supported by experiments on thyroid feeding conducted by Murray, Mackenzie, and Brunns, who definitely established the thyroid gland as an organ of internal secretion essential to metabolic activities.

Although a relationship between iodine and clinical disorders of the thyroid had been suspected for over half a century before Ordtmann made his observations on the prominence of iodine in this gland, no definite proof of this relationship had been forthcoming. Ordtmann's studies were soon followed by Baumann's discovery in 1895 of iodothyrin, an iodine-containing substance obtained from thyroid tissue. Hutchinson, Oswald, and others studied these iodine compounds but not until 1914 was the crystalline iodine compound, thyroxin, isolated by Kendall.

In the meantime Roos had shown that iodine was an essential component of the active agent in the thyroid and it was he who first observed the relation between the iodine content of desiccated thyroid and its influence on metabolism. Hunt also contributed to this important work by his studies of the resistance of animals to acetonitril poisoning. Hunt found the resistance to be proportional to the amount of active thyroid fed, and that the activity of the thyroid used was correlated in turn with the amount of organic iodine in the colloid.

Thus, in brief, by the year 1907 it had been established that the thyroid gland is an organ essential to the normal metabolic activities of the animal; that it has a definite secretion; and that iodine is an essential constituent of this secretion.

II. Anatomical, Physiologic, and Pathologic Correlations

In 1907 Marine published the first of his studies of the thyroid gland. In a review of the anatomy, physiology, and pathology of the thyroid, he described three types of the gland: (1) the normal gland; (2) glandular hypertrophy and hyperplasia (parenchymatous hypertrophies); (3) the colloid gland (goiter).

The normal thyroid gland with its low cuboidal epithelium, moderate amount of colloid (Fig. 1), and small amount of stroma Marine found to be transformed, in hyperplasia, to a gland of increased size, with an increase in blood supply, lymphatic drainage, and stroma. The acinar epithelium becomes columnar and together with a strik-

ing decrease in the amount of colloid, papillomatous invaginations of the epithelium appear (Fig. 2).

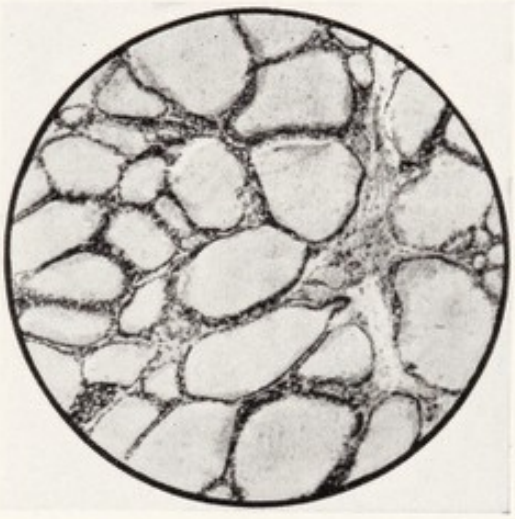

Fig. 1.—Normal thyroid, human. "Note the rounded and moderately uniform size of the follicles; the homogeneous and uniform colloid; the cuboidal epithelium and the normal stroma." (Marine and Lenhart, Archiv. Int. Med., **8**: 273, 1911.)

The colloid gland, on the other hand, portrays the exact opposite of this picture. The epithelium is flattened, the blood supply is

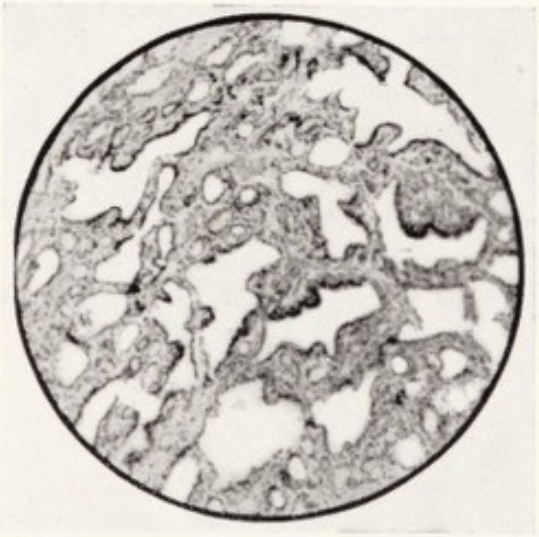

Fig. 2.—Hyperplasia of the thyroid gland. "Note the irregular sized and distorted follicles with infoldings and plications of the lining epithelium; the regular and uniform, high columnar epithelium; the absence of true colloid and the generalized increase of stroma." (Marine and Lenhart, Archiv. Int. Med., **8**: 274, 1911.)

diminished, and everywhere the alveoli are distended with great quantities of deeply stained colloid (Fig. 3).

From a study of the street dogs of Cleveland, Marine was able to show that these changes are normal physiologic reactions to some deficiency. He concluded that parenchymatous hypertrophy is a type of compensatory hyperplasia; that the colloid gland is the quiescent or normal state of a gland which has previously undergone a functional hyperplasia and that such a gland obeys all the biological

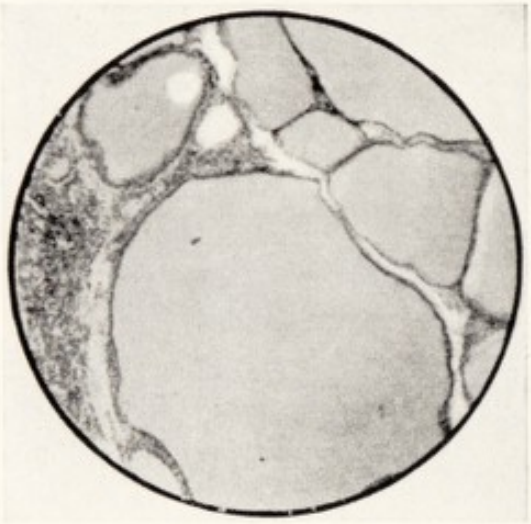

Fig. 3.—Colloid goiter. "Note the great variation in the size of the follicles; their slightly irregular outlines; the normal cuboidal epithelium and the uniform normally staining colloid. Note also the focus of lymphoid tissue in the stroma and its relation to the thyroid follicles." (Marine and Lenhart, Archiv. Int. Med., **8**: 275, 1911.)

laws of a normal gland. These observations were a confirmation of the original conception of Virchow, who thought that after a gland had once undergone hyperplasia, the nearest it could return to normal was the colloid state. According to this conception the anatomy and pathology of the gland can be interpreted as normal reactions to physiologic needs.

III. The Relation of Iodine to the Structure of the Thyroid Gland

(A) IODINE CONTENT OF THE THYROID AND ITS RELATION TO STRUCTURE

In 1897 Oswald first showed that in man and in calves the iodine content of the thyroid varies directly with the amount of colloid in the gland. Marine and Williams taking up this work in an extensive study of the street dogs of Cleveland, the majority of which they found to be goitrous, made the same observations and established that the iodine per gram of thyroid was directly proportional to the amount of colloid present. In other words, there was the least iodine per

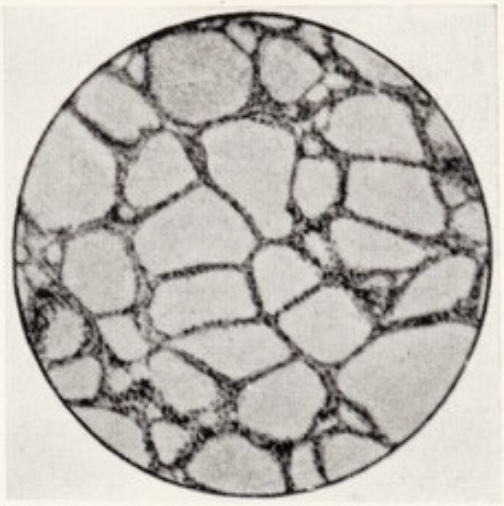

Fig. 4.—Normal thyroid, dog. (Marine and Williams, Archiv. Int. Med., **1**: facing 352, 1908.)

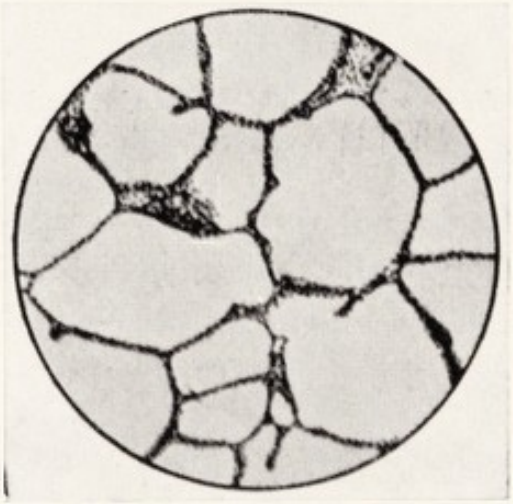

Fig. 5.—Colloid goiter, dog. (Marine and Williams, Archiv. Int. Med., **1**: facing 356, 1908.)

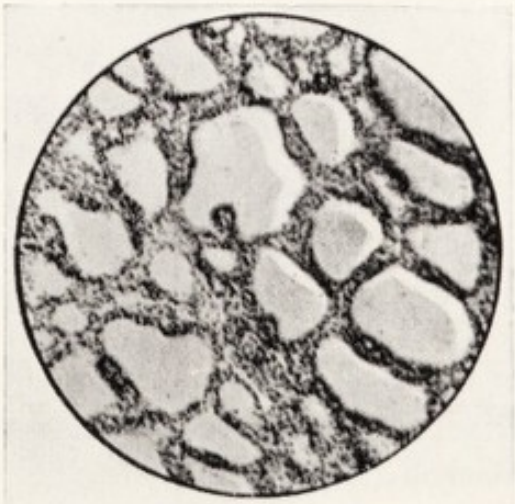

Fig. 6.—Early thyroid hyperplasia, dog. (Marine and Williams, Archiv. Int. Med., **1**: facing 356, 1908.)

gram of thyroid in the hyperplastic glands and a progressively increasing amount through the moderately hyperplastic and colloid glands to the normal (Figs. 4–8).

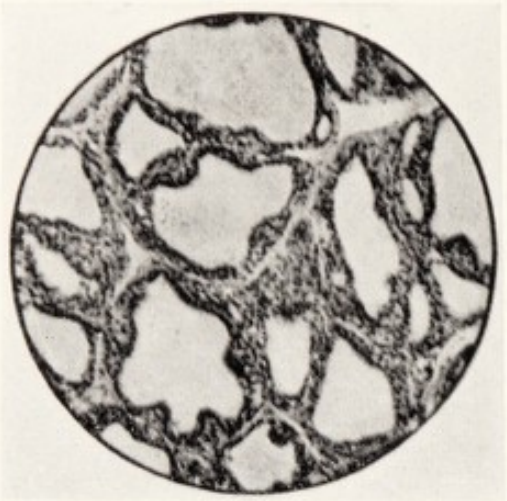

Fig. 7.—Moderate thyroid hyperplasia, dog. (Marine and Williams, Archiv. Int. Med., **1**: facing 360, 1908.)

In subsequent experiments on the sheep, dog, hog, and ox, Marine and Lenhart found a remarkable similarity of iodine content in the normal glands of these animals. The highest iodine content was in the

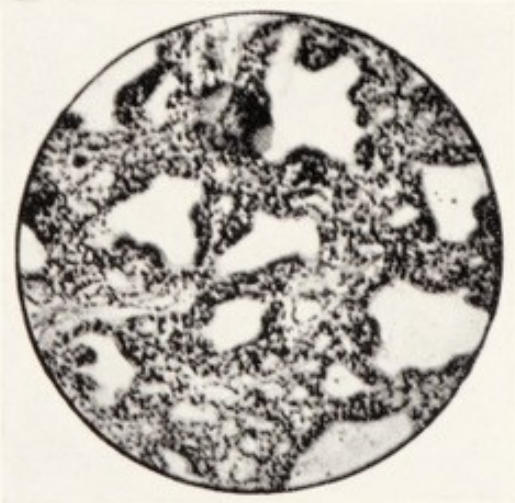

Fig. 8.—Marked thyroid hyperplasia, dog. (Marine and Williams, Archiv. Int. Med., **1**: facing 360, 1908.)

normal and colloid glands, and from this there was a marked drop to the glands in which hyperplasia was histologically evident. The colloid glands beginning to undergo hyperplasia had, therefore, a much lower iodine content than other colloid glands.

Character of gland.	Mg. I. per Gm. of fresh thyroid.
Normal gland	0.777
Colloid gland	0.459
Early hyperplasia	0.139
Moderate hyperplasia	0.078
Marked hyperplasia	0.023

From these observations Marine concluded that the colloid gland is the nearest to normal condition to which the hyperplastic gland can return, not only as to histologic appearance but also as to chemical (iodine) composition. Studies of human glands bore out these findings, the exophthalmic goiter being found to show the lowest iodine content, the normal gland the highest, and the colloid gland just a little less than the normal.

Thus since the colloid gland and the normal gland seemed to be grouped together by their similarity in histologic structure and in iodine content, and since the chief difference between this group and the group of normal or colloid glands which were undergoing hyperplasia was the pronounced drop in iodine content, it became clear that the iodine content was related to the structure in some basic manner.

The conclusion, therefore, seems inevitable that, in Marine's words, "The mode of action of iodine is like that of other normal constituents of the body, viz., (1) the body practices an economy in its use; (2) a normal minimal amount is necessary for the body needs and the body supports a variable reserve; (3) deficiency induces anatomical changes in the tissues concerned, with its storage and elaboration." In other words, since the hyperplasia occurred only in those glands in which the iodine content was low, Marine concluded that the hyperplasia of these glands was the result of an iodine deficiency, and went even further to say that a hyperplastic gland could not revert to the colloid state without the presence of a necessary minimal amount of iodine.

(B) IODINE CONTENT OF THE DIET AND ITS RELATION TO THE STRUCTURE OF THE THYROID

At the time of this work of Marine's there was already a certain amount of literature on the relationship of the structure and iodine content of the thyroid gland to the iodine in the diet. In 1895, Baumann and Roos had observed that the iodine content of the thyroid of the sheep varied with the regions from which the sheep came,

being least in goitrous regions where the glands were of the colloid type. Baumann, in 1896, found that the withholding of iodine caused a hyperplasia of the thyroid gland. In addition, Marine and Lenhart had observed that hyperplasia of the thyroid could be produced experimentally (1) by removing a good part of the thyroid; (2) by removing part of the thyroid of a pregnant bitch in which case the puppies had hyperplastic glands; and (3) by removing all iodine from the diet.

With this background, Marine and Lenhart started their extensive investigations of the effects of the administration or the withholding of iodine in animals with normal, colloid, or actively hyperplastic glands, the results of which appear in the following table:

I. Normal gland.
   (*a*) Iodine given:
      1. Increase in iodine content.
      2. No change in structure.
      3. No hyperplasia of the remaining lobe after the removal of one, but merely an increase in its size.
   (*b*) Iodine withheld:
      1. Gradual decrease in iodine content.
      2. Hyperplasia of the remaining lobe.

II. Colloid gland.
   Same findings as in the normal gland.

III. Hyperplastic gland.
   (*a*) Iodine given:
      1. Immediate increase in iodine content.
      2. *Rapid* return to the colloid state.
   (*b*) Iodine withheld:
      1. Slow increase in iodine content.
      2. *Gradual* return to the colloid state.

From these observations Marine concluded that the ability of the thyroid to take up iodine is directly proportional to the hyperplasia. It thus becomes apparent that in no matter what form iodine is given, it is at once taken up by the thyroid gland, especially if the gland is in the hyperplastic state at the time of the administration.

It is interesting to note at this point the controversy that resulted between Marine and Halsted when the latter, on the basis of subsequent experiments, repudiated his previous observations on the compensatory hyperplasia following removal of one lobe of the thyroid. Halsted said that he had been unable to reproduce his results and

denied that they occurred. Marine, however, in analyzing Halsted's experiments explained his failure to confirm his previous work on the basis that Halsted, in his first series, had not used iodine in the preparation of his field whereas in his subsequent work he had used iodine in disinfecting the skin and the absorption of this iodine was sufficient to prevent the compensatory hyperplasia of the remaining lobe.

We have seen that the three conditions that can cause hyperplasia of the thyroid are: (1) removal of a large part of the gland; (2) iodine deficiency, and (3) prenatal thyroid insufficiency induced by the removal of the mother's thyroid or by iodine deficiency in the mother's diet. In all of these instances it is readily seen that the hyperplasia can be considered to be a physiologic compensatory reaction induced by a lack of *active* thyroid secretion. Thus, in the first instance, the deficiency resulting from the removal of a part of the gland necessitates a compensatory hyperplasia of the remaining tissue for the elaboration of an adequate quantity of secretion for the bodily needs. If iodine is then added to the diet, the hyperplastic remaining lobe, as a result of the presence of an excess of raw material (iodine), is better able to elaborate large quantities of the active thyroid hormone. The thyroid can then produce sufficient quantities of secretion to satisfy the physiologic needs of the body and the stimulus to compensatory hyperplasia having been removed, the gland undergoes involution to the colloid state. In the case of the hyperplasia due to iodine lack, on the other hand, the changes in the gland are the result of the inability of the gland to produce enough of the active material in the absence of an adequate supply of one of the essential constituents of the material. When this constituent, *i. e.*, iodine, is added to the diet, the gland is again able to produce its hormone in quantities sufficient for the bodily needs, and with the deficiency thus corrected, the compensatory reaction of hyperplasia undergoes involution to the colloid state.

In short, it would appear that the true stimulus to thyroid hyperplasia is a physiologic deficiency of thyroid hormone. This deficiency can be produced in three ways: (1) a relative lack resulting from increased demands (as in the hyperplasia of puberty); (2) an absolute lack (as in the compensatory hyperplasia following the removal of a large part of the gland); (3) an inability of the gland to produce enough active secretion to satisfy normal requirements (as in the hyperplasia resulting from dietary iodine deficiency). Any of

these hyperplasias will involute to the colloid state if the gland is put at rest by correcting the deficiency of thyroid hormone, and this result can best be obtained in all cases, as previously outlined, by the administration of iodine.

Further observations on the etiology of thyroid hyperplasia were not long in forthcoming and the picture soon became more complicated by the reports of McCarrison from India, who conducted extensive studies of the thyroid gland in a region of endemic goiter in which nearly 100 per cent of the population was goitrous. His observations led him to the conclusion that goiter is caused by a contagion from a living agent suspended in the water of this region and he found that thymol and other intestinal disinfectants benefited some of his cases.

Later McCarrison, working with pigeons, observed that thyroid hyperplasia resulted when the cages were dirty and the food contaminated with excreta. He found also that feeding an excess of butter or oleic acid produced thyroid hyperplasia. McCarrison concluded that both of these facts may be related to bacterial intervention in the digestive tract with subsequent inadequate absorption of iodine. In any case it must be apparent that no matter what factors of diet or bacterial invasion are called to account for the thyroid hyperplasia of endemic goiter, those factors must operate, although obscurely, through their effects on iodine absorption.

Another significant observation on the effects of iodine feeding on the structure of the thyroid was contributed by Rabinowitch who found by quantitative estimations, that the mitotic figures were increased over a period of three weeks by iodine feeding and that this was then followed by an inhibition and accumulation of colloid. Gray and Loeb confirmed these observations and concluded that the primary effect of iodine is to stimulate an hypertrophy of the thyroid which is soon followed by a secondary depression. Hence the thyroid may respond to a surplus as well as to a deficit of iodine with increased growth activity. Marine, however, was unable to confirm these results.

In summary, we have the following evidence to show that it is not a mere accident that the iodine content of the thyroid varies inversely with the degree of its hyperplasia:

1. The thyroid stores iodine in quantities which bear no relation to the iodine content of other tissues and the rapidity of this storage is in direct proportion to the degree of hyperplasia of the gland.

2. Withholding iodine produces hyperplasia.

3. The administration of iodine prevents hyperplasia of all sorts and causes existing hyperplasia to revert to the colloid state.

IV. The Relation of Iodine to Thyroid Function

(A) Effect of iodine on the normal animal

Iodine in moderate doses is almost without effect on the basal metabolic rate of the normal animal. In larger doses, however, it has a tendency to increase the nitrogen metabolism, and this is accomplished indirectly in some obscure manner by its action on the thyroid gland, for iodine has no effect on the nitrogen metabolism of thyroidectomized animals (Grabfield *et al.*). It is thus apparent that within a wide range the quantities of iodine in the diet do not affect the functions of the gland any more than the wide variations in the iodine content of normal and colloid glands, down to the minimum iodine level necessary to prevent hyperplasia, bear any relation to the structure of the gland. In short, the thyroid can use and store iodine in almost any quantity down to a certain minimum, below which level a hyperplasia of the gland appears, and later, if the deficiency persists and the thyroid is unable to compensate, the clinical evidences of thyroid deficiency ensue.

(B) Iodine content of the active agent of the thyroid

These observations on the essential rôle of iodine in the function of the thyroid gland strongly suggest that iodine is an active constituent of the thyroid secretion.

The first important work on this subject since the studies of Roos in 1893 on the relation between the iodine content and the influence of desiccated thyroid on metabolism came from Marine and Williams who found that thyroid preparations from goiter regions where the thyroid glands of sheep had a low iodine content were relatively inactive. This was in agreement with the conclusion of Oswald and Roos who had stated that the physiologic activity of thyroglobulin varies directly with the amount of iodine in organic combination.

Marine and Rogoff next studied the form in which iodine was taken up by the thyroid and found that in perfused fresh glands the iodine was taken up at once from the perfusate and could not be washed out, although control organs (spleen, etc.) readily yielded all their iodine.

They also found that iodine is at once taken up by the gland in the living animal but that the active principle is relatively slowly formed and liberated. Iodine feeding, moreover, increases the pharmacological properties of hyperplastic glands, produces an involution only after the eighth hour, this finding indicating again that the morphology and activity of the gland are related in time and that the intake of iodine causes an increased storage of the active principle.

In 1915 Kendall took the final step in the demonstration of the part played by iodine in the activities of the thyroid gland. He found that iodine was present in the thyroid in two organic combinations, "A" and "B." The former is insoluble in acid, is physiologically active, and contains 10 per cent of iodine. In hyperplastic goiters (Graves' disease) only one-twentieth of the amount found in normal glands is present. The B combination is acid-soluble and inactive. Moreover, Kendall was able to isolate the A combination in crystalline form and to demonstrate that it had all the properties of thyroid secretion. Kendall thought that this substance was oxyindolepropionic acid in which the benzene ring was reduced and had three iodine atoms attached to the three, four, and five carbon atoms respectively, but Harrington, working out the empirical formula somewhat differently as $C_{15}H_{11}O_4NI_4$, states that Kendall's hypothetical formula is improbable.

It is evident that iodine is a constituent of the thyroid secretion and it is thus that it becomes essential to life. Else has computed that since the body needs 0.33 mg. of thyroxin daily and thyroxin contains 65 per cent of iodine, the gland needs 0.22 mg. of iodine per day.

(C) RELATION OF IODINE CONTENT OF THE THYROID TO ITS FUNCTION

Having seen that iodine is an essential component of the active principle of the thyroid secretion, it is of particular interest to note the numerous observations on the relationship of the iodine content of the thyroid to its activity. Numerous observers have noted that in all pathologic conditions of the thyroid in man and animals the iodine content varies inversely with the degree of hyperplasia. Cannon observed hyperplasia of the thyroid gland after anastomosis of the cervical sympathetic to the phrenic nerve, and following this lead Rahe, Rogers, Fawcett, and Beebe recorded a reduction of iodine in the stimulated lobe after electrical stimulation of the cervical sympathetic.

Seidell and Fenger, working along different lines, found three times as much iodine in the thyroids of sheep in the months from June to November as in the cold months of the year when perhaps the call for greater metabolic activities produced an increased demand for thyroid secretion.

These results coupled with the well-known clinical observation that the iodine of the hyperactive glands of exophthalmic goiter is low, show that the iodine content is always low in glands that are overactive and hyperplastic. This can best be interpreted as signifying that the demands for the active substance are so intense that the thyroid is converting every bit of available iodine to thyroxin as rapidly as possible and is immediately putting this material into the circulation with the result that no active iodine remains in the gland. This interpretation affords an explanation for the simultaneous appearance of an increased cellular activity, a diminution of colloid, and a decrease in iodine content when demands for activity are imposed on the thyroid.

(D) EFFECT OF IODINE ON THE HYPERPLASTIC GLAND

The effects of iodine on the physiologic activity of the hyperplastic gland are more complex. Marine and Lenhart observed that the first effects of the administration of small doses of iodine to dogs with hyperplastic glands was a rapid loss of weight over a period of two weeks and a physiologic action similar to that of desiccated thyroid. This is soon followed by a gain in weight and a remission of the symptoms. Moreover, similar observations have been made clinically on patients with hyperplastic glands. These observations are difficult to explain in the light of the classic pharmacology of iodine, but it does not seem improbable, if the observation of Loeb is correct (*i. e.*, that the mitotic figures, and hence the cellular activity of the gland, are increased over a period of two weeks by iodine feeding) that this primary iodine stimulation of the gland is to be held accountable for the appearance of signs of thyroid hyperactivity. Another explanation of this initial symptomatology might be that the thyroid gland, in its hyperplastic and hyperactive state, is suddenly greatly facilitated in its work by the addition of large quantities of raw material, iodine. Thus with the persistence for several weeks of the functional momentum of the gland and with its relative iodine deficiency overcome, there results a facilitated production of the active agent—a period of hypersecretion with attendant symptomatology.

In a subsequent section the effects of iodine on the function of the hyperactive gland of Graves' disease will be discussed.

V. Relation of Iodine to the Pathology of the Thyroid

(A) IODINE CONTENT OF THE GLAND IN PATHOLOGIC CONDITIONS

Iodine not only plays a fundamental rôle in the anatomy and physiology of the normal thyroid, but is equally important in its relationship to the pathology of the gland.

It would appear that the simplest classification of thyroid pathology is the most satisfactory and hence, with the exception of the various malignancies and inflammatory lesions which do not fall within the field of this chapter, the disorders of the gland will be classified in accordance with the recommendation of the American Association for the Study of Goiter as follows:

1. Toxic goiter.
   - (*a*) Diffuse.
   - (*b*) Nodular.
2. Nontoxic goiter.
   - (*a*) Diffuse.
   - (*b*) Nodular.

The correlation of this system of classification with the histology of the glands is unfortunately more complex than would at first appear. In general, by the nontoxic type of goiter is meant a colloid gland, but this is not always true, for many nontoxic diffuse glands such as adolescent goiter are histologically hyperplastic. In like manner, the toxic diffuse gland is generally thought to show parenchymatous hyperplasia, but it is frequently observed that toxic diffuse goiters are histologically of the colloid type, especially after the administration of iodine, but occasionally even when no iodine medication has been given. This confusion is rendered even more perplexing when we turn to the nodular types, for here, likewise, we find little or no correlation between the clinical symptomatology and the anatomical and chemical findings.

The beginnings of the unraveling of this problem came again from Marine and Lenhart, who found that in 69 cases of goiter the degree of hyperplasia was inversely proportional to the iodine content of the gland, and that the greatest drop in iodine content was from the normal and colloid groups to the early hyperplastic colloid goiters, demonstrating again, as in their animal studies, that there is a min-

imum of iodine that must be present or else hyperplasia results. In addition, it was observed that in four cases of exophthalmic goiter in which iodine had been administered, a complete involution to the colloid state had taken place. Thus it was established that iodine has the same effects on exophthalmic goiter as on the hyperplastic goiter of animals and produces anatomical changes identical with spontaneous involution.

The correlation between colloid goiter in animals and the diffuse nontoxic colloid goiter of man has been studied by Blum who found that this type of human goiter, like the corresponding colloid gland of animals, was not as tenacious of iodine as the normal gland. These observations force us to admit that these pathologic states of the human thyroid are indeed identical with the corresponding states of animal glands, at least in so far as their iodine content and reaction to iodine are concerned.

The next line of attack was on the problem of exophthalmic goiter. This was opened by Rogoff and Goldblatt who attempted, although unsuccessfully, to demonstrate by experiments on tadpoles an increase of active thyroid material in the blood of individuals suffering from exophthalmic goiter, thyroid adenoma, and colloid goiter. These attempts, however, paved the way for the work of Holst and Lunde whose findings in extensive chemical researches may be briefly stated as follows:

1. The iodine of the blood is in two fractions, an alcohol-soluble A and an alcohol-insoluble B.

2. In hyperthyroidism both A and B are increased in proportion to the increased metabolism.

3. When Lugol's solution is given, A increases and B decreases in proportion to the drop in metabolism.

From these findings Holst and Lunde conclude that although the parallelism is not complete, it would appear that the thyroid secretion is contained in B.

If these observations are correct, they offer a splendid new opportunity for the attack on the pathologic physiology of exophthalmic goiter. In any case, it becomes more and more apparent that the fundamental criterion for judging the activity of the thyroid in diffuse goiter must be a determination of the active organic iodine in the gland and in the blood, the two necessarily varying in opposite directions, since as the gland gives up its active iodine the blood receives it.

(B) RELATION OF IODINE IN DIET TO PATHOLOGIC CONDITIONS OF THE THYROID

No less important than the studies of the relation of the iodine content of the thyroid to its pathology, are the observations on the rôle of the iodine content of the diet in the etiology of goiter. In 1867 Marchand published the first reports of analyses of the iodine content of air, water, soil, etc., in regions of endemic goiter and this report showed that iodine was present in diminished quantities in these regions. Marine and Lenhart thought that some additional factor was to blame for they observed that although hyperplasia occurs in response to iodine deficiency it does not explain why everyone in these regions does not have a goiter. They thought that goiter must be produced by an iodine deficiency induced by some failure in absorption or assimilation, or to the presence of an antagonist.

McClendon and Hathaway next studied the distribution of iodine and showed graphically that in the United States and in Switzerland goiter areas correspond to areas where iodine in drinking water is below twenty-two parts per hundred billion. It thus becomes clear that it is the iodine deficiency in these regions that stimulates the thyroids of their inhabitants to undergo a compensatory hyperplasia which subsequently, after the deficiency has been compensated, involutes to the colloid state. Morel, in 1864, had carried this idea even further and said that goiter was the first stage on the road to cretinism. Indeed this statement is doubtless true for the degenerative and atrophic cell changes of cretinism are the result of prolonged and unrelieved physiologic stimulation to meet some deficiency. Cretinism and myxedema are the final stages of failure in compensation. Thus, in spite of the fact that the thyroid is hyperplastic and overactive in the early stages, the body is at the same time suffering from a thyroid deficiency. This deficiency must then lie in the quality of the secretion which in turn may be dependent on the absence of some normal element of nutrition, probably iodine.

In addition to this absolute iodine deficiency, such factors as pregnancy, puberty, menopause, and infection influence the amount of iodine required so that the iodine deficiency may be either relative or absolute. And finally, a goitrigenous substance such as that contained in cabbage may some day be demonstrated to clarify the remaining problems of endemic goiter.

We have already referred to the results of Marine's studies on the effect of iodine in producing an involution of the hyperplasia of exophthalmic goiter and have noted that he observed both histologic and

chemical changes in the glands treated with iodine. Rienhoff has also contributed excellent histologic studies in confirmation of Marine's observations. In addition, Marine found that the symptoms of exophthalmic goiter abated during the course of treatment for from three to four weeks with small doses of iodine in the form of syrup of ferrous iodide or sodium iodide. Marine failed to note in these cases any of the injurious effects commonly described as following the use of iodine, but nevertheless, largely on the basis of his animal experiments, recommended that the dose be small (not over 5 minims of the syrup of ferrous iodide daily for the first week). This limitation of the size of the dose was the result of his observation that the more active glands took up more iodine than the resting glands and that iodine induced a transient sort of hyperthyroidism in experimental animals. For these reasons Marine gave iodine to his patients with Graves' disease in quantities which were insufficient to produce the sudden and striking remissions later obtained by Plummer with larger doses. But Marine considered the preoperative use of iodine to be of definite value and made the observation that "Whatever thyroid operation is made, the other factors being constant, the postoperative reaction and the operative mortality are in general proportional to the degree of active thyroid and lymphoid hyperplasia." Thus, by producing an involution of the hyperplasia by iodine, Marine hoped to decrease the operative mortality.

But it was Plummer who first showed that large doses of Lugol's solution would more promptly produce a marked clinical improvement with lowering of the metabolic rate, slowing of the pulse, decrease of nervousness, and remission of all symptoms except the exophthalmos. It was this contribution which enabled the beneficial effects of iodine observed by Marine to be put to more practical use as they could thus be rapidly and dramatically elicited in the control of hyperthyroidism.

(C) RELATION OF IODINE TO TUMORS OF THE THYROID

We have seen that, in general, the diffuse thyroid disorders react characteristically and consistently to iodine, but when we come to consider the reactions of the adenomatous glands the problem becomes more complex. Some hyperplastic adenomas of the fetal type fail to react at all to iodine, others react only to a limited degree, and finally still others react in a manner exactly similar to that of diffuse hyperplasia. Naturally enough, there soon arose a heated debate as to the true nature of adenomata. Marine chose to consider these nodules as

neoplastic, arising from anlages laid down at different periods in the functional development of the gland and hence differing in structure and in ability to function. Rienhoff considers thyroid adenomata to be "involutional bodies"—islands of tissue that either had regressed or had failed to regress during the cycles of the gland's hyperplasia and involution. Graham considers the adenomata as representing stages of neoplasia, although he formerly thought with Wölfler that, to a large extent, they represented fetal rests. Graham quotes Wegelin's studies of 693 consecutive autopsies made in the goiter region of Switzerland, which show that the incidence of adenomata starts at a very low percentage in subjects under the age of puberty, steadily rising as age advances, until in his oldest groups 100 per cent of the subjects showed nodular thyroids. According to Graham this demonstrates that in the presence of the pathologic physiology of a goiter region, the added factor of age, with its inexplicable tendency to epithelial proliferation, results in the production of adenomatous changes in the thyroid which are partly neoplastic and partly physiologic in their origin.

The debate has raged with equal intensity over the question of the relation of the adenomata to function. Marine states that adenomata may indeed function in a manner quite similar to the normal thyroid. He argues that:

1. "Adenomata are never seen in thyroids that have not been the seat of hypertrophy or hyperplasia.

2. "We must recognize a complete gradation of these tumors from the least differentiated or fetal type through the simple adenomata to the strictly physiologic hyperplasias.

3. "All gradations of iodine content are found from the lowest in the fetal types through the simple adenomata to the highest in the physiologically adult hyperplasias.

4. "The administration of iodine influences these tumors. This influence is least in the fetal adenomata and rises through the simple adenomata and reaches its fullest physiologic effect in the simple and diffuse hyperplasias.

5. "Each tumor tends to undergo a physiologic cycle in phases just as does the physiologically adult tissue. This cycle is least evident in the fetal adenomata which may persist as such throughout a long life with but little change.

6. "The stimulus for growth of these adenomata is the same, or at least comes with the stimulus for overgrowth of the gland as a whole."

Marine concluded that the reaction to iodine is the best criterion for differentiating autonomous tumors from physiologic hyperplasia, and that all encapsulated epithelial overgrowths which do not react to iodine in the time limit within which nontumorous tissue would react, are to be classified as tumors. Hence, according to Marine, Cohnheim's theory that adenomata are due to fetal rests offers the best explanation when it is enlarged to include the conceptions (1) that potential tumor anlages are found at different physiologic periods in the development of the main thyroid mass; and (2) that the stimulus for tumor growth is the same as that for the thyroid as a whole. These new growths may then be tentatively considered as partial tumors with varying abilities to function.

In support of this conception is the work of Graham who showed by experiments on tadpole metamorphosis that adenomata possess the property of taking up iodine and metabolizing it as does the normal thyroid, although not so readily nor to the same degree. There is, therefore, no qualitative difference in the reaction of tadpoles to feeding with adenomatous and with normal thyroids. Graham also observed that in the presence of adenomata the activity of the gland bears no constant relation to their differentiation.

The controversy over the cause of the symptomatology in Graves' disease and in toxic adenoma was given impetus by the writings of Plummer who considered the former to be dysthyroidism, quite distinct from toxic adenoma both in etiology and in its clinical manifestations, and thought that it arose from a lack of saturation of the thyroid secretion with iodine. In this way Plummer accounted for the value of iodine therapy in the treatment of Graves' disease and explained its failure to succeed in some cases of adenomatous goiter.

Graham, on the other hand, states that except for differences in the duration and intensity of the disease, there is no fundamental distinction between exophthalmic goiter and toxic adenoma. Graham, moreover, can find no physiologic, chemical, pharmacologic, or pathologic qualities in adenomata such as would distinguish between the toxic and nontoxic varieties or separate them qualitatively (other than morphologically) from nonadenomatous thyroids. He therefore concludes that the terms dysthyroidism and hyperthyroidism are equally applicable in cases of exophthalmic goiter and so-called toxic adenoma.

If, then, toxic adenoma and Graves' disease are fundamentally identical conditions of hyperthyroidism, how can we explain the ob-

servations by Marine and Lenhart, Graham, and Cattell, all of whom report that there is no specific relation between the clinical picture and the chemical or histologic condition of the gland in nodular goiter?

It is generally believed that in diffuse enlargements of the thyroid a close correlation exists between the iodine content, the hyperplasticity of the gland, and the symptomatology, but this is not true. It is well known that the hyperplastic gland of adolescent goiter produces no toxic symptoms. Marine notes that often an incomplete exophthalmic goiter syndrome may exist with a normal thyroid, that the thyroid may be markedly hyperplastic with complete absence of symptoms, or finally that in a given case of exophthalmic goiter the histologic structure and iodine content of the thyroid may be reversed without modification of the symptom-complex.

The varying symptom-complexes presented by adenomata differ from those presented by the hyperplastic gland only in the fact that the lack of correlation is carried further. Adenomata associated with the symptoms of toxicity may be undifferentiated, partially differentiated, or completely differentiated; they may be single, multiple or diffuse; and lastly, they may be present in a hypertrophic and hyperplastic or in a colloid gland, in each case presenting the same clinical picture as far as toxicity is concerned.

Again, with regard to the response of exophthalmic goiter and of "toxic adenoma" to iodine, the same generality holds true, *i. e.*, the reactions are qualitatively the same, but differ in respect to their regularity and extent. Cattell, working at the Lahey Clinic, found that 87.9 per cent of the patients with exophthalmic goiter who had been treated with iodine showed involutional changes in the thyroid and 6.7 per cent showed increasing hyperplasia. He also noted that the clinical improvement after treatment with iodine bears a relation to the structure of the gland and especially to chemical changes, but that there is a group of patients in whom the gland shows marked involutional change and a high iodine content, who yet continue to suffer from severe exophthalmic goiter. Cattell concluded, therefore, that the pathology of exophthalmic goiter is not constant.

In view of these findings, it would seem that the failure of the adenomata to show a constant chemical and histologic correlation with the clinical picture and their similar failure to react consistently to iodine is no proof that their reactions are in any sense qualitatively different from the reactions of the nonadenomatous gland in its various phases of hyperplasia and involution.

Graham explains these qualitative differences by stating that the adenomata differ from the rest of the gland primarily in that they have a less adequate blood supply and that innervation is probably wanting. As a result, these growths are less sensitive to changes in the body as a whole or to chemical changes in the blood, and hence their reaction is slower, or in extreme cases totally absent. To be sure, the argument that the nerve supply is diminished is of less consequence since transplanted thyroid tissue is known to undergo hyperplasia and involution in response to physiologic needs in the same manner as the normal gland, but it is interesting to note in regard to the rôle of the deficient blood supply that when iodine is given to a patient with a hyperplastic adenoma, the first part of that adenoma to undergo involution is the periphery where the blood supply is best. Adenomata can then be regarded as behaving in every respect in a manner similar to normal thyroid tissue with the exception that an insufficient blood supply prevents their reactions from taking place within the same time limits or to the same extent.

It would appear, however, that thyroid adenomata are at times somewhat more autonomous than the above would imply. When an inactive adenoma suddenly becomes active there must be some cause for such activation. Certainly there is nothing to warrant the assumption that the adenoma, deficient in blood supply and devoid of nerves, could respond in a hypersensitive manner to a general disturbance in the same way that the normal thyroid does in Graves' disease. In the latter condition the stresses and strains of man's environment play on the thyroid and perhaps stimulate it through the nervous system. In addition, a relative thyroxin deficiency induced by an overconsumption by the body, drives the gland to produce more thyroxin until a vicious circle is established and the body finds itself driven in turn by the gland. It is inconceivable that such a hypothetical sequence of events could occur in the condition called "toxic adenoma" when it is a well-known fact that in this condition the adenomatous tissue is conspicuously independent of factors ordinarily influencing the normal thyroid. Hence there must be in these islands of thyroid tissue, left marooned by nerve and blood stream alike, some mysterious semi-autonomous cycle which, when once initiated in response to a physiologic need, continues and lives out its physiologic phases of hyperplasia and involution irrespective of the state of the rest of the gland. Just as a castaway carries on his affairs in accordance with the impetus he received at the time he

left the world of civilization, so the adenoma may be so isolated that it carries on in the direction in which it started, and being insulated from further stimuli, it continues to evolve in its own preordained cycle.

As to carcinomata of the thyroid gland Marine and Johnson found that no iodine was absorbed by tumor tissue in two cases of cancer of the thyroid. The majority of other workers have found that thyroid neoplasms contained no active iodine, but Abelin found this substance in a metastasis from a thyroid neoplasm. The most famous case of all is that of Von Eiselsberg who observed both tetany and myxedema in a patient after total thyroidectomy for cancer of the thyroid. The tetany soon cleared up, but the myxedema persisted for some time until simultaneously with the appearance of a lump in the sternum, the myxedema disappeared completely. Upon removal of the sternum the myxedema recurred, indicating that in this instance the metastasis had been functioning. Such instances are so rare in the literature, however, and so many attempts have been made to cause involution of thyroid cancer by iodine feeding, that it seems more plausible to think of them as cases in which adenomatous thyroid cells had been carried into the blood stream and had multiplied in an attempt to overcome the deficiency.

VI. The Rôle of Iodine in Prophylaxis and Treatment of Goiter

(a) endemic goiter

Despite the recency of the work demonstrating the relationship of iodine to the function and pathology of the thyroid gland, this drug has been used in one form or another in the treatment of goitrous conditions since the year 1200 when Roger von Salerno found that the administration of sponges and seaweeds benefited his patients. It was not, however, until Coindet's discovery in 1829, that it was known that the iodine content of the sponges and seaweed was the active agent in von Salerno's treatment. Then followed Chatlin's suggestion that since the iodine distribution was low in those regions known to be endemic for goiter, goiter might be prevented by iodine feeding. But the true progress of iodine therapy and the initiation of the use of this drug in the prophylaxis of endemic goiter is again largely the result of Marine's studies.

In 1917 Marine and Kimball examined the school children of Akron, Ohio, and found that of 2305 pupils not treated with iodine, 495 developed goiter, whereas of a group of 2190 pupils treated with

2 Gm. of sodium iodide twice yearly only five became goitrous. Of the glands of 1182 children with thyroid enlargement who took the prophylactic dose, 773 decreased in size, while of the glands of 1048 children with thyroid enlargement who did not take iodine, only 145 decreased in size.

From this study Marine and Kimball concluded that iodine lack is the immediate cause of endemic goiter, and that iodine is a complete prophylactic agent. They also noted that in fetal life, puberty, and pregnancy the need for iodine and the liability to goiter is greatest, and that iodine prophylaxis is, therefore, most essential during these periods.

Marine, continuing to study the relationship of prophylactic doses of iodine to goiter, soon came to the conclusion that very small quantities were sufficient and estimated that 1 mg. of iodine per day will prevent goiter. He furthermore observed that in longstanding cases of goiter iodine does no good. And finally he recommended that in the treatment of adolescent goiter thyroid extract should be given at the same time or the gland will be unable to take up the iodine. Marine states that 5 mg. of iodine a day is sufficient for the treatment of such a gland.

Plummer working along the same lines, confirmed Marine's observations as to the value of coupling desiccated thyroid therapy with the iodine in the reduction of the adolescent goiter, offering as an explanation that the gland must be put at complete rest before the colloid can be absorbed. Thus with the work of the gland facilitated by the administration of iodine and with part of its work removed by the feeding with thyroid extract, the enlarged gland of adolescent goiter can be put to rest and may in some instances undergo a reduction in size. After adolescence, however, Plummer feels that iodine cannot be used without risk, because by that time the goiter is usually adenomatous and may be activated by iodine therapy.

(B) EXOPHTHALMIC GOITER

The credit for the first trial of iodine in the treatment of Graves' disease goes to Trousseau who in 1864 by accident gave iodine to a patient instead of digitalis and noticed that benefit resulted. This observation was not applied, however, this failure being largely due to the warnings of Kocher against the production of hyperthyroidism which he had observed was induced by the indiscriminate use of iodine therapy.

The striking temporary clinical improvement following the administration of iodine led Plummer to adopt his measures of preoperative iodine therapy in Graves' disease. Marine was the first to explain this result by his suggestion that large doses of iodine cause a fall in metabolism by bringing about a prompt involution of the hyperplasia. This is accomplished in all probability by the stretching and distention of the alveoli with colloid, thus causing an occlusion of the perialveolar lymphatics and capillaries and a pressure retention which temporarily blocks excretion until the acinar cells have accommodated themselves to the pressure and the vascular capacity of the alveolar capillaries is restored.

Plummer's hypothesis, on the other hand, states that anything that will stimulate the thyroid will give the clinical picture of exophthalmic goiter. In such cases the normal hormone, thyroxin, is not completely iodized. This incomplete thyroxin as it leaves the gland can enter into catabolic reaction faster than the normal, stable molecule, and raise the metabolic rate more rapidly. Iodine feeding changes the character of the molecule and iodizes it, thus rendering it normal and reducing the metabolic rate and clinical symptomatology.

It is to Plummer that we are indebted for the preoperative treatment now universally used in Graves' disease. He recommends that 10 minims of Lugol's solution be given three times daily for seven days before operation. In the control of a crisis as much as 50 minims in three hours is given at the Mayo Clinic, with the result, it is stated, that the condition is brought under control in a few hours.

In addition to the preoperative use of iodine in Graves' disease, Plummer, Graham, and others recommend its postoperative use in small quantities for some weeks to prevent regeneration hyperplasia in glands that have not been completely involuted preoperatively.

Graham concludes that the only indication for iodine is hypertrophy and hyperplasia of the thyroid, irrespective of the clinical diagnosis. In such glands involution can be brought about and the symptoms are at least temporarily controlled.

Fraser observed that, under this treatment, the soft hyperplastic thyroid of Graves' disease becomes hard, and he infers that this is an indication that involution has occurred and that it is time to diminish the dosage. Frazier and Mosser agree with Marine that iodine exerts its effect by increasing the colloid and producing an artificial involution by compression of the acinar cells. In addition, these workers, after prolonged iodine administration to dogs with hyper-

plastic glands, observe a stage of exhaustion of the acinar cells resembling thyroiditis, and conclude that this condition is similar to that occurring in Graves' disease after prolonged iodine therapy.

Wolcott, Starr, Segall, and Means in careful clinical studies of the effects of iodine in cases of exophthalmic goiter, report that the treatment is successful in 92 per cent of their hospital cases, but add that its benefit is only temporary. Means states that the basal metabolic rate falls at the average rate of 3.7 points per day during the course of this treatment. Lahey also finds that Lugol's solution is of value preoperatively in the control of metabolism, clinical symptoms, and operative risk, but says that at the Lahey Clinic not a single cure has been obtained by its use.

(C) TOXIC ADENOMA

There is no such unanimous accord as to the advisability of the preoperative use of iodine in the clinical condition called "toxic adenoma." Plummer, reasoning from his hypothesis of dysthyroidism, denies the value of iodine in this condition, while Graham strongly defends it.

Coller and Potter assert that 46 per cent of their patients in whom adenomatous goiter was associated with hyperthyroidism failed to respond favorably to iodine, while in only 11.7 per cent of the patients with exophthalmic goiter did they fail to observe a drop in the basal metabolic rate. These workers hold that patients with adenomata react in general quite differently and not so uniformly to iodine as do patients with exophthalmic goiter, but they recommend the preoperative use of iodine in cases of toxic adenoma on the grounds that it can do no harm and seems to give benefit in at least half of the cases.

Graham writing on this same controversial subject, claims the indication for iodine is the condition of the thyroid itself. When the gland is hyperplastic, iodine is indicated in proper quantities irrespective of whether the goiter is of the adenomatous or the exophthalmic type. Iodine, however, is never indicated when the goiter is in the colloid state, and in this condition may even be harmful.

Graham, moreover, observes certain quantitative differences between the reaction of an adenoma and an exophthalmic goiter to iodine. The former can be controlled by smaller quantities of iodine, because the amount of iodine needed is in direct proportion to the amount of hyperplasia and hypertrophy, and hence to the storing power of the gland (Marine). In summary, Graham holds that iodine

is indicated up to the point of saturation of the thyroid. Beyond this point, clinical experience shows that iodine may be harmful rather than beneficial whatever may be the variety of toxic goiter treated.

Crile and Dinsmore also consider iodine to be of benefit in the preoperative treatment of toxic adenomata, and in the Cleveland Clinic patients with either the nodular or the diffuse type of toxic goiter receive preoperative iodine treatment.

Many interesting studies have been carried out in attempts to elaborate the mechanism of the action of iodine in the control of hyperthyroidism. The work of Holst and Lunde in Oslo, to which we have previously referred, is of interest in this connection because they established that in these circumstances the alcohol-insoluble (organic) B fraction of the blood iodine was decreased while the alcohol-soluble A was increased. The decrease of B, moreover, is proportional to the decrease of metabolic rate. From this it is concluded that inorganic iodine inhibits the thyroid and thus lowers the level of the active thyroid principle in the blood stream.

Sturgis *et al.*, Wilhelmj and Boothby, and others have studied the effects of iodine on the increased metabolism induced by injections of thyroxin in animals and find that it is without effect.

From these and other considerations, it would appear:

1. That iodine exerts its effect in controlling the toxic symptoms of adenoma and exophthalmic goiter alike by a direct effect on the function of the thyroid gland.

2. That this effect is brought about by the storing of colloid with the production of an artificial involution and by the mechanical blockage of secretion.

3. That toxic adenomata respond to iodine qualitatively in the same manner as does exophthalmic goiter, but exhibit differences in the regularity and extent of their reactivity.

4. That iodine is indicated whenever the gland is hyperplastic, and hence should always be tried preoperatively in cases of toxic adenoma no less than in cases of exophthalmic goiter.

(D) DANGERS OF IODINE THERAPY

Despite the apparent clarity of the above indications for iodine administration it must be remembered that there is much evidence to suggest that the use of iodine is not wholly devoid of danger.

Fleischman and others find that iodine is dangerous in the treatment of colloid goiters and claim that it may induce hyperthyroidism.

Jackson reports 50 cases of iodine hyperthyroidism which occurred only in cases of adenomatous goiter. This condition most frequently occurs between the ages of thirty-five and forty and develops within a period of two months with characteristic symptoms of hyperthyroidism. Thrills, bruits, and exophthalmos, however, do not occur. The symptomatology is similar to that of toxic adenoma and the average basal metabolic rate in these cases is plus 31 per cent. Despite this clinical picture of thyroid activity, the glands present the histologic picture of colloid adenomata.

It is thus apparent that occasionally an adenoma which was previously nontoxic may be rendered active by iodine administration. It is not known how this is brought about, but it would appear to the writer that two factors may be held responsible.

The first possibility is based on the well-known work of Loeb, who showed that iodine stimulates the mitotic activity of thyroid cells, and on that of Marine who showed that iodine increases the heat production of rabbits beginning on the fifth day. Thus the administration of iodine could conceivably induce hyperthyroidism by direct stimulation of the adenomatous tissue.

The second possibility is that the adenomatous tissue, deficient as it is in blood supply, is perhaps unable to produce appreciable quantities of secretion, but with the saturation of the blood with iodine, the tissue is able to get more iodine and to elaborate thyroxin with greater ease and hence begins to produce greater amounts of the active substance, thus inducing the symptoms of toxicity.

Hartsock in a summary of the effects of iodized salt, believes that this is contraindicated for all but children up to the age of puberty. He shows that adenomatous colloid goiters may be perfectly quiet and within two weeks after beginning the use of iodine may become overwhelmingly active producing a basal metabolic rate up to plus 75 per cent.

The evidence thus indicates that iodine is dangerous if given in large quantities to patients with adenomatous goiter. But as to the use of iodized salt in goiter regions, it would seem that if iodine were added in only the minute traces that Marine considers ample for prophylaxis, such quantities, so inappreciably small as to be no larger than those contained in the water of nongoiter regions, could not induce iodine hyperthyroidism any more than the iodine in the water of normal regions induces hyperthyroidism in the inhabitants of those parts.

In conclusion, the present status of the rôle of iodine in the prophylaxis and treatment of thyroid disorders may be summarized as follows:

1. Goiter results from an insufficient intake of iodine.

2. Congenital goiter occurs in the presence of a thyroxin deficiency in the mother and can be prevented by giving iodine if the mother has a normal gland, or by giving desiccated thyroid to the mother with a deficient gland.

3. Goiter can be prevented in those born with a normal thyroid by maintaining a sufficient iodine intake unless the efficiency of the thyroid is later lowered by disease.

4. Iodine relieves hyperthyroidism but does not cure it and should be used only in preparing patients for operation.

5. Following operation, sufficient quantities of iodine to prevent compensatory hyperplasia tend to prevent recurrence.

6. In favorable cases, adolescent goiter may yield to treatment with small quantities of iodine.

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CHAPTER II

BIOCHEMISTRY OF IODINE

D. Roy McCullagh

Preliminary Note.—Many statements pertaining to the biochemistry of iodine have been made in appropriate chapters of this volume and much of the literature has been reviewed. It seems well, however, even at the expense of some repetition to prepare this chapter as a distinct entity as only thus can the biochemistry of iodine be properly appreciated. We shall, therefore, offer a brief historical survey and discussion of the distribution of iodine in nature and its biochemical relation to animal economy in health and disease.

I. HISTORICAL SURVEY

For more than one hundred years the biochemical study of goiter has, to a large extent, centered around studies of iodine metabolism and the effect of iodine compounds on metabolic processes. In particular a review of the early literature on the subject is very interesting and instructive. Theories have been established and overthrown, and in several instances reestablished after decades of intensive research.

A Parisian saltpeter manufacturer discovered iodine in 1811 and biochemical investigations of the compound followed immediately. Courtois, the discoverer, was using kelp in his manufacturing process and it was found that kelp contained large quantities of the new element. Since the time of ancient Greece, sea water and sea plants other than kelp have been used for the treatment of goiter. Among many other well-known references indicating that the sea and its plants were considered efficacious in the treatment of goiter is a statement by the original Methodist, John Wesley, who in 1760 instructed those of his flock who suffered from "swollen glands of the neck" to drink several glasses of sea water daily.

In 1814 the blue color reaction of iodine with starch was discovered. This was followed by a study of the distribution of iodine in nature

and it soon became known that the marine plants which were thought to be efficacious in the treatment of goiter had a very high iodine content. One is not surprised to find, therefore, that in 1820 Coindet suggested that endemic goiter was due to iodine deficiency. After various investigations the French government decided to supply iodized salt to the inhabitants of those areas where goiter was particularly prevalent. The scheme was discontinued, however, on account of the many cases of iodism which followed the injudicious use of iodized salt.

For almost thirty years very little advance was made, although several well-known chemists continued to report that in areas where iodine was plentiful goiter was not at all prevalent. The water of certain springs which had the reputation of being efficacious in the treatment of goiter was found to be very high in iodine content. In 1849 and 1850 investigations were commenced with renewed vigor. Chatin, a professor of pharmacology in Paris, deserves very great credit for his persistent and careful work. He reinvestigated the problems of iodine distribution and by a careful correlation of very extensive data, he was able to hypothecate that goiter was due to iodine deficiency. He was, however, doomed to suffer many disappointments. The French Academy of Science appointed a committee to investigate his findings and his work received very harsh criticism both from physiologists and chemists. Physiologists could not believe that such small amounts of any element could be of such great practical significance and chemists severely criticised Chatin's analytical procedures. The chemical procedures available at that time were undoubtedly inadequate, but in the hands of the master, Chatin, they gave results which were fundamentally true.

The French Academy of Medicine did not take the reports of the Academy of Science too seriously and once again attempted the administration of iodized salt to school children. Unfortunately doses as high as 1 Cg. of potassium iodide were given daily and the experiment was once again discontinued on account of the toxic effects of such large doses. For another thirty years very little advance was made. Various theories were propounded, toxic goitrigenic substances were suggested then as now, and Pasteur's work gave rise to the germ theory of the etiology of goiter.

No real advances in the biochemistry of iodine were made until 1895. It was found that patients suffering from postoperative hypothyroidism were relieved by the administration of dried thyroid

glands of animals. Moreover it was found that the feeding of desiccated thyroid substance caused symptoms closely simulating those of hyperthyroidism. The Swiss government appointed a commission to investigate the matter and the work of Baumann is now classical. He demonstrated that iodine is a normal constituent of the thyroid gland and that it is present in combination with a globulin. He immediately followed this discovery by demonstrating that goitrous glands are low in iodine content. Fortunately Magnus-Levy at about the same time devised methods of studying the metabolic rate so that the physiologic advances continued hand in hand with the chemical studies. Since then there has been continuous investigation and advance in all matters pertaining to the thyroid gland.

The advances in knowledge of the physiology of the thyroid gland were greatly promoted by the discovery, made about 1891, that the parathyroid glands are morphologically and physiologically separate structures and that the health of experimental animals is particularly dependent on their normal function. It is impossible to review the enormous amount of work which has been accomplished but an attempt to correlate the findings of this century will be made in the rest of this chapter.

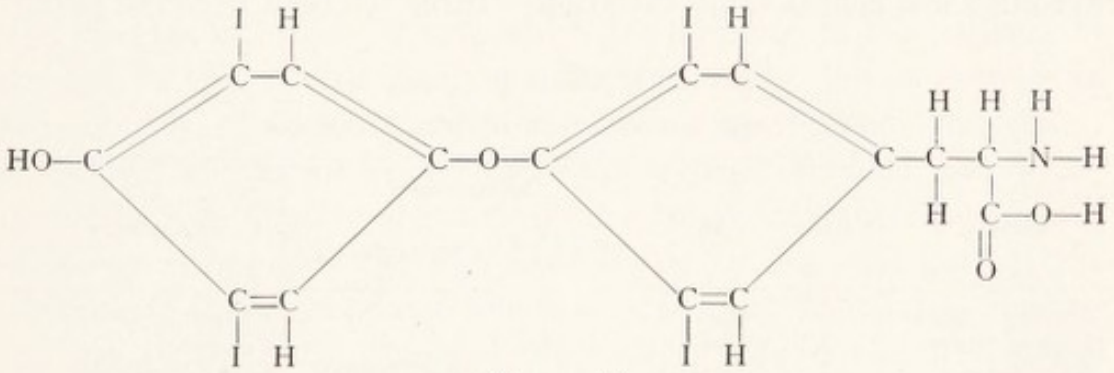
II. DISTRIBUTION OF IODINE IN THE BODY

The distribution of iodine in animals, plants, and in a large number of biological materials has been investigated by von Fellenberg, McClendon, Cameron, and others.

(*a*) **Analytical Methods.**—Until recent years there have been no satisfactory analytical methods for the investigation of the biochemistry of iodine, and even at the present time, all of the available methods are tedious and unreliable except in the hands of experts. The best known procedures are those of McClendon, of Kendall, and of von Fellenberg. Certain modifications of von Fellenberg's method have been used very extensively. In my hands the modification suggested by Lunde and Class appears to be the most satisfactory. It is interesting to note that although satisfactory methods for the estimation of iodine have been available only within the last few years, the outstanding work of some of the earlier investigators has been in the main, confirmed. The difficulty throughout has been that the quantity of iodine available in many materials is so small that even the best micromethods are not more than barely adequate. For instance, 10 cc. of blood contains only a little more than 1 gamma of

iodine (0.000001 Gm. or 1 μg.). It is now quite possible to estimate this quantity of iodine with an accuracy of plus or minus 5 per cent.

(*b*) **Iodine Compounds of Biological Importance.**—Most of the iodine in biological material is in organic combination. The first of these organic compounds to be described were those isolated from marine plants; for instance in the sponge and in the coral, iodine is found in the form of iodogorgonic acid (diiodotyrosine). This compound is closely related to those compounds found in the thyroid gland. In 1916 Kendall finally succeeded in isolating a crystalline compound from the thyroid gland. He isolated 33 Gm. of this substance from about three tons of fresh thyroid tissue and made extensive chemical and physiologic investigations. This proved to be very much more active physiologically than any compound previously isolated. Kendall called this compound "thyroxin." He was of the opinion that it was an indol derivative. Harington has shown thyroxin to be beta-tetra-iodo-(3, 5, 3^1, 5^1)-4-(4^1-hydroxy-phenoxy)-phenyl-alpha-amino-propionic acid, with the following structure.



(Thyroxin)

It seems very probable that thyroxin *per se* is found only in traces in the thyroid, and that it is in protein combination, the protein usually being called "iodothyroglobulin." At present it is impossible to say whether or not thyroxin represents the most active iodine compound in the gland. Cameron and Carmichael found that iodine as it is present in desiccated thyroid is about three times more active than the same amount of iodine in the form of thyroxin. Moreover, it has been impossible so far to obtain more than about 14 per cent of the iodine in the thyroid gland in the form of thyroxin and it would appear that there is much iodine in the gland which is not in this form. Recently Harington and Randall have succeeded in isolating diiodotyrosine from the thyroid of the normal hog. This compound probably accounts for more than a quarter of the iodine in the gland.

At present it is impossible to say whether or not the thyroid gland secretes more than one iodine-containing substance. Several substances containing iodine can be extracted from the gland, but there is no proof that any one of these substances is the hormone of the thyroid gland. Existing evidence leads one to believe that there is a greater probability that iodothyroglobulin is the thyroid hormone than that thyroxin is the only active secretion.

(*c*) **Quantities of Iodine in Various Tissues.**—Extensive studies of the iodine in blood and in thyroid tissue have been made. The maximum content of iodine in the thyroid is about 25 mg. or 5 to 6 mg. per Gm. of the dried gland, an average of about 0.2 per cent of the gland tissue. About the highest values reported for any tissue, are those of Cameron who found 1.16 per cent in the dried thyroid of the dog fish. Although there are great variations in the amount of iodine in the adult human thyroid in disease the values are fairly constant in healthy individuals who have received a normal diet containing a sufficient but not an excessive amount of iodine. Fetal thyroids show considerable variation. Table 1, taken from the paper

TABLE 1

THE IODINE CONTENT OF HUMAN THYROIDS

Locality.	Number.	Age.	Iodine content.		Analyst.
			Mg. per Gm. of dried wt.	Mg. in glands.	
United States	5	Fetal	0.29	—	Fenger
United States	5	Fetal	0.05	—	Fenger
Switzerland	7	Newborn		min. 0.0004 max. 0.053	von Fellenberg
United States	3	Infants		0.13	Remington, McClendon, et al.
United States	1	2 years		0.42	Remington, McClendon, et al.
United States	1	2½ years		0.73	Remington, McClendon, et al.
United States	2	16 and 17 years		15.5	Remington, McClendon, et al.
United States	27	Adults		min. 2.49 max. 23.7 ave. 8.27	Remington, McClendon, et al.
Austria	20	Adults		8.05	Hergloz
Germany	7	Adults		3.34	Jansen and Roberts
Scotland	15	Adults		7.8	Rowett Institute

of Schohl and Bing, gives a report of the findings of various investigators. Blood contains 10 to 15 gamma of iodine per 100 cc. About two-thirds of the iodine in the blood is in the organic form which is

insoluble in alcohol. The amount of organic iodine in the blood appears to be an excellent measure of thyroid activity as it is low in individuals with hypothyroidism, and high in individuals with hyperthyroidism. The work of Lunde, Veil, and Sturm is particularly interesting in this regard. The amount of iodine in tissue other than blood and the thyroid gland probably corresponds to the amount found in the blood. It appears that in different species of animals the percentage of the total iodine of the body found in the thyroid gland varies greatly. Marine believes that most of the iodine in the human body is in the thyroid tissue. It seems probable that in humans, at least 50 per cent of the iodine is usually stored in the thyroid gland.

III. THE EFFECT OF IODINE AND ITS COMPOUNDS ON METABOLISM

The most outstanding physiologic effect which has been noted as produced by iodine or iodine compounds is an increase in the basal metabolic rate. For example, in man, the injection of 2 mg. of thyroxin may produce an increase in the basal metabolic rate of 20 per cent. The changes in metabolic rate which are observed in the presence of diseases of the thyroid gland are unquestionably due to changes in the amount of iodine compounds circulating through the tissue. Moreover, all the other symptoms of hyperthyroidism and hypothyroidism are directly or indirectly due to alterations in the amount of iodine compounds available. Iodine is an essential part of the molecule of those compounds which alter the metabolic rate. Harington has synthetically prepared desiodothyroxin, that is, a chemical compound which is exactly the same as thyroxin except that the iodine of the molecule is replaced by hydrogen. This compound has no effect whatsoever on the metabolic rate. In addition to this evidence there is the well-known fact that many iodine compounds other than thyroxin produce similar effects, for example, iodized protein and diiodotyrosine.

Iodine is also essential for the normal growth and development of animals and plants. It has been known for a long time that the metamorphoses of tadpoles could be stimulated by iodine and iodine compounds. Thyroid tissue itself is particularly active in this regard. Gudernatsch in 1912 observed that thyroid feeding stops growth and accelerates metamorphosis in very young amphibians. In mammals, particularly in humans, it is well known that the thyroid secretion is essential for growth. Topper and Cohen have stated

that the administration of thyroid extract to normal children or to children suffering from cretinism will stimulate growth. On the other hand, the administration of thyroid extract to rats definitely diminishes their growth. These growth changes cannot be said to be due to iodine as such, since similar amounts of pure iodine do not alter growth rates. It must be emphasized that iodine *per se* is not the active principle of the secretion of the thyroid gland but that it is essential for the activity of the compounds of which it is a part.

The mechanism through which these iodine compounds exert their influence is not known. Kendall[1] offers the following explanation:

"These results show that thyroxine must act as an agent which helps some chemical reaction to occur in the body and that it is not destroyed by this reaction. The reaction which it helps is undoubtedly intimately associated with the processes of combustion, and it probably acts as a catalyst. A catalyst familiar to many is the effect of manganese dioxide in some reactions. One of the first chemical experiments performed at school used to be the separation of oxygen from potassium chlorate. Since a high temperature is required before the reaction will take place with any speed, manganese dioxide was always added to assist the process. The manganese dioxide causes a prompt and rapid liberation of oxygen, although it is not consumed in the reaction. Without thyroxine, the chemical processes of the body will proceed slowly, and life be maintained sluggishly. The addition of thyroxine hastens the chemical reactions on which muscular and mental activity, glandular action, heart-beat, and indeed life itself depend."

There are many people who cannot completely agree with this conception: (1) Kendall discusses the subject in such a manner that it leads one to believe that thyroxin itself is the active secretion of the gland. It seems more probable that the activity is due to iodothyroglobulin. (2) It appears that Kendall pictures the active iodine compound as acting in a manner comparable to that of certain catalytic agents. To believe this, one must assume that the action of this iodine-containing hormone takes place in the cells where the metabolic processes occur.

If thyroxin or iodothyroglobulin act as catalytic agents in the cell itself, one would expect that their addition to isolated but normally active tissue would increase the rate of oxygen uptake; but an increase in the metabolic rate of isolated and therefore denervated tissue has

never been observed. Kendall, however, is not alone in his beliefs. Aub and his collaborators found that animals under urethane anesthesia showed an increase in metabolic rate when thyroxin was administered. They concluded that the hormone acts directly on the cells and that the nervous system is not essential for its activity. However, under urethane anesthesia the nervous system is not completely inactivated but is only partially inhibited. Further experimental evidence is necessary before this conclusion can be established.

There is much evidence to indicate that iodothyroglobulin exerts its influence through the sympathetic nervous system and related mechanisms. Abderhalden and Wertheimer demonstrated that when the sympathetic nervous system is paralyzed with ergotamine there is no change in metabolism after the administration of thyroxin. It is known that the basal metabolic rate is changed when sympathetic tonus is altered. It must be admitted, nevertheless, that it is somewhat difficult to account for all of the changes seen in thyroid diseases on a basis of alterations in the autonomic nervous system.

IV. IODINE IN RELATION TO DISEASE

A simple goiter consists of a thyroid gland, the development of which at all stages is essentially the same as that of the normal gland, except in regard to the rate and amount of growth; that is to say it is histologically and developmentally the same as a normal gland but it has increased abnormally in size. This condition occurs in all countries but in certain areas it is endemic. The consensus of opinion is that the condition is due to a deficiency of iodine. The iodine content of the goitrous gland is low and it has been shown by Marine and Lenhart that when, in young animals, the iodine content of the gland falls below a certain level an enlargement of the gland follows. The determining factor as to the iodine content appears usually to be the amount of iodine in the food. It has also been shown that the iodine excretion of persons in areas of endemic goiter is below that of normal individuals, indicating that the intake must be low.

It has been suggested that factors other than iodine deficiency are of importance in the production of goiter. The three most outstanding etiologic factors suggested are: (*a*) goitrigenic diets which are not iodine-deficient; (*b*) pollution of water supply, and (*c*) changes in other parts of the endocrine system.

(*a*) Calcium and magnesium have been said to stimulate the production of goiter. Von Fellenberg has shown that in many areas

in which there is a supply of salts of calcium and magnesium there is only a very small amount of iodine. Since endemic goiter is not present in those areas where there are excessive lime salts but ample iodine, it seems probable that an excess of lime salts is not an etiologic factor in the overgrowth of the gland. The most striking evidence that the inorganic element of real importance is iodine is the experiment of Marine in Akron, Ohio, where by feeding small doses of iodine he was able almost completely to prevent the appearance of goiter in school children in a region of endemic goiter.

Recently, extensive researches have been conducted in regard to the goitrigenic activity of certain diets fed to laboratory animals. The best known of these is a diet of cabbage fed to rabbits. The mechanism of the production of goiter in this manner is as yet unknown. It is possible that even though there is ample iodine in the diet certain substances may interfere with the iodine metabolism. It is known that a considerable portion of iodine is secreted in the bile and reabsorbed in the gastro-intestinal tract. It is not at all impossible that indigestible substances such as cabbage when fed in excess might unite with iodine and carry it out of the gastro-intestinal tract. In this manner an actual iodine starvation might be produced even in the presence of sufficient iodine in the diet.

(*b*) McCarrison believed that in certain districts in India, along the Gilgit River, the etiologic factor responsible for endemic goiter is a water-borne infection. There is very little evidence to indicate that this is generally the case although it is very possible that here again there may be something which interferes with the iodine metabolism. It is somewhat surprising, moreover, to find such specific age and sex susceptibilities to infection.

(*c*) Recently Loeb and his associates have brought definite evidence to indicate that in animals and birds hyperthyroidism can be produced by the administration of certain pituitary extracts. This work has not yet been confirmed but it gives great promise of throwing further light on the physiology of the thyroid gland.

That the adrenals are closely associated with the thyroid and in some cases may be the etiologic factor in the production of hyperthyroidism has frequently been stated. This subject is discussed in another chapter.

Hypofunction of the thyroid gland in undeveloped children results in a condition known as cretinism. This is a condition frequently found in regions of endemic goiter, and is due to iodine deficiency in

the mother. If the diet contains sufficient iodine the condition seldom develops.

Endocrinologists were somewhat surprised some time ago when Plummer proposed the treatment of hyperthyroidism with inorganic iodine (Lugol's solution). The mechanism through which the action occurs is not entirely analyzed but certain factors concerning the interesting results of its use are known. The percentage iodine, as well as the total iodine of the thyroid gland of a patient suffering from hyperthyroidism, is usually small while the iodine content of the blood is very greatly increased. The increase in organic iodine in the blood is much greater than the increase in inorganic iodine. It seems probable that the iodine compound of the blood which is increased is iodothyroglobulin.

When Lugol's solution is administered to patients suffering from hyperthyroidism their metabolic rate decreases and their general condition improves. These changes, however, are only transient and the condition usually returns to the original state within a few days or weeks. During the period of improvement in symptoms the amount of organic iodine in the blood is greatly decreased although the amount of inorganic iodine is greatly increased. The decrease in organic iodine in the blood (iodothyroglobulin) parallels the decrease in the basal metabolic rate and the improvement in symptoms. At the same time the thyroid gland stores a great deal of iodine. Finally, however, the acini of the thyroid gland become filled with colloid material and the gland becomes very rich in iodine. The gland then recommences to secrete large amounts of organic iodine into the blood. The subsequent increase in basal metabolic rate and the increase in the severity of symptoms are paralleled by an increased amount of organic iodine in the blood. It appears that the most logical time for surgical intervention after the administration of Lugol's solution would be that moment when the curve of organic iodine in the blood is at its lowest point.

V. IODINE REQUIREMENTS AND THE METABOLISM OF IODINE COMPOUNDS

Numerous experiments have been made in order to determine how much iodine is required in order to keep a normal man in iodine equilibrium. Since a portion of the iodine is excreted in the feces and some in the urine it is necessary to analyze the food, urine, and feces in order to study the iodine metabolism. Most of the iodine

appears to be excreted in the urine. The amount of fecal iodine appears to be more or less in proportion to the amount of indigestible material in the diet. With a total daily intake of from 50 to 80 gamma of iodine, von Fellenberg finds that there is a slight retention. He finds that exercise increases the rate of excretion of iodine and that fasting and rest diminish it. In other words, an increase in metabolism is associated with an increase in excreted iodine. It may be that the thyroid hormone which is required for normal function is broken down more rapidly during exercise with a resultant increase in iodine secretion.

Orr and Leitch say that for equilibrium in the adult male it is necessary to have at least 15 gamma of iodine per day (0.000015 Gm.) but in a child about 50 gamma are required.

This brings us to the question of the prophylactic dose. Kimball and Marine in Akron gave doses of 2 Gm. of sodium iodide in divided doses for a fortnight, twice a year. These doses would be without question much less effective than the same amount of iodine taken over a longer period of time. From the point of view of what we know of iodine requirements their doses appear to be quite large, although the doses used in New Zealand are of the same order. Marine has suggested the use of smaller doses (5 to 10 mg. per week) for prophylactic doses in children and 10 mg. weekly for pregnant women to prevent congenital goiter. Most of the Swiss workers have used very much smaller amounts of iodine. One-tenth mg. per day is probably ample for the prevention of goiter. At the Cleveland Clinic 10 mg. of iodine once a week throughout the year is advised for children and for women during periods of pregnancy.

For a more complete discussion of this subject and a very excellent list of references, the reader is referred to the monograph by Orr and Leitch in the special reports of the Medical Research Council, 1928, pp. 122–135. The author is very greatly indebted to Dr. Bing for the use of the manuscript entitled "Iodine in Nutrition" written in collaboration with Dr. A. T. Schohl. This paper will appear in the reports of the White House Conference on Nutrition.

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1. Kendall, E. C.: The Story of Thyroxine, Chemistry in Medicine, Chapter VI, pp. 232–238, New York, The Chemical Foundation, 1929.

Note.—For other references in this article the reader is directed to the monograph by Orr and Leitch, cited above.

CHAPTER III

THE RÔLE OF THE THYROID GLAND IN THE ENERGY SYSTEM

GEORGE CRILE

ALL life exists in cells. Cells consist of water, electrolytes, colloids, and solutions of characteristically different concentrations such as those which are present in the cells, in their suspending medium, in the nucleus and in the cytoplasm of the cells. These differences in electrolytic concentration are dependent on the properties of the semipermeable membranes of the cells; that is, to a certain degree of permeability to certain ions. It is to the difference between the electrolytic concentration on the two sides of the membranes that the electric charge or potential of the cells is due.

Since animals and plants have the constituents of the sea, both plants and animals are the survivors of the struggle among all the possible combinations of electrolytes, colloids, solutions, molecules, and atoms in the sea, and so important in that struggle was the rôle of iodine that as our ancestors gradually emerged from the water, they evolved a gland for the preparation of the needed iodine. It is no mean biological tribute to iodine to find an important gland evolved for the sole purpose of varying the conductivity, capacity, and potential of the cells of animals, thus forming an essential factor in the regulation of energy transformation.

Animals may be regarded as motorized plants, set free from their wooden cage, and endowed with mechanisms for the adaptive transformation of energy in fight or flight, in defense against infection, and in the expression of the emotions. But plants have no muscular activity, no need for fight, or flight, or emotion, hence plants have no need for the mobilization of iodine as have animals; therefore, the tree has no thyroid gland.

The plant cell and the animal cell *per se* are essentially the same in their patterns—nucleus and cytoplasm, lipoid film and electrolytic content, in their lipoid-protein relation, in their mode of cell

division, in their electric properties, in their metabolism, in their similar response to heat, to electricity, to change in electrolytic solution, to anesthetics, to poisons, to narcotics; that is, in all their basic essential features the plant cell *per se* and the animal cell *per se* are identical. It is therefore by the assembly of the animal cells into organs and of the organs into an organism which is subject to an adaptive unifying control by action currents or electric energy, that the animal is distinguished from the plant. The thyroid gland is the basic organ of the energy-transforming or kinetic system which adaptively controls the animal organism. The presence of a thyroid

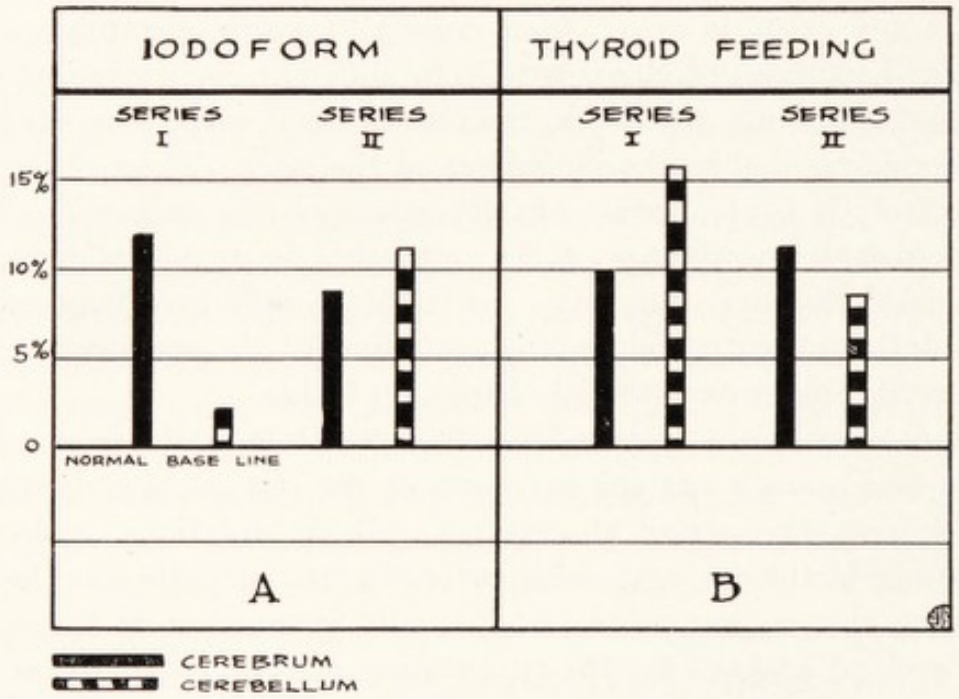

Fig. 9.—Increase in electric conductivity of cerebrum and the cerebellum produced by iodoform and by thyroid feeding.

gland with its hormone distinguishes the animal from the plant more than does the presence of a nervous system, for the plant has lines of communication which are analogous to those of the nervous system in animals.

In our experiments we have demonstrated that iodine in organic or in inorganic form causes a greater control over the electric conductivity of animal tissues than does any other agent (Fig. 9), and that it also possesses to a degree beyond that of any other agent, the specific power of raising the electric potential and capacity of tissues and cells. In other words, iodine is the most potent factor in the control of the activity of the cells.

During a number of years in association with Amy Rowland and Maria Telkes, we have studied in our laboratory the effects of iodine on the electric conductivity and capacity of various animals and plants; we have also studied its influence on the action of adrenalin, and, of greatest significance, have observed the influence of sodium iodide and of thyroxin on the electric potential of animals, including observations of amoebae and of certain fruits. Our results show that thyroxin and sodium iodide have a greater effect on electric conductivity than has any other agent. When an animal, even an amoeba, is first iodized and then given a control dose of adrenalin, the effect of the adrenalin on the temperature, conductivity, and capacity of the animal is heightened. Likewise, in an iodized animal, electric and nerve stimulation is facilitated.

Exactly the opposite effect is noted when animals are deprived of their normal quota of iodine by the removal of the iodine-products factory and storehouse, namely, the thyroid gland. The loss of iodine renders all of the cells of the victim less permeable, therefore less responsive to adrenalin and to nerve stimulation; it lessens their electric capacity, and their physical and chemical activity. In clinical terms, the thyroid hormone—an organic iodine-containing compound—holds the key to the activity of the animal by controlling the great physical constants of the cells of the body—conductivity, capacity, heat, and potential, and as a consequence, it controls the physical and the chemical activity of the animal, or in other words, its adaptive existence.

The conductivity or permeability of cell membranes governs the activity of cells, whatever the cells are doing. The secretion of digestive juices, muscular contraction, fertilization and growth, the production of mental or emotional processes, are all governed by changes in the conductivity, in the potential, in the capacity, and in the chemical action of the cells, changes which are due to the specific action of the organic iodine which is made by the thyroid gland.

In clinical terms, if too much iodine is present in the organism, the conductivity, capacity, potential and chemical activity of the various organs and tissues of the body are abnormally increased. Every cell, every organ, is doing more than its normal work—not a different kind of work, but more work. The brain teems with ideas; the digestion is efficiently exalted; the kidneys and skin provide greater elimination; the pupils are more widely dilated; the heart shows more powerful contractions; the metabolism is elevated.

When there is a deficiency of iodine, the permeability, capacity, potential, and chemical activity of the cells are lowered, with resultant mental dulness, low metabolism, low gastric motility, and low acidity or anacidity.

But while iodine in the form of the thyroid hormone causes the energy transformation of the cells, of the glands, and of the whole organism to be increased, it has no power of releasing the energy adaptively. That is to say, the thyroid gland governs the rate of oxidation and the potential of the cells, but obviously it has no control over the use of the energy that is thus provided. The energy expenditure is governed by other systems which are constructed in an entirely different way.

The units of the kinetic or energy transforming system are: first, the organ that governs the rate of energy transformation—the thyroid gland; second, the system that expends the energy made available by metabolism controlled by the iodine supplied by the thyroid gland, the brain and all the nerve tissue, in other words, the entire nervous system, and the adrenal glands; third, the system that is driven—that which executes the "will" of the brain by using the energy made more available by the thyroid—the entire muscular system, voluntary and involuntary, and that part of the glandular tissue which is adaptively driven.

From these considerations it is clear that the thyroid gland is not responsible for the actual execution of muscular, mental, and glandular work. The thyroid gland loads the gun; the nervous system, supplemented by the adrenal glands, fires it. Therefore, under normal conditions, in hyperthyroidism and in hypothyroidism, the thyroid gland is responsible for the charge of the cells, for the feeling of well-being or the contrary, while the nervous system and the adrenal glands are responsible for the discharge of energy or for the work done, and it is the "work done" that is displayed in "symptoms."

CHAPTER IV

ENDEMIC GOITER—ITS MANIFESTATIONS AND THE RÔLE OF IODINE AND OF SURGERY IN PREVENTION AND TREATMENT

GEORGE CRILE

THE principal regions in which endemic goiter occurs are the great watersheds—the valleys of the Alps, Carpathian, and Pyrenees mountains in Europe, of the Himalayas in Asia, of the Peruvian Andes

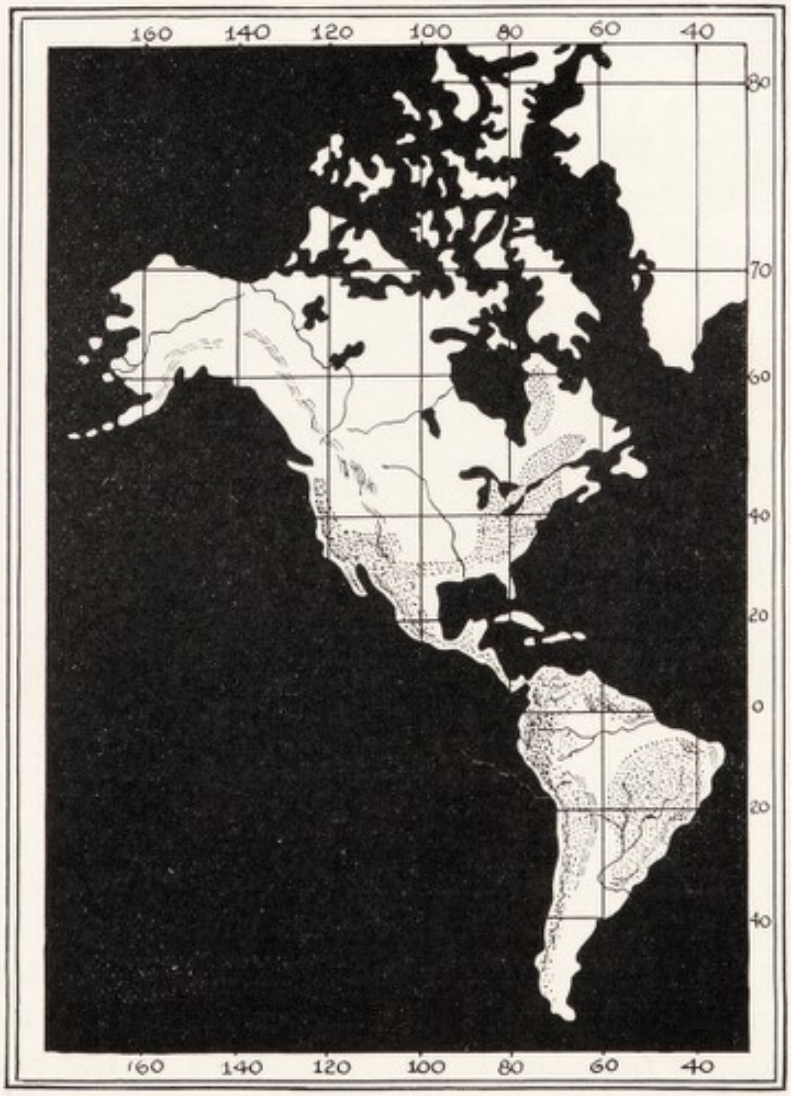

Fig. 10.—Map showing approximate distribution of endemic goiter in the Western Hemisphere. (After McCarrison.[1])

in South America, of the Rocky Mountains and the Great Lakes Region in the United States (Figs. 10, 11). These appear to be the principal goiter centers but in all mountainous regions there seems to be an increased incidence of goiter. In contrast to the high incidence in these regions the lowlands, especially those near the sea, are relatively goiter-free. A consideration of this distribution should

Fig. 11.—Map showing approximate distribution of endemic goiter in the Eastern Hemisphere. (After McCarrison.)

lead at once to the assumption that goiter is a geologic deficiency disease. Animals developed from the sea still bear the ancient formula of the sea. It is a striking and significant but an obvious fact that the formula of protoplasm is more constant than that of the earth's crust, for only the soluble compounds in the earth's crust could enter into the structure of protoplasm. So in the high watersheds of the world such essential elements of protoplasm as the salts

of sodium, iodine, potassium, and magnesium have been carried in solution back to the sea.

The demand for common salt for animals, especially in these watersheds, has long been appreciated but the need for these other elements, especially for iodine, was not fully appreciated until the epoch-making investigations of Marine and his co-workers.

The genesis of endemic goiter, then, is found in a lack of available iodine in the environment. How is this lack manifested? By the overdevelopment of the thyroid gland which is known as simple goiter or by the presence in the fetus of fetal rests which develop into adenomata.

THE RÔLE OF IODINE IN THE PREVENTION AND TREATMENT OF GOITER

Endemic Goiter.—Based on the work of Marine and Kimball the prophylaxis of endemic goiter has been studied in various countries. On theoretical grounds it would appear that the ideal method of prophylaxis would be to prepare some food product by which iodine could be received in an amount equivalent to that found in the food products in nongoiter countries especially in districts near the sea. Attempts to approach this ideal method have been made by adding iodine to table salt as suggested by Dr. Sloan.[2] The use of the salt in some instances was not without adverse effects because the manufacturers of salt probably did not use uniform methods. No ill effects appeared in children but in some cases adenomata in adults appeared to become activated as the result of the ingestion of the iodized salt. If iodized salt is to be successfully used by a community as apparently has been the case in Detroit the salt should be prepared with the precautions suggested by Vaughan, namely, before being put on the market the salt should be analyzed for its iodine content. The dosage for the community would thus be controlled just as the dosage for the individual is controlled by the druggist. Certainly so important a drug as iodine with the possibility of so many adverse effects in certain cases should not be left to the judgment of a manufacturer or distributor. The proper preparation of iodine for administration to the patient with hyperthyroidism requires the utmost care on the part of the pharmacist. Equal care should be employed in the preparation of the dose for prophylactic use when iodine is given in other than the ideal method suggested above.

One important dictum regarding its use is that it should be given

discontinuously. For some reason when given continuously over long periods of time, even in small doses, it tends to produce hyperthyroidism. It may be administered twice yearly—in the spring and fall—according to the plan of Marine and Kimball[3] namely, 2 Gm. of sodium iodide given over a period of two weeks twice yearly, or in smaller doses not oftener than once a week. It is our practice to

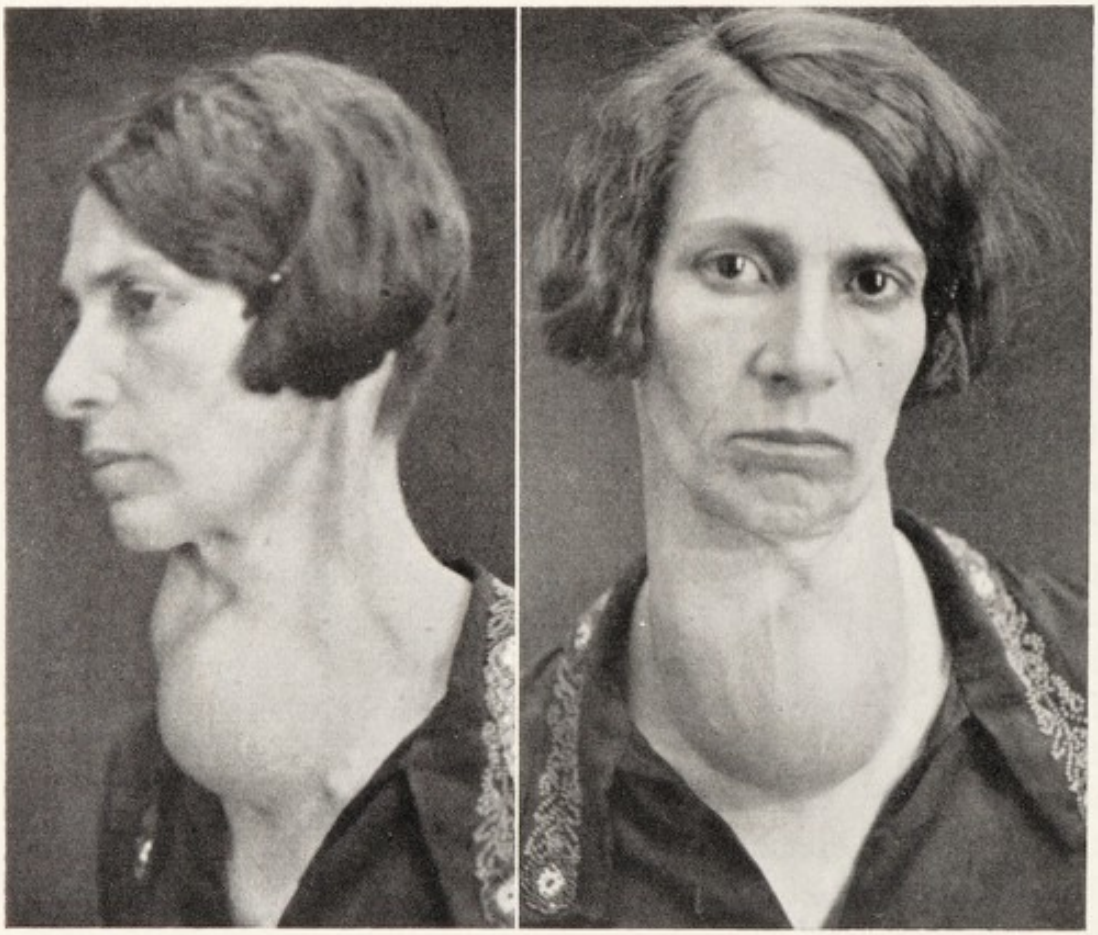

Fig. 12.—Fetal adenoma. The patient, a woman forty-one years of age, had had a goiter for twenty-eight years during which it had shown periodic enlargements and recessions. Symptoms of early hyperthyroidism were present. At operation the right lobe which was of about the size of a grapefruit was removed. On pathologic examination this was found to contain two cysts measuring 90 and 30 mm. in diameter respectively, and a discrete nodule measuring 20 mm. in diameter. Sections showed acini of fetal type.

prescribe one tablet of iodostarin, containing 1/10 mg. of iodine, to be taken once a week. When thus given to an adolescent child, iodine in this dosage appears to be sufficient to supply the energy requirements of the child and thus to prevent enlargement of the thyroid gland. When given throughout the period of pregnancy it appears to prevent the development of adenomatous goiter in the offspring.

Millions of children in various parts of the world are now being benefited by the prophylactic administration of iodine and if we do our duty the next generation should be relatively goiter-free.

Adenomatous Goiter.—While simple goiter in children may be prevented or cured by the administration of iodine, iodine cannot remove the fetal type of adenoma either in children or adults (Figs. 12, 13). On the contrary, if iodine is given over a period of time to children or adults having fetal adenomata, hyperthyroidism may be

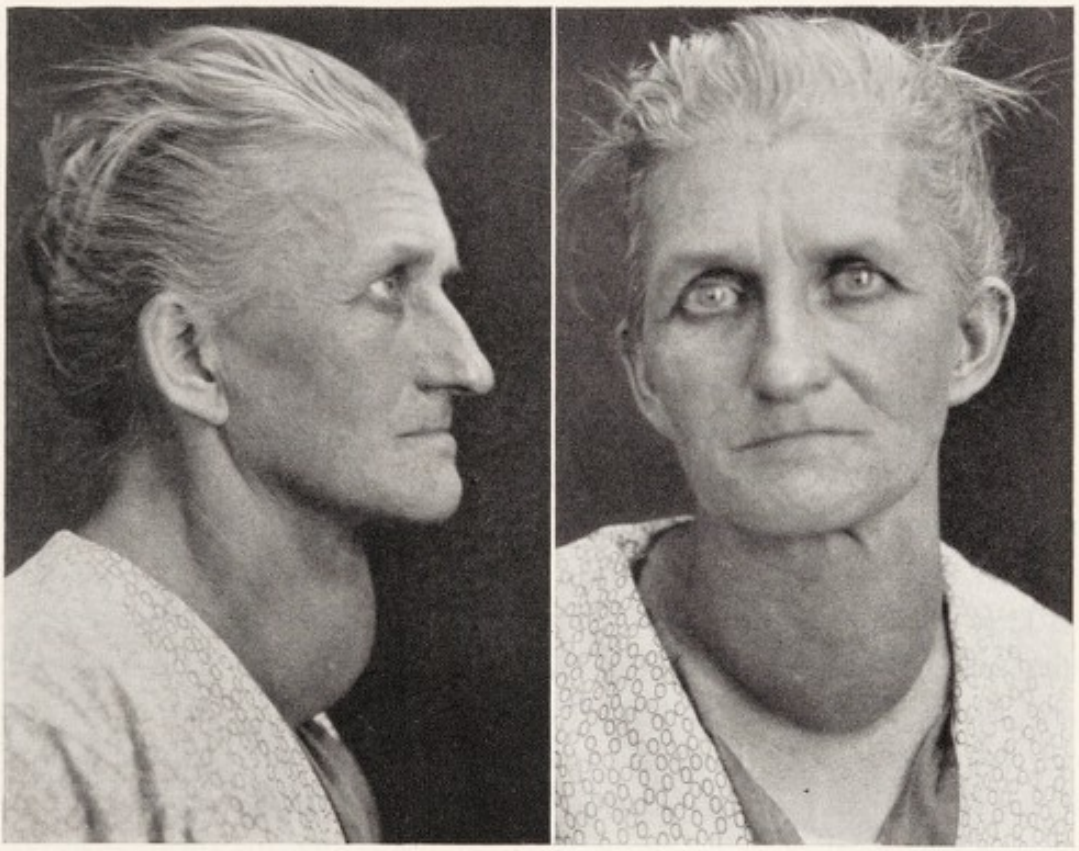

Fig. 13.—Fetal adenoma. The patient, a woman forty-one years of age, had had a goiter for about five years which had increased in size since birth of a child about two years previously. She showed mild symptoms of hyperthyroidism. On pathologic examination of the gland which was of about the size of a small grapefruit, numerous cysts were found varying from 5 to 50 mm. in diameter. Sections showed acini of fetal type.

induced in a certain percentage of cases. In a small series of cases observed by Hartsock,[4] adenomatous colloid goiters were apparently activated by the ingestion of iodized salt.

Hyperplasia.—The relation between hyperplasia and the iodine content of the thyroid gland was shown by Marine, both experimentally and clinically. As stated in Chapter II he found that the administration of iodine to patients having hyperplastic goiters caused

the hyperplastic goiter to revert to a colloid goiter, and demonstrated this effect of iodine in cases in which after one part of the hyperplastic gland had been removed and iodine had been given for one month the remainder of the gland reverted to the safe colloid state.

Following Marine's work there arose a widespread belief that hyperthyroidism was an iodine-deficiency disease which could be cured by the administration of small doses of iodine over long periods of time. This theory was tested on a large scale for a number of years and was proved to be fallacious. Meanwhile, many cases of hyperthyroidism were made worse.

Later, Plummer[5] revived the theory that iodine therapy would be effective in cases of hyperthyroidism but he gave large doses of iodine in the form of Lugol's solution during a period of rest in bed as a preparation for thyroidectomy.

The use of Lugol's solution proved to be a valuable aid to the surgical treatment of hyperthyroidism. The success of Plummer's method led once more to the illogical deduction that iodine is a cure for hyperthyroidism and for adenomatous goiter in adults. Again this deduction was proved to be fallacious.

As Crotti has so clearly stated, iodine is not an appropriate therapeutic agent for the treatment of goiter in adults. The surgical indications are clearly defined.

The Stimulating Effect of Thyroid Extract on the Structure and Function of the Thyroid Gland.—In cases of surgically induced myxedema, it is observed that for a certain period, usually from six months to one year, there is a steadily increasing thyroid deficiency. As Hartsock has stated (Chapter V) this is paralleled by functional deficiencies in all other organs, that is, the mental and emotional processes and the digestive processes are depressed, muscular weakness is present, there is scanty menstruation and loss of libido, and there is a gradual increase of lowered metabolism. The reason for this is that the remaining thyroid tissue has brought about a functional deterioration of the thyroid itself.

In such a case, if thyroid extract is given in progressively increasing doses, the metabolism is brought up to the normal rate and the function of all the tissues and organs is increased accordingly. Among the tissues and organs whose functions thus increase we must include the thyroid gland.

Halsted[6] and Marine[7] have shown that the structure of the thyroid gland is governed by iodine. We have seen clinically many cases in

which hyperthyroidism has been induced by excessive thyroid extract; and with the administration of thyroid extract we have seen the hypothyroidism which followed a thyroidectomy converted into hyperthyroidism, in cases in which the gland has increased in size and in vascularity, and full-blown hyperplasia has been induced. When so induced, the condition of the thyroid and of the entire individual is identical with that in any other case of hyperthyroidism, and this induced hyperthyroidism responds to surgical treatment, just as did the original hyperthyroidism. In other words the experienced, skilful clinician may, within certain limits, govern the thyroid by thyroid extract.

The Effect of the Thyroid Hormone on the Sex Organs.—That the thyroid hormone profoundly affects the sex organs and their function is well established by its action in cases in which adolescence has been delayed. This action is strikingly illustrated by the following case:

An American woman, whose mother and herself, each with a deficient thyroid gland, had been under the management of the late Theodor Kocher for many years, came to the clinic after the death of Professor Kocher. No thyroid gland could be palpated. An amount of thyroid extract which was just sufficient to keep the metabolic rate within the minus normal limit was administered. When this patient was about forty years old, we became impressed with the power possessed by thyroid extract over the growth of the thyroid gland itself. Accordingly, the dose was steadily increased until the basal metabolism reached the higher limit of the plus normal rate. At this rate the entire personality underwent a change, new emotions were experienced, and the patient was married in her forty-second year, and bore a fine, normal baby within a year, and another a year later. After the birth of her second child, this patient, at the age of forty-four, still required no thyroid extract. The thyroid was then readily palpable.

Here we apparently have a case in which the function of the entire organism including the thyroid, was stepped up by the administration of thyroid extract. This awakened the reproductive organs, and the stimulus of pregnancy forced the growth of the thyroid, thus overcoming the thyroid deficiency.

Menopausal Thyroid Deficiency.—The tendency to increased weight, lassitude, indigestion, dry skin, falling hair, slow pulse, decreasing activity, and absence of libido which are characteristic of the menopause all tend to indicate that at the period when the ovarian

function ceases there is a slowing down of thyroid function with its body-wide effects. This is confirmed by metabolic estimations, which show that the basal metabolism ranges from minus 15 to minus 25. But the final proof of this state of hypometabolism is seen in the conclusive evidence presented by the striking clinical effects of the administration of thyroid extract. The patient loses her obesity and breathlessness, regains her psychic, mental, and emotional values, and the skin becomes moist and soft. In short, the patient is taken out of the hypometabolism phase and put into a normal condition. So definite is this clinical result that the patient can herself readily regulate the dosage of the thyroid extract, using her general state subjectively as her guide.

If the thyroid hormone thus affects the sex organs and their function, logically we would suppose that the hormones of the sex organs would affect the thyroid gland. However, the ovarian hormone can have but a partial effect on the activity of the thyroid gland for we see many cases in which hyperthyroidism has occurred after the normal menopause. On the other hand, there is clinical evidence that the thyroid is influenced by the sex hormones for we see many cases of thyroid deficiency in the fourth and fifth age decades, especially among women.

Interpretation of the Prevalence of Goiter in Women.—Based on the conception that the function of the thyroid pertains to the control of basal metabolism, we can understand why the thyroid enlarges in the autumn and continues enlarged throughout the winter in both sexes, in man and in the lower animals, as it is a means for the maintenance of the temperature of the body against the external cold. If the thyroid gland is the principal organ affecting metabolism, then if there is an increased biological demand in one sex for increased metabolism over periods of time, far above the demand, one would expect the thyroid to be enlarged in that sex more often than in the other.

In the case of women, especially in the earlier days, they were pregnant during most of the period between adolescence and the menopause. In those days adding all the months of separate pregnancies together, women spent from six to twelve years of their lives in the state of pregnancy, with which there was no comparable metabolic experience on the part of the male. One would expect, therefore, that in the female there would have developed a tendency to enlargement of the thyroid gland far exceeding that in the male.

Not only is the state of pregnancy stimulating to the thyroid gland but the menstrual period is also marked by an enlargement of the gland.

The Rôle of Surgery in the Treatment of Simple Colloid Goiter and Adenoma.—*Simple Goiter in Children.*—In children no surgical measures are required except in the case of deformity or compression of the trachea or in those cases in which hyperthyroidism is present

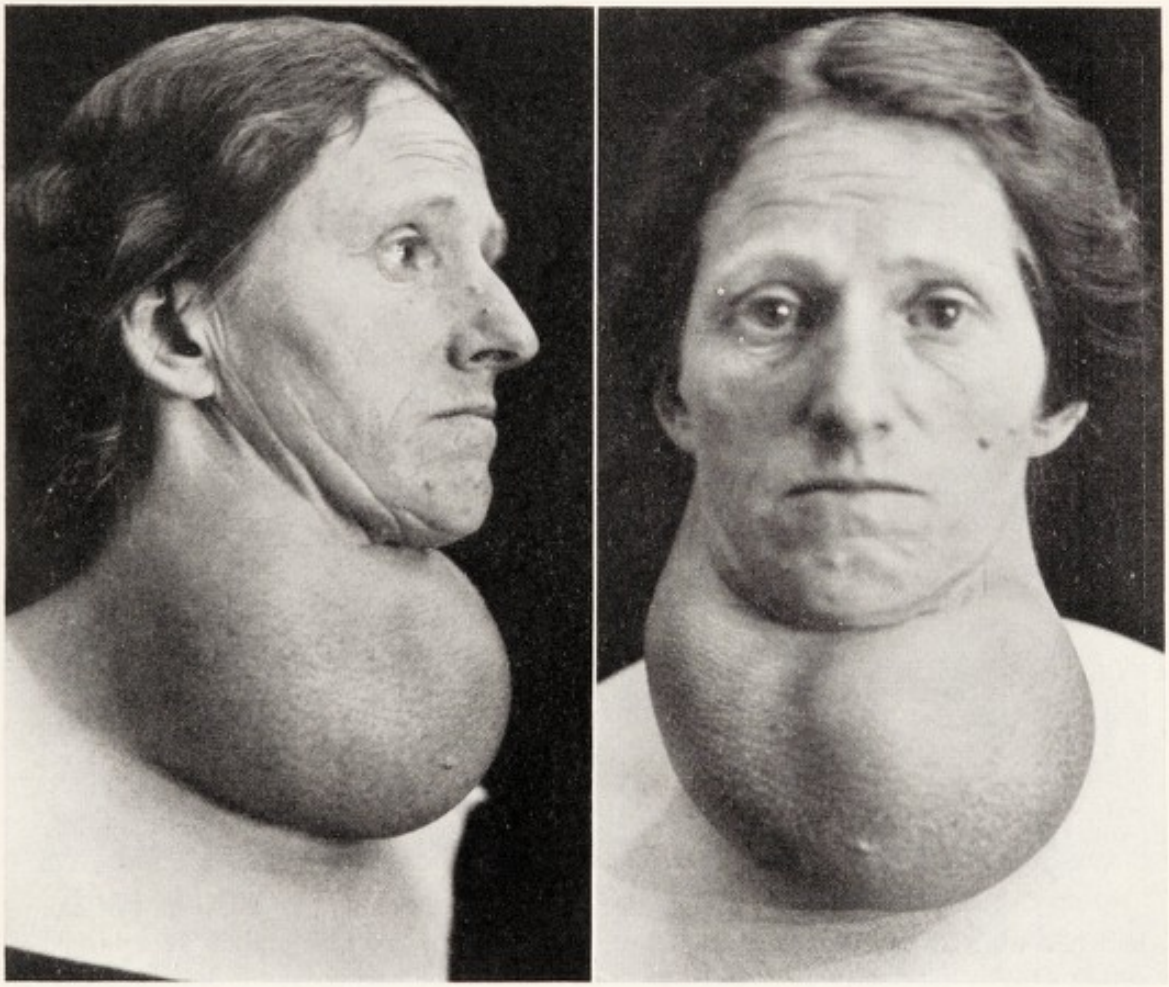

Fig. 14.—Colloid adenoma. The patient, a woman forty-five years of age had had a goiter for eight years which was increasing in size. There were no symptoms of hyperthyroidism.

(Chapter IX). Occasionally a congenital goiter of large size should be removed.

A curious fact pointed out by Kocher is that in the presence of some of these large goiters the metabolism may be markedly below normal and may return to the normal following a bilateral resection. However, from birth through the period of adolescence there is rarely any indication for the removal of a simple colloid or adenomatous goiter.

At any age colloid goiter and colloid adenoma in themselves have no surgical significance, but if for cosmetic reasons a patient wishes such a goiter removed the operation is so safe that the patient's desire may be complied with (Figs. 14–16). The routine technic is described in Chapter XXXII.

There are several conditions, however, that should lead the physician to advise a thyroidectomy. The first of these is the presence of a chronic myocarditis that cannot be accounted for otherwise. Kocher,

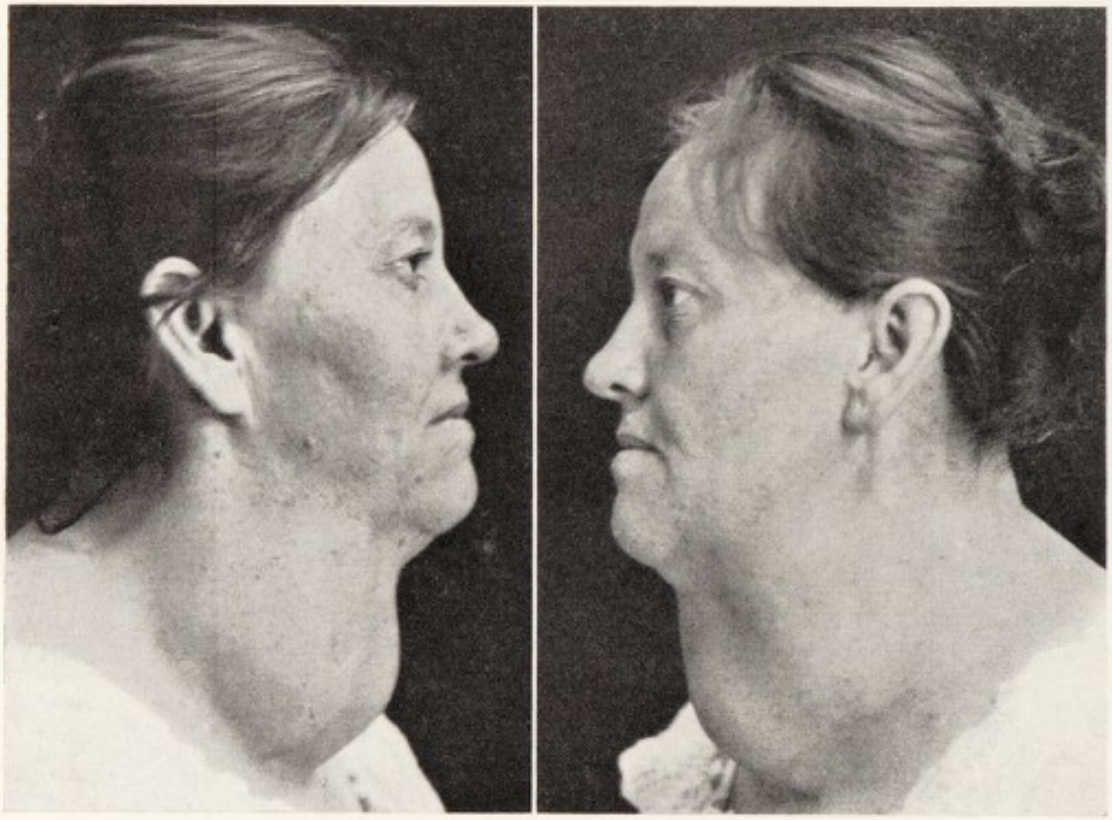

Fig. 15.—Cystic colloid goiter. The patient, a woman forty-five years of age had had a goiter for nineteen years since the birth of her first child. It enlarged rather rapidly especially after birth of third child. She had no symptoms of hyperthyroidism. At operation two large masses were found one as large as a honey-dew melon the other as large as a grapefruit extending well up in the neck below the ear.

long ago, called attention to the effect of a massive goiter upon the heart. The extremely large blood vessels may throw upon the heart continuous extra work, as in the case of an arteriovenous aneurysm.

Or there may be an interference with the venous return, as evidenced by a wide distribution of dilated veins, involving the neck, the chest, and the abdomen. A. T. Bunts independently, and Swift[8] in the literature, have shown that intrathoracic goiter may obstruct the vena cava so as to produce a back pressure on the venous tree

including the sinuses of the brain, thus causing an internal hydrocephalus. Swift reported a group of cases of benign tumors, dermoids, and intrathoracic goiters in which such effects were produced.

A goiter may descend into the chest, displace the heart, and further embarrass the circulation, thus throwing an added burden on the myocardium and causing its hypertrophy, and eventually a myocardial breakdown.

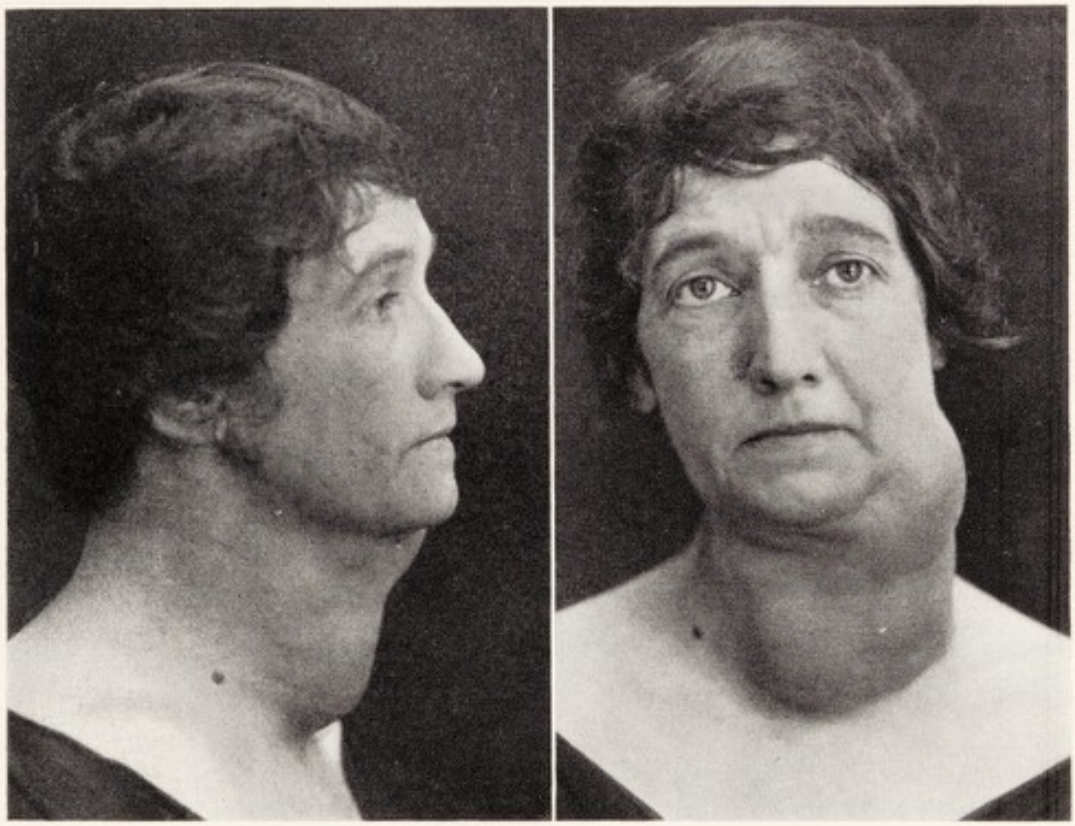

Fig. 16.—Colloid adenoma. This patient, a woman forty-two years of age had had an enlargement of the thyroid gland for thirty-one years. When she was eighteen years old she took thyroid extract and the gland immediately increased in size. There had been no symptoms of hyperthyroidism. The right lobe had been removed by Dr. Crile eighteen years before, after which the left lobe continued to increase in size. At operation an adenoma of about the size of an orange and another high in the neck of about the size of a tennis ball were removed.

Finally, although there may be no obvious obstruction or interference with the heart or vascular trunks, a colloid adenoma is often associated with a myocardial lesion. The outstanding clinical fact is that in such cases prompt improvement in the heart and the circulation usually follows thyroidectomy.

Another effect produced by a large goiter is upon the organism as a whole, as manifested by nervousness, some sweating, fatigue,

slight cyanosis of the nails, and an irritable heart. Such effects are produced by a goiter which is so wedged in against, or so encircles, or bends the trachea as to cause an interference with the free exchange of air, which is especially noted on exertion or under the excitement of some emotion (Fig. 17). Once the presence of cyanosis is established, the sequence of sweating, fatigue, slight tremor, myo-

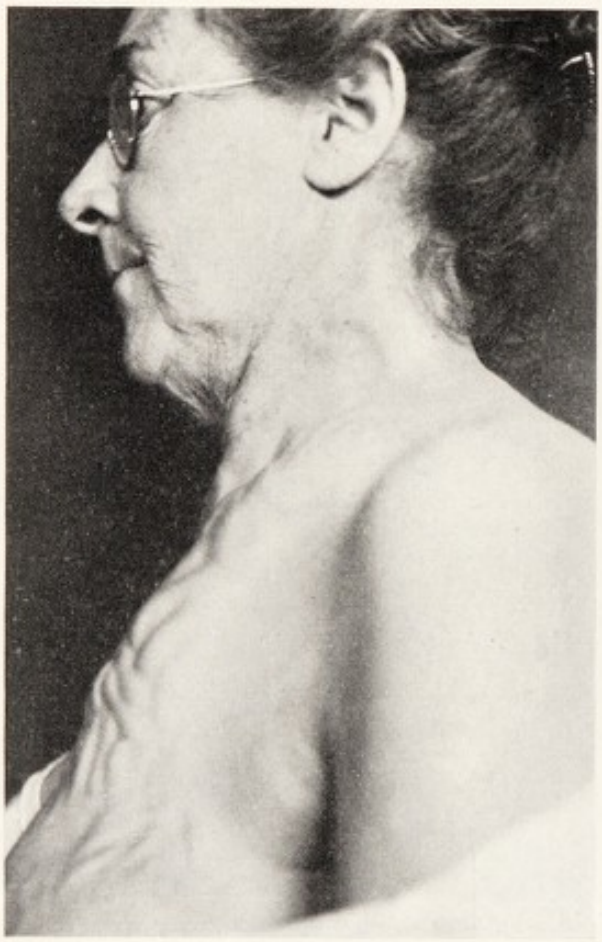

Fig. 17.—Compression of the trachea by goiter. This patient, a woman fifty-three years of age had had a goiter for fourteen years which had recently begun to increase in size and to cause choking sensations and shortness of breath. At operation the right lobe of the gland was found to be 4 or 5 times its normal size; the left lobe was not as large but had extended behind the trachea which was compressed posteriorly and bilaterally. Pathologic diagnosis: Exhaustion atrophy with regeneration hyperplasia.

carditis, and irritable heart, is accounted for by the effect of cyanosis on the output of adrenalin. In such cases the basal metabolic rate is usually not increased.

Whether this reasoning be correct or not, the gratifying clinical fact is that following thyroidectomy these symptoms promptly disappear. These large goiters are rarely the site of malignancies.

In contradistinction to the colloid goiter, the simple adenomata have a certain malign significance as is described in Chapter XXII. They may produce pressure, distortion, or displacement of the trachea or hyperthyroidism (Fig. 18).

It follows that since a solitary adenoma is the simplest, the easiest, and the safest goiter to remove, it is in the interest of the patient to advise its removal at any age. Nor is it safe to make an exception in the case of the relatively small adenoma which arises in the middle lobe for we have seen malignancy develop in such an adenoma.

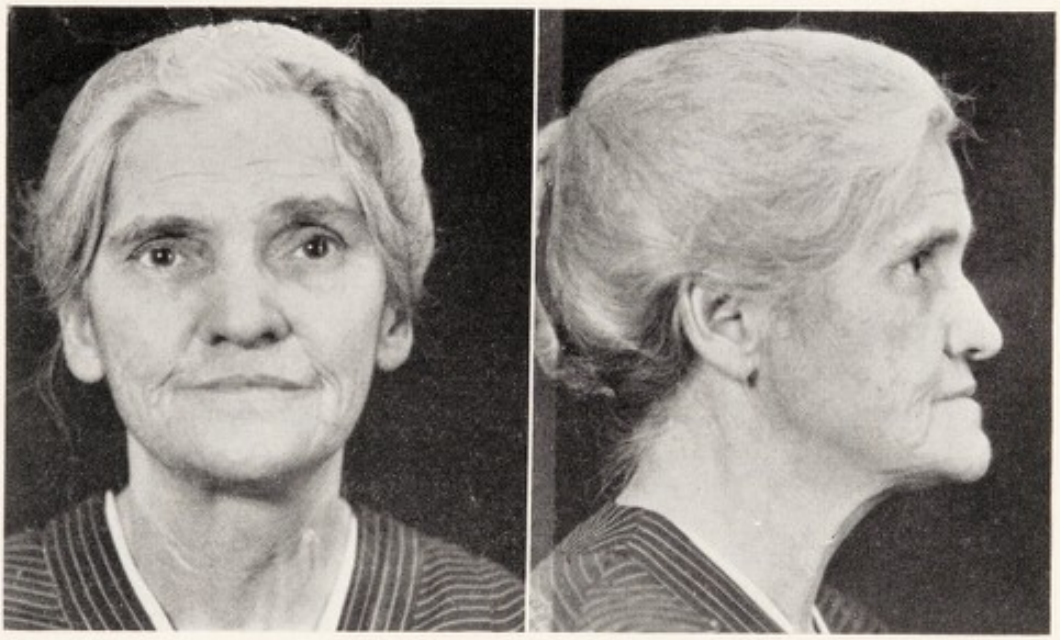

Fig. 18.—Colloid adenoma producing symptoms of hyperthyroidism. The patient, a missionary sixty-two years of age, had had a slight enlargement of the thyroid gland for several years. She had broken down under stress of increased work about one and one-half years previously and symptoms of hyperthyroidism developed. Two lobectomies were performed, the interval between them being five months. This photograph was taken just before the second operation at which the right lobe was found to be about four times its normal size in spite of the lack of external enlargement. Goiters of this type have given rise to the popular term "inward goiter." Pathologic diagnosis: Multiple colloid adenomata with cystic degeneration, slight diffuse hyperplasia.

The fragile vessels in an adenoma are easily ruptured by a blow, by the strain of coughing, etc. The resultant hemorrhage produces a painful, tender swelling, which usually has little significance. But in the case of a large adenoma that is partially obstructing the trachea, the additional enlargement at the site of the hemorrhage may cause a sharp increase in the respiratory-distressed condition which is an urgent indication for operation.

Another statement which should be made regarding the adenomata is that even in children, the so-called "fetal adenoma" may not respond at all to iodine therapy, but if the expectant mother is given iodine during pregnancy, fetal adenomata will not appear in her children. In other words, it is possible by giving iodine to one generation to prevent goiter in the next.

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CHAPTER V

THE MECHANISM OF HYPERTHYROIDISM AND OF HYPOTHYROIDISM

GEORGE CRILE

HYPERTHYROIDISM

THE state of universally increased permeability of the billions of cells of the body, whereby there is conferred upon the body increased activity both as to growth as a whole and to function, is clinically known as hyperthyroidism, Basedow's disease, Graves' disease, or exophthalmic goiter.

Hyperthyroidism is a state of hyperpermeability of all of the cells of the organism. This hyperpermeability of all of the cells of the organism at once accounts for the symptoms of this condition. It accounts for the rapid development of the body and the mind in children with hyperthyroidism, just as it accounts for the accelerated differentiation in tadpoles to which thyroid tissue has been fed. It accounts for increased metabolism.

The membranes of the cells of the organs of the body, being more permeable, are correspondingly more easily stimulated; the nerve cells are equally sensitized, and having an increased oxidation, are easily stimulated, these conditions accounting for the abnormal responsiveness to stimuli of all kinds, for the increased appetite and the activity of the digestive organs, for the soft, moist skin, the increased circulation and sweating, the increased acuity of vision, the abnormally acute hearing and sensitiveness to touch, taste, and smell.

This hyperpermeability accounts for the keen and abnormally active brain which in a child is matured beyond its years, for the exalted emotions, the tears that come easily, the brilliant eyes, the vivid personality. Life is on a sensuous edge, and all because the permeability, hence oxidation and potential, of the cells of the body are abnormally increased.

The tumultous action of the heart in hyperthyroidism is explained by the increase in the permeability of every cell of the neuromuscular

mechanism of the heart. As a natural result there is an increase in the pulse pressure, quickened circulation, a higher systolic pressure, a more rapid heart. The activity of all of the nerves and muscles of the body is equally stepped up, as is seen in the quickened neuromuscular responses, the tremors, the incessant activity, and restlessness.

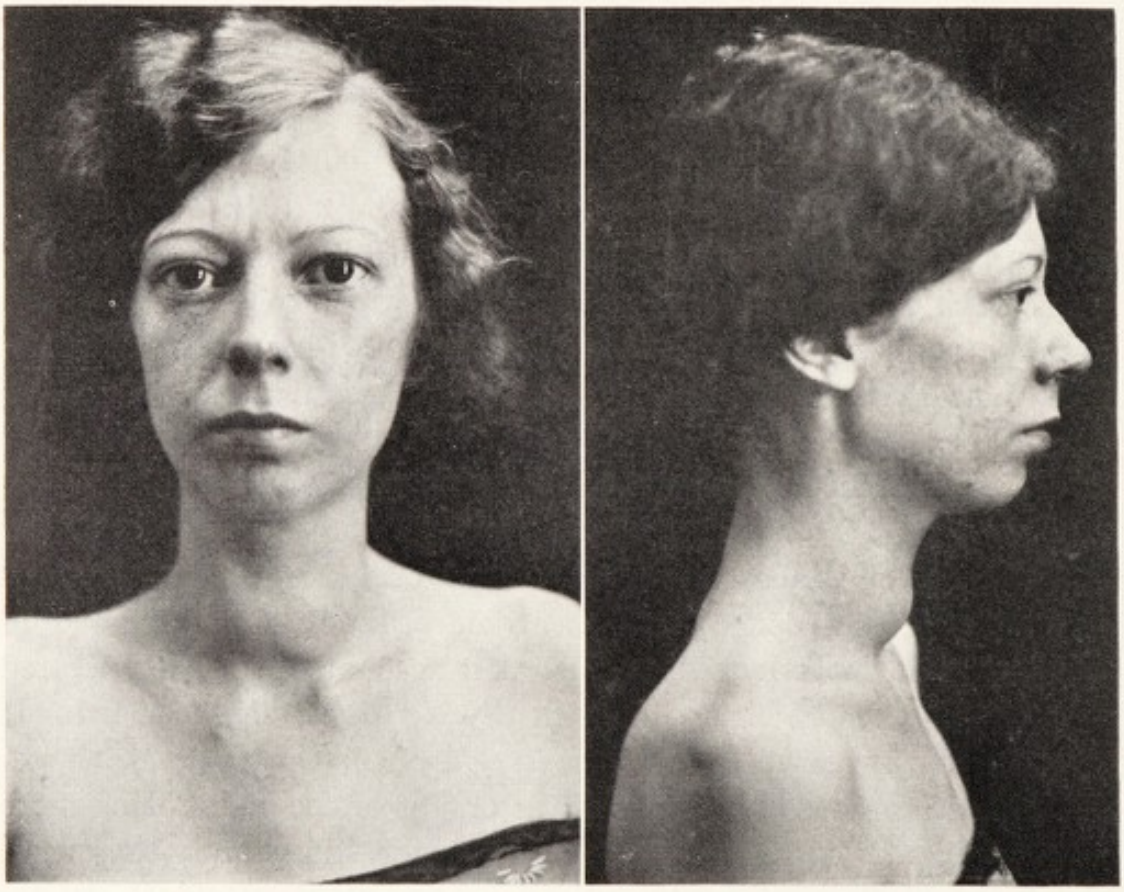


Fig. 19.—Hyperthyroidism. The patient, a woman twenty-three years of age had had a slight enlargement of the thyroid gland for one year. The history was typical, that is, the patient had always been very active, nervous, and ambitious. She went through high school in three years and was in college for two years, all her marks having been A or B. She had always been socially active. During the preceding six months she had been very nervous and her eyes had become prominent. She presented the typical symptoms of hyperthyroidism. Clinical diagnosis: Adenomatous goiter with marked hyperthyroidism. Pathologic diagnosis: Colloid adenoma; moderate hyperplasia.

In the digestive tract we find not only increased appetite, but increased digestion, increased gastric motility, and intestinal peristalsis. In cases of acute hyperthyroidism, the barium meal may be found in the sigmoid in three hours.

Under these conditions not only every cell and every organ of the body, but the entire personality is speeded up. In a child differen-

tiation is advanced as in Gudernatch's tadpoles. In college students the intellect is keen, the memory is accurate, and there is capacity for sustained attention and for sustained mental work. If the activation does not reach the stage in which destructive changes have been produced, these accelerated personalities are vivid leaders of their group. They tend to be attractive, ambitious, musical, dramatic, and easily attain Phi Beta Kappa rank (Fig. 19).

We must admit that there is no specific criterion whereby the diagnosis in the borderline cases may be established, that is, we are unable to determine at what stage altered function on the outer boundaries of normality ends, and hyperthyroidism begins. We do know, however, that hyperthyroidism is not associated with a normal gland, and we know that the thyroid is an essential link in the disease.

Morphological Pathology of Hyperthyroidism.—The only microscopical change thus far noted in the structure of the thyroid in hyperthyroidism is hyperplasia, which is present in the majority of cases. But hyperplasia is not specific for hyperthyroidism; it may exist in the absence of hyperthyroidism, as in pregnancy, in tuberculosis, even in cretinism. Hyperthyroidism, in turn, may be present without hyperplasia. That is, hyperplasia and hyperthyroidism are related, but are not identical.

In a given case of hyperthyroidism in which hyperplasia is present, the hyperplasia is rapidly converted into colloid goiter by the administration of iodine. Physiologic rest, the cutting off of the sympathetic nerve supply, the division of the adrenal nerves, tend to convert a hyperplastic gland into a colloid gland.

The important point is that in hyperthyroidism there is no constant morphological pathology in the thyroid gland. It is becoming more evident that the disease does not originate in the thyroid at all—the thyroid has the disease imposed upon it.

HYPOTHYROIDISM—MYXEDEMA AND CRETINISM

In hypothyroidism, myxedema and cretinism, growth is slowed, sexual activity is depressed or suspended, digestion is enfeebled, and gastric acidity is diminished. There is a tendency to constipation, the mental and emotional states are depressed, the activity of the skin—sweat glands, oil glands, and hair follicles—is lessened, the kidneys and liver show lowered factors of safety, the capacity of the heart muscle is lowered, the eyes are dull, there is a tendency to a low body temperature and the patient is sensitive to cold, the re-

flexes are slowed, basal metabolism is lowered, and there is a marked lessening of response to the injection of adrenalin, in contrast to the increased response shown in hyperthyroidism—Goetsch test. The only notable increase is in weight. The individual is dull, cold, emotionless, contented. He is a mechanism in low gear.

Hypothyroidism is frequently seen in two phases of life; in the adolescent period when all the ductless glands are under the greatest

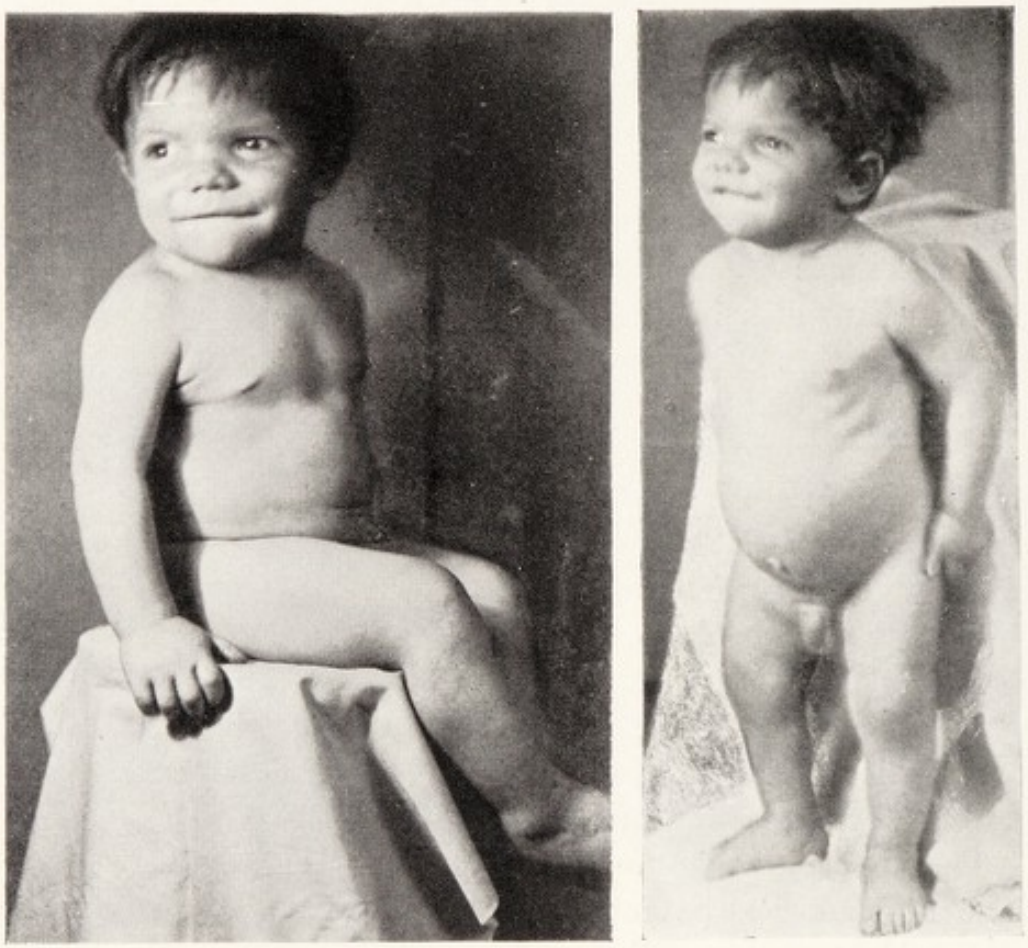


Fig. 20.—Typical case of cretinism. This child, seven years of age, could not stand alone and could not talk well. Weight, 31 pounds; height, 33 inches. Thyroid extract was prescribed and eight months later the child had grown 3 inches in height and was talking and walking.

stress, and also especially in women in the fourth and fifth decades. (See Chapter VI.)

A depressed metabolism is as inevitable a consequence of thyroidectomy for hyperthyroidism as the depressed oxidation of a combustion engine when it is throttled. The skin is dry because of the lessened permeability, hence lessened cellular activity. The hair falls out because the activity of the nutritional cells of the base of the

hair has been retarded. The mental dulness, the disordered digestion, the dry skin, the gain in weight, the sensitiveness to cold, the full, sleepy, mollusk appearance—all find a normal explanation.

It is obvious that the specific treatment of postoperative hyperthyroidism, as of the hypothyroidism of adolescence and of the menopause, is the administration of thyroid extract.

In the cretin in whom extreme hypothyroidism is congenital owing to the lack of normal thyroid hormone, the permeability of the membrane surrounding each of the billions of units of structure and function—the cells, is below normal; it follows that the power of growth and the power of function is below normal; hence the cretin is a dwarf and there is a lag in all his functions (Fig. 20). This lack of function is most noticeable in the brain. How natural it is, then, that when the thyroid hormone in sufficient dosage is given to a cretin there follows a specific increase in conductivity, and hence in growth and functional activity.

Quinine cured malaria and mercury cured syphilis, long before the causes of these protean diseases were known. What quinine is to malaria, thyroidectomy is to hyperthyroidism and thyroid extract to hypothyroidism. Just as enough quinine must be given at the proper stage to effect a cure, so in hypothyroidism sufficient thyroid extract must be prescribed to secure maximum results and in hyperthyroidism a sufficient resection must be made at an early stage of the disease.

CHAPTER VI

CLINICAL ASPECTS OF HYPOTHYROIDISM

CHARLES L. HARTSOCK

THE internal secretion of the thyroid gland is necessary for the well-being of the human organism, from birth until death. Hyposecretion therefore results in disturbances which vary with the degree of insufficiency and with the age at which its onset occurs. Hence there are marked variations in the resultant clinical pictures which cause some difficulty in classifying them satisfactorily, but the following simple classification permits a discussion of cases of hypothyroidism from an etiologic and clinical point of view.

1. Myxedema—severe hypothyroidism of adults.
2. Cretinism—severe hypothyroidism of children.
3. Postoperative or postradiation hypothyroidism and hypothyroidism due to exhaustion of the thyroids by untreated hyperthyroidism. Patients in whom this latter condition occurs may show symptoms of both hypothyroidism and hyperthyroidism so that the condition is frequently called "dysthyroidism."
4. Incipient hypothyroidism—mild and atypical cases of any age.

Etiology.—Hypothyroidism occurs most commonly in the goiter belts and we may assume that iodine deficiency is the leading etiologic factor in the production of this disease, but other factors, such as acute and chronic infection, emotional strain, senile deterioration, or physiologic strain such as is produced by puberty, pregnancy, and the menopause, may be the more immediate causes of the thyroid failure.

Cretinism may be the result of congenital athyroidism, of an hereditary tendency to thyroid disorders or of a marked iodine deficiency in the mother during pregnancy.

Thyroid disorders seem to have a definite hereditary character and colloid goiter, tumorous formations, hyperthyroidism and hypothyroidism are often seen in the same family. All of these conditions cannot be ascribed solely to an iodine deficiency but their familial

occurrence seems to point to some hereditary instability of the thyroid gland.

Acute and chronic infections of the thyroid are uncommon but when they do occur the end-result is usually a hypofunction of the gland.

Arteriosclerosis and senile changes are common causes of hypothyroidism, the activity of the gland being lessened by a lowered blood supply.

Subnormal function of the thyroid gland occurs after thyroidectomy or radiation much more commonly than is generally supposed. If cases in which thyroidectomy has been performed or radiation applied are studied from ten to fifteen years later, a moderate to a severe grade of hypothyroidism will be found in a large percentage.

When infection, senile changes, or other disease processes are associated with a deficient iodine intake the incidence of hypofunction will be increased and in the so-called "goiter regions" where iodine is lacking in the normal diet, mild and atypical forms of this disease are very prevalent as a complicating feature of other diseases.

DETECTION OF HYPOTHYROIDISM

The outstanding effect of hypothyroidism is hypometabolism. A low metabolic rate causes diminished function of every cell of the body. Diminished function of various organs is also a result of the great majority of diseases. For this reason, hypothyroidism is frequently unrecognized and its signs and symptoms are attributed to other causes. It is notably a disease which presents few signs but many symptoms, so that examination of the patient usually does not reveal anything sufficiently striking to suggest this condition as the probable diagnosis. I have found the only satisfactory method for detecting this disease is to suspect it as one suspects focal infection as a possible explanation of vague disturbances, especially when these are related to the neurasthenic or exhaustion syndrome. Such symptoms as fatigue, depression, mental sluggishness and retardation, indigestion, constipation, menstrual and sexual disorders, and many others can be so easily and apparently satisfactorily explained on a nervous or other pathologic basis that we fail to look for a still more fundamental cause of the subnormal function.

Even when hypothyroidism is suspected, however, it is not always easy to confirm the diagnosis. Determination of the basal metabolic rate is of course helpful, for without a low metabolic rate, hypothy-

roidism cannot be present. However, the reverse is not true and many of the conditions which we wish to distinguish from hypothyroidism also are accompanied by hypometabolism. Absolute basal readings are difficult to secure and until a patient is accustomed to the test, errors of from 10 to 20 per cent which are always on the plus side frequently are made. Such an error may cause the physician to disregard many cases in which the test appears to present a normal reading but in which the real metabolic rate is minus 10 or minus 20. It is common also to think of normal readings as varying from minus 10 to plus 10. I think this is an erroneous practice and believe it would be better to regard all minus metabolic rates as suspicious and to have the estimation repeated, especially if the general picture suggests the possibility that hypothyroidism is present. The swing toward the minus side in hypothyroidism is so much less than that toward the plus side in hyperthyroidism that small variations become of much more importance. I have found frequently that a second estimation of the basal metabolism made after a patient has been taking thyroid extract for a month is lower than the first. This shows how easy it is to overlook the incipient case for evidently the first reading usually is too high. If estimations of from zero to minus 10 per cent were neglected, many cases in which accurate readings were really lower would be overlooked.

To detect these cases and also to distinguish hypothyroidism from hypometabolism due to other causes is important and the only sure method is the therapeutic test. The dangers attending the administration of thyroid extract to those who do not need it, appear to be great in the eyes of some physicians but my own observations lead me to believe that there is no danger in such treatment when the patient is watched carefully; and without such treatment many patients who need this specific therapy would unquestionably fail to be benefited. The tolerance of some patients whose metabolism is only slightly below normal is sometimes surprisingly large. This will be discussed further in connection with treatment. It might be mentioned at this point that the clinical examination of the thyroid is of no diagnostic value whatsoever, but sometimes the presence of a large gland, of an adenoma or of a surgical scar will give a clue which otherwise would be unsuspected.

Other signs and symptoms will be discussed in the description of the various clinical types of hypothyroidism.

MYXEDEMA

The most obvious physical sign of severe hypothyroidism in adults is a characteristic thickening of the skin, especially of the face, eyelids, and the supraclavicular region of the neck. This swelling or edema formerly was thought to be due to deposits of mucin in the tissue, and for this reason the term "myxedema" was introduced and still continues to designate the clinical picture which results from marked diminution of thyroid function in adults. Following the introduction of methods for the measurement of the metabolic rate it was found that in many cases in which low metabolism was due to thyroid deficiency, this characteristic condition of the skin was very slight or was completely absent. For this reason it is better to confine the term "myxedema" to the classical syndrome in which a group of other characteristic signs and symptoms is practically always present and to use another term to describe those cases in which this sign is absent, especially as cases in the latter group show such marked variations in the clinical picture that they are all too frequently overlooked. It is better to describe such cases under the separate classification of *incipient hypothyroidism*. I realize that these two types apparently differ only in degree and that many of the incipient cases, if unrecognized, would go on to the myxedematous stage. It is for this very reason that I consider it advisable to present the clinical picture of the premyxedematous stage more definitely in order that these cases may be recognized earlier. The early cases are more likely to be overlooked than is any other definite clinical entity and this is due in part to the unfortunate choice of the word *myxedema* to describe a condition in which the symptom which gives it its name does not appear in the early stages. When myxedema is present the thyroid deficiency is marked and frequently of long standing. The onset of symptoms has often been so gradual that the patient has been entirely unconscious of the fact that his health has been far from normal, so that he does not consult a doctor until the beginning of rather marked mental changes.

In the advanced stage of the disease the patient may complain of almost any symptom which can result from a low metabolism. A summary of the literature discloses that symptoms referable to every organ in the body have been attributed to thyroid deficiency and have been relieved by the administration of thyroid extract. It is obviously, impossible, therefore, to describe all the symptoms which may be present in myxedema and I shall describe only those signs

and symptoms which are generally present. In the discussion of incipient hypothyroidism I shall describe the more unusual signs which, of course, may also be present in cases of true myxedema.

Patients with myxedema present a characteristic appearance of the face which should practically always be considered as diagnostic. The features are coarse, the eyes are puffy, the hair is dry and coarse, and frequently very sparse (Fig. 21). The speech may be slow, and the patient gives the impression of slow cerebration, the memory being especially poor for recent happenings. If left alone for a short

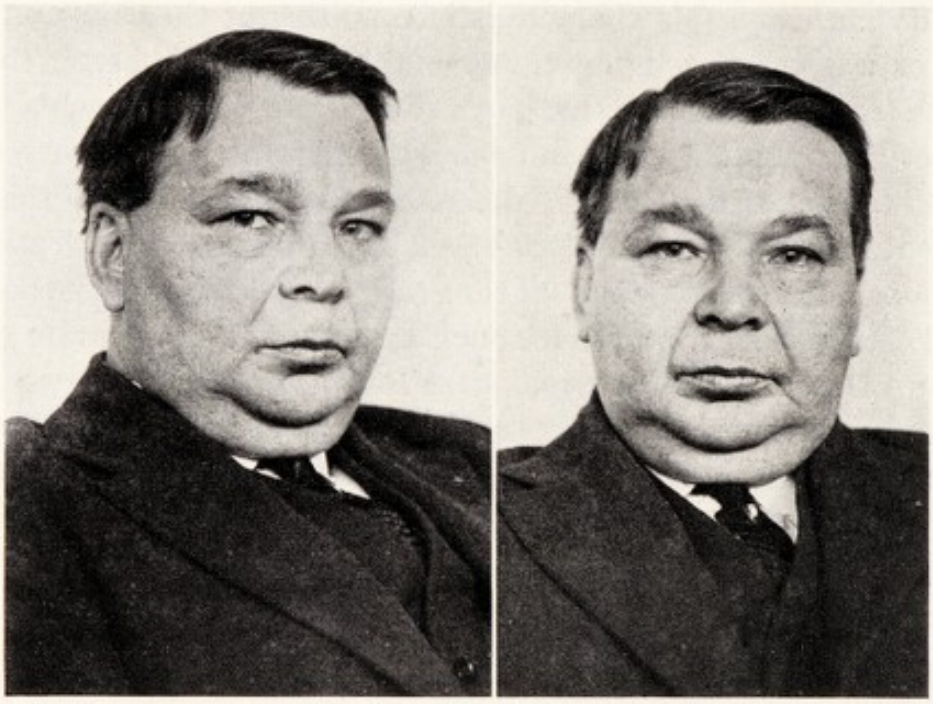


Fig. 21.—Hypothyroidism. The patient, a man fifty years of age, had had a tonsillectomy two years before which had been followed by development of symptoms of myxedema. The thyroid was palpable but small. Pulse rate 66; basal metabolic rate, minus 16; blood pressure 110/60.

time the patient may fall asleep. The mood is usually quiet and placid but melancholia and depression with marked anxiety may be present.

The patient is always physically tired, and frequently complains of soreness and stiffness in the muscles and joints. In spite of being overweight these patients suffer from the cold and require heavy clothing and heavy bed covering. Digestive symptoms are common, constipation is practically always present.

Physical examination reveals a low temperature, a dry skin which feels thick and edematous especially in the face, hands, feet and supra-

clavicular fossae. The nails are brittle and ridged. The pulse is slow and the blood pressure is low, the pulse pressure being especially low. Albumin is frequently present in the urine and there is nearly always some anemia which occasionally is marked enough to suggest pernicious anemia. Free hydrochloric acid frequently is absent.

The differential diagnosis is not difficult but sometimes when cases are insufficiently studied the patients have been treated for years for Bright's disease, arthritis, anemia or torpid liver. On the other hand, the diagnostician who is familiar with this condition and keeps it in mind rarely needs the metabolic test to enable him to diagnose the disease. If determination of the basal metabolic rate should be necessary, the reading is usually sufficiently low to confirm the diagnosis, and the administration of thyroid extract for a few weeks will produce such marked improvement as to make assurance doubly sure.

CRETINISM

Cretinism is the term applied to the marked retardation of physical and mental development produced in children by severe thyroid deficiency. This condition is frequently congenital and the retardation of development begins at birth, but rarely, except in the most marked cases, is it discovered until the child is found to be slow in the development of activities and of normal functions, such as teething, talking, and walking. Even then, recognition of the condition is often delayed because the characteristic appearance usually does not develop clearly until about the second year. It is then noted that the growth is stunted as the result of a general disturbance of the nutrition of the osseous system (Fig. 20). The skin is rough and dry. The hair is coarse, often giving the appearance of tow. The features are bloated. The tongue is thick and protrudes, giving a beast-like expression in very severe cases. The teeth appear very slowly and are prone to decay. The bridge of the nose is low and in typical cases the entire picture is unmistakable. In milder cases cretinism must be differentiated from rickets, birth injury, mongolianism, dwarfism and achondroplasia. Careful study will easily differentiate these conditions, but except for rickets, it is better to treat any of them with thyroid extract until the diagnosis is definitely determined, than to leave a case of cretinism untreated. The results of the deficiency during the period of rapid growth are permanent so that the earlier a case of cretinism is treated the more nearly will the patient approach

the normal. In these cases treatment is often very inadequate even though the condition is recognized early. I believe it is advisable to administer the thyroid extract to the point of toxicity in order to determine the appropriate dosage.

Cretins are not common in the North American goiter districts but sporadic cases occur with sufficient frequency to indicate the necessity for vigilance on the part of physicians and especially of pediatricians in order that this condition may be recognized early. Moreover, in goiter districts there are very large numbers of children, whose physical and mental condition is retarded by a low-grade cretinism, which is not pronounced enough to produce the characteristic symptoms. These cases are similar to cases of incipient hypothyroidism without myxedema. The prophylactic treatment of goiter by the administration of iodine to children and to expectant mothers should greatly lessen the incidence of this condition. Better standards for determining the juvenile rate of basal metabolism also would give a great impetus toward the correction of these mild insufficiencies of the thyroid gland in children.

In severe cases of cretinism the prognosis is poor on account of the marked retardation, which usually has occurred before the patient's condition is recognized by the physician. The remarkable physical changes, which do occur even after a short period in cases subjected to adequate treatment, are almost unbelievable.

POSTOPERATIVE HYPOTHYROIDISM

Hypothyroidism may develop in any patient who has been subjected to operation or irradiation of the thyroid. In the case of large colloid goiters the secretion of the gland is often already deficient before the operation, which may be performed to relieve pressure or for cosmetic reasons. Naturally the secretion will be lessened further by the removal of a large portion of the gland. Fortunately this type of goiter is rapidly disappearing in the goiter belts as the result of the prophylactic use of iodine. After thyroidectomy is performed for hyperthyroidism the percentage of recurrences is diminished in proportion to the amount of the gland that is removed. In no small number of cases, however, the reversion of the remaining hyperplastic gland to normal brings with it a deficiency. This deficiency may be overcome after several months or it may continue permanently. It may not be detected for some time as it is likely to be concealed by the striking improvement in the patient's former symptoms.

After three to five years, however, many of these patients are seen again, still enjoying comparatively good health, but presenting symptoms of mild hypothyroidism, the history of which may be elicited only after careful investigation. It is well worth while, therefore, to study all postoperative cases from this point of view.

The picture in this type of hypothyroidism differs in many ways from that of even incipient or advanced hypothyroidism owing to

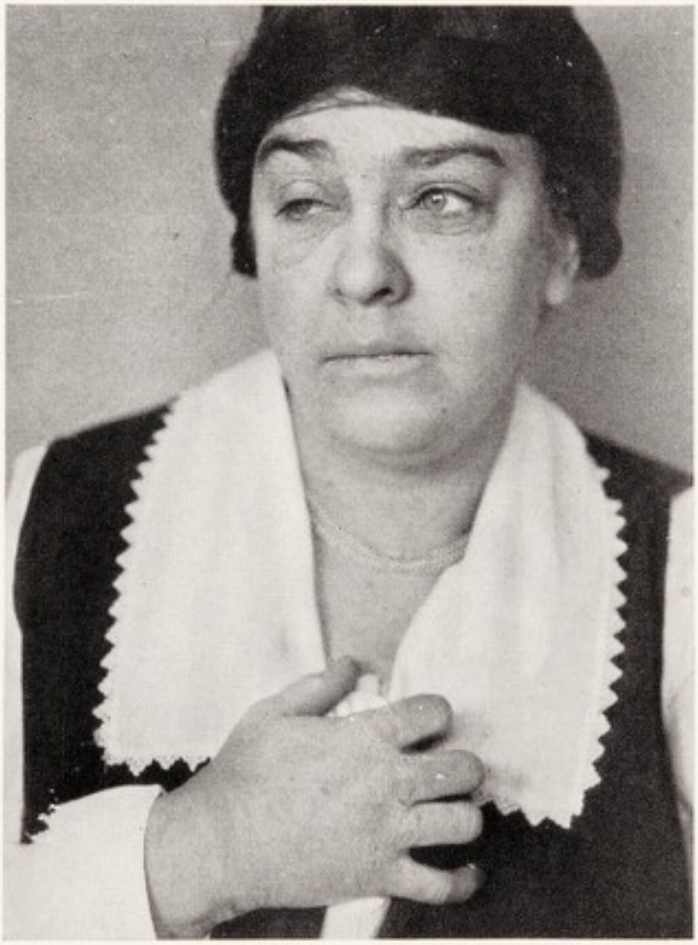


Fig. 22.—Postoperative hypothyroidism. Patient thirty-one years of age showing characteristic facies and hand of myxedema. Photograph taken six months after the removal of a large simple goiter.

the fact that the deficiency was produced suddenly in a patient whose metabolism previously probably was markedly increased rather than normal. The sudden and wide fluctuation of metabolism may account for the apparent difference in the aspects of these two groups of cases. To be sure, the underlying disturbance of metabolism is fundamentally the same, but in a sufficient number of cases the difference in the effects produced certainly justifies classifying this type of hypothyroidism separately. As previously mentioned, cases in

which hypothyroidism follows *thyroidectomy* or *irradiation* are considered as in the same group as those in which hypothyroidism has resulted from spontaneous exhaustion due to untreated hyperthyroidism as the etiology and resultant clinical pictures are similar.

While many of these patients present symptoms which have previously been described as characteristic of hypometabolism they differ in that the effects of the hypometabolism seem to center on one particular system producing syndromes which are characteristic of other diseases and sometimes are difficult to differentiate except by pro-

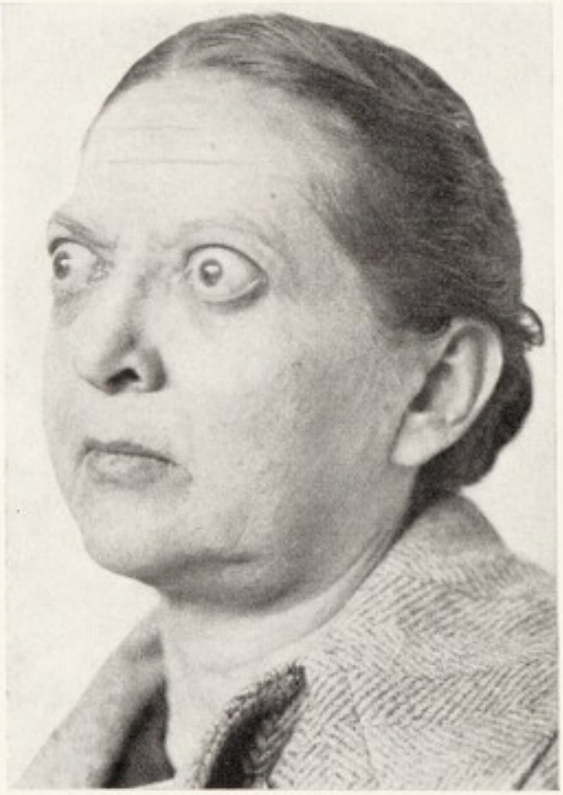


Fig. 23.—Postoperative hypothyroidism. Patient fifty-five years of age showing thin hair and characteristic facies of hypothyroidism. Photograph taken six months after operation for extreme hyperthyroidism with exophthalmos.

longed observation. The reason for this is not clear unless it is because the particular system affected had been weakened by previous disease. The most severe effects of this type of hypothyroidism are usually noted in those systems which are affected by hyperthyroidism, that is, the nervous, ocular, cardiovascular, and gastro-intestinal systems.

The nervous system is especially affected. Emotional instability is common. Fears and anxieties with periods of depression occur frequently. The emotional crises of nervous exhaustion, psychas-

thenia, and melancholia seem to occur more frequently than usual and the response to treatment with thyroid extract is convincing enough to lead to the conviction that these crises may bear some etiologic relation to the hypothyroidism.

Peculiar persistent headaches and neuralgias are found in the severer cases, these symptoms seeming to be related to hypotension and the resultant impairment of the cerebral circulation. However, in two cases in which these symptoms were severe enough to warrant the making of encephalograms a marked cerebral atrophy was found and it has occurred to me that if it were possible to examine more of these patients in a similar way it might be found that cerebral impairment is the cause of many of the vague nervous symptoms which are manifested so often.

The ocular muscles are especially affected in hypothyroidism. When exophthalmos has previously been present the condition of the muscles is more serious and more difficult to correct. Often it is the only symptom which keeps the patient from feeling perfectly well and it may be a very serious handicap.

The incidence of myocardial degeneration is increased among patients having hypothyroidism of this type and may be the only effect observed. The etiology of myocardial degeneration is very frequently overlooked especially if the pulse rate is increased. A clue is frequently found in the very low amplitude of the electrocardiographic waves. In the presence of dyspnea and cardiac failure the estimation of the basal metabolic rate is frequently unsatisfactory. Hence, it has been my custom to observe the effects of very small doses of thyroid extract in cases of myocardial failure of unexplained origin, especially in cases in which the thyroid has been removed or has been subjected to irradiation. Remarkable results of this treatment frequently are seen.

Possibly the commonest complaints are referred to the gastrointestinal tract; these are never serious as they are usually disturbances of appetite, gaseous eructations, and constipation. Achlorhydria follows thyroidectomy in about 35 per cent of the cases in which the symptoms have been sufficiently pronounced to lead to a study of the gastric secretion. Achlorhydria, of course, occurs frequently in individuals above fifty years of age, but I think the evidence indicates that the incidence of achlorhydria is increased in many cases of hypothyroidism. Vomiting occasionally occurs. I have found no way to control it except by thyroid administration.

In brief, then, it may be stated that hypothyroidism is a frequent sequel of the various methods of treatment of hyperthyroidism and of colloid goiter. The effects of hypothyroidism in these cases in which the thyroid secretion has been depleted by operation, irradiation, or disease differ somewhat from those in cases of spontaneous hypothyroidism, the former tending to be manifested with more intensity in certain systems rather than by the production of the general effects of hypometabolism.

INCIPIENT HYPOTHYROIDISM

There are varying degrees of lack in any deficiency disease, the milder grade producing less definite and more obscure symptoms than those present in the advanced stages. This is particularly true of the milder forms of thyroid deficiency. In its earliest or mildest stages the disease absolutely lacks any pathognomonic signs and symptoms and the diagnosis is further obscured by the tendency of the hypometabolism—as in the type of hypothyroidism last described—to exert a selective action on the various organs and systems of the body, thus producing disturbances which are characteristic of other conditions, such as anemia, constipation, dysmenorrhea, etc. The fact that specific diagnostic methods are lacking and that other diagnoses can be made, which apparently explain the symptoms, results in a failure to recognize the underlying condition in many of these cases. A knowledge of the wide variety of disorders, which may result from mild or incipient hypothyroidism, apprises us of the fact that low metabolism caused by thyroid deficiency must be considered as an etiologic factor much more frequently than is usually supposed. It is true that in the presence of hypothyroidism a mistaken diagnosis does not mean life or death to the patient or, as a rule, even serious disability, but still the fact remains that the well-being of many people could be improved if this condition were more frequently detected in its early stages.

Incipient hypothyroidism occurs at all ages. In children mild deficiency may be the cause of behavior problems, or of a mild degree of physical or mental inertia, which often is not abnormal enough to be given much consideration. In children of this type startling results occasionally follow the administration of small doses of thyroid extract.

At puberty and in the early teens diminished endurance and a tendency to anemia, nervous disorders, dysmenorrhea, or digestive

disturbances often can be explained as due to a mild degree of hypothyroidism.

Extreme physical and nervous exhaustion in young adults, the depressions of middle life, and aggravated symptoms of the menopause may be partially explained on this basis. Late symptoms which simulate senile changes frequently are distinctly improved by the administration of thyroid extract.

If we review the body by systems we find that each may be affected by this disorder which is as protean in its aspects as is hyperthyroidism. Nervous disorders such as headaches, neurasthenia, mild psychic disturbances, especially affective disorders, fears, anxieties, poor memory, and difficult concentration, are frequently seen.

Cases are reported in which disturbances of the special senses, tinnitus, poor hearing, and weakness of the ocular muscles have been benefited by treatment with thyroid extract.

Circulatory symptoms are referred chiefly to the heart and are caused by myocardial degeneration. Mild anginal symptoms occasionally occur. Hypothyroidism is supposed to predispose to premature arteriosclerosis. The associated hypotension and bradycardia often cause vague nervous disturbances which are referred to the circulatory system.

The respiratory system is not frequently affected but the tendency to take deep sighing respirations, often seen in nervous people, is frequently favorably affected by treatment with thyroid extract.

Gastro-intestinal symptoms are extremely common. Anorexia, distress after eating, belching of gas, vomiting, obstinate constipation, and occasionally diarrhea occur.

The genito-urinary system usually escapes any effects of mild thyroid deficiency, albuminuria occurring only in the late stages of myxedema.

The menstrual function is especially susceptible to extremely mild thyroid deficiency and every type of disturbance may be seen from amenorrhea to profuse menorrhagia especially at the menopause. That these disturbances may be due to hypothyroidism is evidenced by the improvement which results from the administration of thyroid extract in small doses.

Sterility is a well-recognized result of this condition, and in all cases of sterility both the male and the female partner should be studied to see whether or not hypothyroidism is present in either.

Joint symptoms, muscular aches and pains, skin disorders and many other minor disorders are reported from time to time to be the result of hypothyroidism. The ordinary effects of hypometabolism, asthenia, obesity, subnormal temperature, and susceptibility to cold, dry skin and brittle nails, and tendency to excessive drowsiness are of course frequently seen and one or more of the features usually are present in every case.

The variations which may occur are surprising. Some patients show a very marked degree of nervous energy; some patients instead of being obese, are thin and emaciated and gain weight on thyroid medication; some complain of insomnia. It is obvious, therefore, that there is no definite clinical picture of this incipient type of hypothyroidism. Hypothyroidism should be suspected when such conditions cannot be explained as due to some other cause and if the diagnosis cannot be established, a brief therapeutic trial of thyroid extract will not do any harm provided the patient is kept under careful observation.

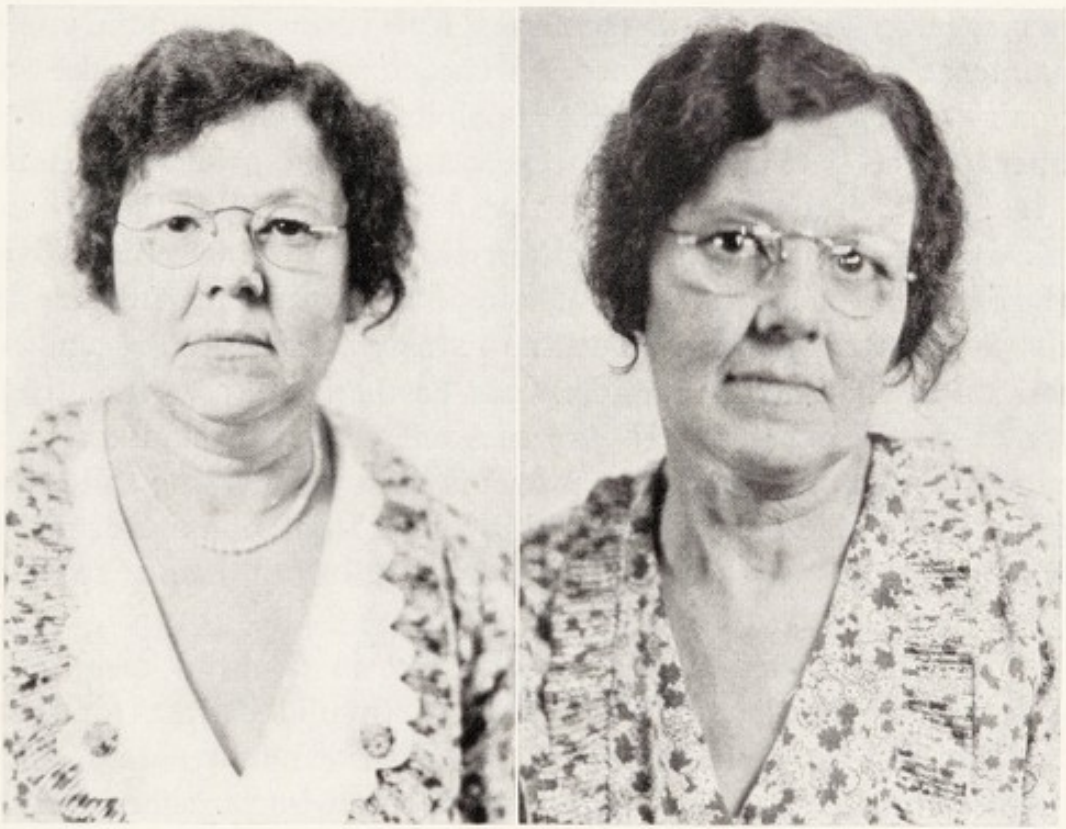
TREATMENT

The treatment of hypothyroidism of any type consists merely in the substitution of thyroid extract for the deficient secretion. Any form of prepared gland or the active principle, thyroxin, may be used. The gland extracts are satisfactory but the products of the many manufacturing companies vary greatly in their relative potency. One should select one or two extracts and become familiar with the results that may be expected from each and then be sure that the patient uses the one that is prescribed. Only in this way can satisfactory results be obtained. One should also be familiar with the action of thyroxin, for some patients in whom gland extracts are ineffective respond to this, and at times the reverse is true.

No matter how mild or severe the case, I prefer to begin with small doses and to increase the dosage gradually until the replacement is sufficient to bring the metabolism to normal, although many prefer to start immediately with doses sufficient to restore the patient to normal, this dosage being calculated on the basis of the metabolic rate. There are two criticisms of this method. First, the patient will not always tolerate large doses immediately and in consequence becomes frightened for they are often familiar with the warnings in regard to the use of thyroid extract for reducing and any untoward symptoms will often dissuade them from making any further trial of this medication. Patients who have previously had hyperthy-

roidism are also fearful of a return of their former trouble and must be handled cautiously. The second criticism is that any method of calculation is very unreliable. The condition of some patients with a very low metabolism will become normal under dosage with very small amounts of thyroid extract and others whose basal metabolic rate is only slightly below normal will tolerate large doses.

A very important point in the treatment of hypothyroidism, which for some reason is almost universally disregarded, is that the patient



A B

Fig. 24.—Response of patient with hypothyroidism to treatment with thyroid extract. A, Patient presenting typical facies of hyperthyroidism. B, Same patient after treatment for only one month. Note diminished edema of face especially about the eyes.

should continue to receive adequate doses after the metabolism has reached the normal level. Very frequently I have seen patients, in whom marvelous results have followed thyroid medication, who have been advised to discontinue medication completely for a while. It seems to be the opinion that the thyroid function is restored to normal by the thyroid extract while in truth it is only a substitution for a deficiency which will probably continue as long as the patient lives.

I have found that there is a seasonal variation in the amount of thyroid extract required, more being necessary in cold weather. Patients who travel should be warned that it may be necessary to vary the dosage with their geographical location. It seems to be especially true that distinctly less amounts are necessary when patients sojourn for any length of time along the seashore. Whether or not it has any beneficial effects, I advise the use of as much fresh sea food as possible, but usually do not prescribe iodine together with thyroid extract. Early in the course of treatment a determination of the basal metabolism should be made every month until the normal level is reached and the proper maintenance dosage determined. A check of the patient's pulse and inquiry concerning the symptoms of palpitation, tremor, and insomnia are made weekly to check overdosage. A very good point to remember is that it is well to administer the thyroid extract early in the day and to avoid giving it late in the afternoon and in the evening. Even when the metabolism is well below normal very unpleasant palpitation is often experienced when the patient assumes the recumbent position at bedtime, if thyroid extract has been taken as recently as five or six hours before. In any case one commonly finds that the subnormal symptoms are more pronounced in the morning and therefore the dose should be given at this time. I do not think it makes much difference whether it is taken on a full or an empty stomach or whether it is given in enteric capsules.

I have mentioned the therapeutic test in doubtful cases, that is, the administration of small doses of thyroid extract for short periods. This can do no harm if the patient is carefully observed and it will often give brilliant results in an otherwise puzzling case. I have never seen any symptoms of overdosage remain permanently after the administration of the thyroid extract was discontinued. Many physicians have a great fear of this drug and hesitate to use it in proper amounts to give the maximum benefit. However, frequent observation and occasional checks of the metabolism take away all dangers which pertain to the use of thyroid extract.

CHAPTER VII

DIAGNOSIS OF HYPERTHYROIDISM

JOHN TUCKER AND ROBERT H. MCDONALD

THE key to the diagnosis of hyperthyroidism is the physiologic action of the thyroid hormone. The thyroid hormone increases the rate of oxidation in every organ, every cell, of the body, thereby raising the electrical potential of all of the organs and cells. This increased electrical potential is equivalent to increased electrical stimulation of every organ, every cell, of the body and causes each organ, each cell, to do more work—whatever that work may be whether in the expression of the emotions; the acuity of the special senses, and of common sensation; the activity, hence tenseness of the striped and nonstriped muscles; the increased activity of the ductless glands or of the glands of secretion and of excretion. In other words, increased activity of the thyroid carries with it an increased activity of every organ, increasing every function.

THE PRELIMINARY EXAMINATION OF THE PATIENT

In many cases, the presence of hyperthyroidism is evident to the clinician at a glance, but there are incipient and borderline cases in which a carefully elicited history and a painstaking physical examination are required before the diagnosis can be made with certainty. The differentiation of these borderline cases from certain nervous conditions such as neurasthenia, neurocirculatory asthenia, and latent tuberculosis is of extreme importance to the patient in view of the differences in the treatment of these conditions. Even in cases of well-marked hyperthyroidism, however, it is very essential that a complete survey be made in order to evaluate the result of a thyroid disturbance upon the organism in general and to detect concurrent pathologic changes which may alter or modify the treatment of the hyperthyroidism itself.

On account of the nervous and mental irritability which marks many thyroid disturbances it is necessary to exercise a great deal of

patience and perseverance in order to elicit in orderly sequence the various symptoms from which the patient has suffered. It is necessary to secure his confidence by listening attentively and by manifesting a genuine interest in his history. The interview should take place amid quiet surroundings and preferably without the presence of a third person.

Following the patient's recital of symptoms the examiner should ask questions designed to elicit information regarding points which the patient did not mention. Such interrogation should proceed in orderly fashion through the various systems, with particular reference to the organs of special senses, the skin, the nervous system, and the cardiovascular system. During this stage of the examination the observer will be able to form a good opinion of the mental alertness of the patient.

The actual examination of the patient should be carried out in a room where privacy and quiet preclude external stimulation as far as possible. The patient should be allowed to lie in a comfortable position upon the couch. Preliminary observation will tell the physician much concerning the patient's nervous irritability. The state of nutrition should be noted, and the skin should be carefully examined as to texture, temperature, the degree of vascularity and to determine the presence of perspiration or dermatitis. The eyes should be carefully observed in view of the numerous changes which are frequently seen. Widening of the palpebral fissures is seen early and gives a suggestion of exophthalmos which should, however, be confirmed by the use of the exophthalmometer. Hypertonus of the levator palpebrae superioris is associated with several eye signs which will be described in a subsequent chapter.

The thyroid gland itself is best examined with the patient lying comfortably on the back, the neck extended, and the head supported. Such a position draws the gland upward exposing it from behind the manubrium sterni and allows inspection to determine its size, shape, and contour. The gland can best be palpated by standing behind the patient's head and placing the fingertips, pointing downward, along the front and side of his neck. On deglutition the gland is drawn upward under the observer's finger due to the attachment of its capsule to the hyoid bone; thus, an estimate should include not only the isthmus but also the lateral lobes which can be felt easily under the relaxed sternocleidomastoid muscles, and the pyramidal lobe, if present, should be palpated. The gland itself should be examined

for symmetry, remembering the possible presence of an asymmetric pyramidal lobe, usually just to the left of the midline. Its texture should be noted as it may vary from the stony hardness of a neoplasm to the elastic vascular texture of hyperthyroidism. The presence of nodules in the gland should also be noted. The degree of vascularity may be determined by the presence of pulsations, thrills, or bruits. The presence of tenderness is a sign which is of definite value. Considering the possibility of displacement of the trachea due to thyroid enlargement, an examination of the other structures of the neck should be made.

Routine examination of the chest should be supplemented by careful palpation and percussion in the substernal notch as well as over the manubrium sterni, in order to determine the presence of possible intrathoracic extensions of the gland or aberrant intramediastinal thyroid tissue. Occasionally on deglutition such tissue is palpable when the examiner's fingers are pressed deeply in the substernal notch. Considering the possibility of pressure of thyroid tissue upon the trachea or a bronchus, auscultation of the chest should be done.

Cardiac examination is of special importance. The location of the apex beat gives a clue as to the size of the heart, although its actual size must be confirmed by percussion and must be carefully checked with the patient in the sitting and the standing position, and when possible with regard to its reaction to exercise. Irregularities of rhythm especially should be sought. The presence of murmurs should be carefully noted. The signs of failure of compensation are of marked importance. The physical examination of the heart should be supplemented by electrocardiographic studies which will be described later.

Routine abdominal examination should be supplemented when necessary by *x*-ray studies, with the purpose of locating peptic ulcer and changes in motility. The neuromuscular system should be checked, bearing in mind the question of tonus, tremors, and the state of nutrition. The characteristic fine tremor is best observed by extending the arm with the fingertips widely separated.

SIGNS AND SYMPTOMS

Presence of Goiter.—The diagnosis of hyperthyroidism too often is based on the presence of a goiter together with the presence of an increased basal metabolism. An enlargement of the gland which

can be easily seen or readily palpated impresses one with the idea that the physiology of the thyroid gland may be disturbed, and yet if no "goiter" is evident, there may be sufficient doubt in the mind of the physician to cause a misinterpretation of the other signs and symptoms which are presented. Hence he may ascribe to psychoneurosis a group of symptoms which, aside from an absent goiter, are indicative of hyperthyroidism. A large goiter may be accompanied by no symptoms while a small hyperplastic gland may be very active physiologically and yet be hidden behind the neck muscles or be partially retrosternal in position so that its presence cannot be detected except at operation. It is evident, therefore, that from the standpoint of diagnosis we must consider the physiology rather than the gross anatomy of the thyroid gland.

The pressure from an enlarged gland not infrequently causes interference with swallowing, a feeling of a lump in the throat, a choking constriction or even pain in rare instances.

The hyperplastic gland is diffusely enlarged, has a firm elasticity, or may show large or small nodules throughout the organ, some of which may be fluctuant as the result of cystic degeneration. One pole, both poles or the isthmus may show enlargement or may vary in size. A thrill or bruit may be present over the lower or upper pole indicating increased vascularity, and increase in the caliber of the thyroid arteries, or in rare instances compression of the carotid artery. Pulsation of the thyroid arteries is usually felt and sometimes may be seen.

In older patients in whom the gland is more likely to contain adenomata the degree of hyperplasia is harder to estimate clinically. It is usually less in degree and consequently the hyperthyroidism may be correspondingly less severe.

Basal Metabolism.—Obviously the basal metabolism is increased in hyperthyroidism. There is a constant, sustained basal rate which is sensitively poised and easily raised by mental, and especially by emotional excitement, by infection and even by the routine daily activity, as the patient with hyperthyroidism is so keenly sensitized that the routine, normal activities are accentuated, hence the basal rate is abnormally accelerated.

Thus, one of the characteristics of the basal rate in hyperthyroidism in addition to the elevation of the sustained basal rate is the abnormally high swings which occur with daily activity, under the influence of excitation, of infection, or after the injection of adrenalin—

which, by the way, should never be made. This picture is precisely the opposite to that presented by hypothyroidism. In hypothyroidism nothing alters the sustained low rate very much except thyroid extract. In the state of hyperthyroidism no possible accuracy could be established by having the patient come to the laboratory for a basal rate under such conditions, for the reading would be abnormally high. On the other hand, the patient with myxedema might be held up and robbed on his way to the laboratory, but his basal rate would be low and dependable.

As to the diagnostic value of the basal metabolic rate, its elevation and the readiness with which it changes have a diagnostic value. There are, however, certain exceptions which should be noted. The basal rate may not be increased during a period of natural remission brought about by the use of iodine such as sodium iodide or Lugol's solution; during a remission due to radiation therapy; or in the presence of cardiac disturbance in middle-aged or old people who have had mild, unrecognized hyperthyroidism for years and in whom, with the development of arteriosclerosis, circulatory failure is beginning to be manifested.

Brain and Central Nervous System.—The cells and organs constituting the nervous system are more highly accelerated in hyperthyroidism than those of any other system, as indicated by the following:

In patients with hyperthyroidism, prior to the degenerative stage there is seen an abnormally good memory and the power of sustained attention. In almost every history it will be shown that high scholastic standards are attained with apparently very little effort. Emotionalism is a prominent symptom. The emotions are quite easily aroused, running an intense course and ending abruptly.

As a corollary there are irritability, quick responses, high speed activity. Usually, there is no complaint of pain, just as in the state of aroused emotion in the normal person no pain usually is recognized. The patient with hyperthyroidism has the feeling that everyone about her is too slow, and this becomes an added annoyance.

Due to this hyperactivity of the brain and central nervous system the attitude and behavior of the typical patient with hyperthyroidism as he sits in the examining room are so characteristic that few physicians can mistake the diagnosis. The patient is obviously agitated and restless. Some part of his body is usually in motion—

he cannot sit quietly and relax. The movements are not typically clonic in type but purposeful. Usually there are flushing of the skin of the face and upper thorax, visible pulsation in the neck arteries, and often a body-wide impulse which is synchronous with each cardiac systole. A casual inspection of the hands may show gross involuntary movements which are both of the intention tremor and rest tremor type, but rarely resemble the tremor of either Parkinson's syndrome or of multiple sclerosis, and yet the movement is not always fine but may show rhythmic involvement of the tendons. Indeed in the severe cases a true mania or delirium may be present. The patient shows a striking inability to concentrate. He describes his symptoms in a fragmentary manner and rarely follows one trend of thought for more than a few moments. His memory, too, is faulty and he may show thalamic symptoms such as an inclination to laugh or weep.

Thus the most striking signs and symptoms noted at the beginning of the examination of the patient are in the mental, motor, and sensory spheres. Nerve pains, monoplegia or hemiplegia are described by some authors but certainly are unusual symptoms.

Dieulafoy has suggested classifying Basedow's disease as a bulbar neurosis. He has stated that the cardiac acceleration, which is so characteristic of a hyperactive thyroid gland is due to "paralysis of the nucleus of the vagus nerve." To him this is indicated especially by the occurrence of tachycardia, dyspnea, and gastric disturbances. We must remember, however, that in Dieulafoy's time the importance of increased metabolism was not fully appreciated nor had a method for its estimation under basal conditions been devised. But we must not overlook the possibility that bulbar or midbrain disease may occur with or be the result of hyperthyroidism.

Special Senses.—All the special senses—seeing, hearing, touch, pain—are highly stepped up in acuity. There is a subjective feeling of warmth and an intolerance to external heat.

The Skin, Hair, and Nails.—The skin shows continuously the changes noted in the normal subject when under a major emotion. It is soft, moist, warm, pliable, vascular.

In the earlier stages the hair seems to be active in the sense that the individual hairs seem to stand up, the general effect being that of the state of emotion. Some patients seem to think that the hair curls more easily. In the later stages of hyperthyroidism the hair falls out and the nails become brittle.

Muscles.—The muscular system is profoundly affected in hyperthyroidism as is indicated by tremors, by a low threshold to stimuli, by muscle tension, and in the later stages by the wasting of muscle tissue.

The Face.—The face bears the expression of emotionalism—emotional fatigue. The lines are deeply engraved. There may be edema of the sockets and the eyes are staring and may exhibit exophthalmos and dilation of the pupils (see Chapter XVI). The mouth is restless and sensitive. The entire face picture gives the impression of a perspiring, flushed, excited and fatigued emotional state.

The Teeth.—The altered secretion of the mouth, the trembling tongue, the tendency to dental decay—all seem to be of the order seen in the long drawn-out emotional distress incident to strain caused by sickness and death in family life.

Lungs.—The increased respiratory exchange is a consequence of increased metabolism. The patient with hyperthyroidism is breathless even during conversation and in some instances his vital lung capacity is lowered.

Cardiovascular System.—Increased heart rate and force of contraction are constant features of hyperthyroidism. The effect of the increased force and rate, the widening of the terminal vascular veins in the tissues and organs, notably in the skin, produce as a physical consequence an increased pulse pressure.

An interesting corollary to the stepped-up efficiency of the heart-nerve-muscle mechanism is the extraordinarily prolonged, excessive heart action without heart failure. It is a remarkable fact that a heart so long overtaxed unceasingly day and night can continue to work so efficiently. It would seem that while the thyroid's hyperactivity drives the heart excessively it equally increases its efficiency to perform its task. The incessant pounding of the heart, especially when there are extrasystoles and auricular fibrillation, is one of the outstanding features of the disease. Often a capillary pulse may be observed which is due to vasomotor relaxation plus the increase in pulse pressure. Occasionally anginal or anginoid pains occur. As a rule these appear in patients of middle or advanced age and represent the effect of increased cardiac work in the patient who has "irritable" or sclerotic coronary arteries. The pulse rate is usually above 90 and the pulse volume is rather larger than normal, and shows normal diastolic but elevated systolic pressure such as we often see in an agitated, excited individual, so that the pulse pressure may be

markedly increased. We often have seen a pulse pressure of 90 to 100 mm. of mercury. In an examination of the precordium a general enlargement of all chambers of the heart may be recognized. There is a palpable precordial impulse over the right ventricle often followed by a diastolic impact over the conus arteriosus which would suggest anterior-posterior enlargement and a slight widening of the heart dulness to the left and upward. Most probably this enlargement is due to a slight dilatation of all portions of the heart rather than to work hypertrophy.

Blood Picture.—This subject is discussed in Chapter X. We shall state here only that there is a change in the serum-albumin and serum-globulin relationship, and a change in the cellular elements.

Ductless Glands.—The reaction of the adrenal, pituitary and parathyroid glands in hyperthyroidism is seen in the sensitivity of the organism to adrenalin, and in the increased activity of the sympathetic and parasympathetic symptoms. It is possible that the hypophysis is stimulated, for growth is forced when the disease occurs in a child or during adolescence. A child with hyperthyroidism is usually mentally and physically about two years ahead of its age.

Digestive System.—In hyperthyroidism there is a sharp increase in the appetite and in the power of digestion, but rarely can the patient eat a sufficient amount to avoid loss in weight. The fire created by the hyperactive gland is sufficient to burn up food more rapidly than it can be assimilated. The gastric motility is increased as is intestinal peristalsis. Some observers find an increase in the amount of gastric juice and an increased acidity. Other observers find diminished acidity and diminished gastric juice. There is good reason to think that those who find increased gastric acidity and increased gastric juice are more probably correct because the excessive sensitivity to excitation, the swift change in gastric secretion due to emotional excitation, could easily invalidate the findings of the test meal. The findings in animal experimentation also have elements of uncertainty as to gastric acidity for hyperthyroidism cannot be produced in animals by feeding with thyroid extract.

Another fact that tends to lessen the probability of the correctness of the evidence that there is a lessened acidity and lessened gastric juice in hyperthyroidism is that in hypothyroidism there is uniformly a low metabolism, and often an anacidity. Since hypo- and hyperthyroidism are opposite states, the accurate finding of low acidity in

the presence of hypometabolism would argue for a high acidity rate in the presence of hypermetabolism.

Again, as has been stated, in hyperthyroidism there is an increased appetite, an increased power of digestion, and an increased gastric motility. Therefore, one would expect that there would be an increased means by which this increased function is carried on. It would be far more likely that the psychic state defeated the technician whose evoking of fear and anxiety caused the suppression of the secretion that he was seeking to obtain.

Clinically and logically, we may conclude that the gastric juice is stepped up in efficiency just as are all other functions.

The acceleration of the function of the small intestines has been proved by *x*-ray examination. This is expressed by diarrhea.

It should be borne in mind that often symptoms referable to the abdomen are due to excessive pulsation of the abdominal aorta or to a cutaneous hyperesthesia which is general over the body.

Pancreas.—That the pancreas is activated in hyperthyroidism is seen in the great capacity for carbohydrate metabolism and by the disturbed carbohydrate metabolism as evidenced by the incidence of diabetes associated with hyperthyroidism.

The Kidneys.—There are changes but rarely failure in kidney function in hyperthyroidism. That failure rarely occurs would be expected because the thyroid hormone would increase the capacity of the cells of the kidney to do their work.

Polyuria or pollakiuria is present in hyperthyroidism principally as the result of the increased fluid and food intake as well as of the increase in metabolism. However, if sweating is a prominent symptom pollakiuria may still be present without any increase in the total amount of urine passed in twenty-four hours. This is such a variable symptom that it is not a diagnostic aid. Glycosuria, on the other hand, occurs often enough to warrant a routine blood sugar estimation in all cases.

The Bones and Joints.—As shown by Marine, there is a change in the chemistry of the bones in hyperthyroidism, but this change is not of diagnostic value.

Sex Function.—As to libido in hyperthyroidism, one sees the opposite state to that of hypothyroidism. The libido is increased in hyperthyroidism and is diminished in hypothyroidism. Either amenorrhea or dysmenorrhea may be seen. Pregnancy usually does not occur in hyperthyroidism, especially in the advanced stages.

SUMMARY

In hyperthyroidism there is a body-wide increase in the activity of every organ of the body, from the crown of the head to the sole of the foot. We see that every organ, every tissue, is more actively performing the work it normally performs, so that the basic sciences of physiology, biochemistry, pathology, and every branch of medicine and surgery must be called upon to elucidate the problems presented by this protean disease.

CHAPTER VIII

THE DIFFERENTIAL DIAGNOSIS OF HYPERTHYROIDISM

E. PERRY MCCULLAGH

THE clinical conditions which require special study in establishing the differential diagnosis of hyperthyroidism may be considered as falling into several main groups: (1) Conditions in which the history and physical findings are consistent with those of hyperthyroidism yet the basal metabolism is not elevated; (2) conditions in which the chief features are nervous phenomena similar to those seen in hyperthyroidism; (3) diseases which present cardiovascular changes which could be due to hyperthyroidism; (4) conditions in which there is a high basal metabolism without history or physical findings suggestive of thyroid dysfunction; (5) conditions in which there is a loss of weight without obvious cause.

HYPERTHYROIDISM IN REMISSION

In the first group the normal metabolism may be the result of a natural remission, due to radiation therapy or, as is much more frequently the case, a remission due to the administration of iodine. The rather promiscuous use of Lugol's solution within the past few years has materially increased the difficulties in the diagnosis of hyperthyroidism.

The history in these cases usually discloses a gradual increase of nervous restlessness, a sense of heat, a tendency to hyperhidrosis and a tremor which may be felt by the patient for some time before it can be satisfactorily demonstrated. Ordinarily there is a loss of weight in the presence of a good appetite and also a tendency to forceful tachycardia especially on exertion. The force of the heart's action is mentioned as frequently as is its increased rate. Energy is decreased but little, but muscular strength and endurance are diminished. Mild dyspnea is common. All these symptoms, however, may disappear during the remission. The most helpful of all physical findings

is the appearance of the patient as described in Chapter VII, the appearance of the eyes together with the other eye signs described in Chapter XVI being especially significant.

In the presence of the above history and findings, especially if a goiter is present, hyperthyroidism may usually be diagnosed with certainty.

Since hyperthyroidism is associated with hyperplasia and increased vascularity of the thyroid gland the character of the goiter, if it is palpable, is of great importance. The highly hyperplastic gland with its diffuse enlargement, elastic consistency, pulsating superior thyroid arteries, thrill, and bruit requires no comment here. They have been discussed in Chapter VII.

In this group of patients the Goetsch test is often strongly positive and is helpful. Such a patient still has the disease; the symptoms in all likelihood will increase again and a thyroidectomy should be performed.

Illustrative Case.—The patient, a farmer's wife, twenty-three years of age, entered the Cleveland Clinic on February 2, 1931. The history contained the following significant facts: On June 4, 1930, pain and tenderness suddenly developed in the right upper quadrant of the abdomen. She vomited incessantly for a month and lost 50 pounds in weight. A diagnosis of cholecystitis was made. Subsequently she regained some of the weight but noticed some palpitation and forceful beating of the heart on slight exertion. She became nervous and a tremor of the hands developed. She felt warmer and perspired more freely than usual. Her appetite was good but in August she again began to lose weight. Hyperthyroidism was suspected. The patient was given Lugol's solution in varying amounts and has continued its use. When seen in February, she was somewhat better than in August, but still felt a sense of stimulation, she tired easily and had a forceful tachycardia on exertion. She had a large appetite, felt slightly warmer than normally and had a tremor.

The significant findings on physical examination were the following: weight 161 pounds, previously 195 to 200 pounds; pulse rate 80 to 90; temperature 98.4° F., blood pressure 128/80. The eyes were brilliant and slightly staring in expression. The actions of the patient were quick. The anteroposterior measurement of both eyes was 22 mm. Both fissures measured 13 mm. Convergence was normal. No lid-lag was present. The tonsils had been removed and two teeth extracted. The thyroid was diffusely enlarged and about twice its

normal size, of rubbery consistency, slightly nodular and exhibited no thrill or bruit over the superior thyroid arteries.

The cardiac dulness was slightly increased to the left to 9.5 cm. from the midline. The sounds were slightly more forceful than normal, were regular in rate and rhythm, and no adventitious sounds were heard. The skin was of fine texture and was slightly moist. There was a very slight fine digital tremor. Tenderness was elicited on deep pressure below the tip of the ninth and tenth costal cartilages.

Laboratory Data: Repeated urinalyses gave normal findings. Blood counts were normal. Blood Wassermann and Kahn tests gave negative findings. Fasting blood sugar, urea, uric acid, chlorides, calcium, and phosphorus estimations gave normal findings. A roentgenogram of the chest showed a normal picture. A cholecystogram after the oral administration of sodium tetraiodophenolphthalein showed a poorly visualized gallbladder.

Estimations of the basal metabolism made with the patient in bed on the mornings of the first and second day after admission to the hospital were plus 15 and plus 9 per cent respectively.

The Goetsch test gave a strikingly positive result. The blood pressure during the control period was 120/70 and the pulse rate was 95. After the injection of 6 minims of adrenalin the pulse rate rose to 120 and was the same ninety minutes later. The systolic blood pressure rose to 150 and was 140, ninety minutes after the injection, the diastolic pressure fell as low as 50 and ninety minutes later was 65. There was no change in the respiratory rate or in the size of the pupils. Flushing, hyperhidrosis, asthenia, nervousness, and tremor were produced, all of which persisted for more than an hour.

During the period of preoperative observation the pulse rate varied from 72 to 100 while the patient was at rest.

A subtotal thyroidectomy was performed on the fifth day in the hospital and the patient was discharged on the thirteenth day.

The pathologic examination of the excised portion of the thyroid gland revealed diffuse hyperplasia, a few small lymphoid areas, a large amount of colloid, and no adenomata.

Discussion: This case is not unusual but is cited to illustrate the following facts:

1. In patients with hyperthyroidism in whom there has been a partial or complete remission of symptoms as the result of the administration of iodine, the diagnosis can usually be well established by a careful history and examination.

2. Hyperthyroidism may still be present even if the basal metabolism falls quickly to the normal level when the patient is at rest.

3. In such a case eye measurements and the Goetsch tests are useful aids in the diagnosis.

It should be borne in mind also that if the metabolism of a patient who is taking Lugol's solution falls to normal while the patient is at rest, it does not necessarily follow that the lowering of the metabolism is due to iodine and that the patient has hyperthyroidism.

As has been stated in Chapter VII the presence of a goiter is by no means essential to the diagnosis of hyperthyroidism.

DISEASES OF THE NERVOUS SYSTEM WHICH SIMULATE HYPERTHYROIDISM

Conditions which may present nervous phenomena which suggest hyperthyroidism include many of the neuroses and psychoses, encephalitis, chorea, Parkinson's disease, occasionally alcoholism, and arteriosclerosis, especially when it is chiefly of the cerebral type.

Neuroses of the Menopause.—It may appear to be elementary to speak of difficulties in the differential diagnosis of hyperthyroidism from the neuroses of the menopause. The physician is frequently confronted, however, by a patient suspected of having hyperthyroidism who after adequate study may be found to have the type of sympathetic imbalance which is so common at the climacteric. One is forced to the conclusion that in such cases an erroneous diagnosis is frequently made and that many patients in this group are subjected to needless surgery.

It is always well to bear in mind, however, that these two conditions, hyperthyroidism and the menopause, not infrequently occur together, since in women with goiter, hyperthyroidism frequently appears in the fourth decade.

Illustrative Case.—The patient, a woman fifty years of age, came to the Cleveland Clinic because she had not been relieved of the symptoms of hyperthyroidism by an operation done elsewhere five months previously. She had had a goiter for ten years. A hysterectomy had been performed for the removal of uterine fibroids seventeen months previous to her admission to the Cleveland Clinic.

Ten months previously the patient had begun to notice increasing nervousness, palpitation on excitement or exertion, hyperhidrosis and emotional instability. These symptoms persisted following her operation and within the two months preceding her admission to the

Cleveland Clinic she had lost 15 pounds in weight, and insomnia, weakness, and hot flashes had developed.

The history revealed the important facts that the loss of weight had been associated with a poor appetite, that there had never been a sense of stimulation, but only fatigue, and that the palpitation and nervousness were practically not bothersome, except when a hot flash occurred, as frequently happened.

Examination revealed the following significant findings: Pulse rate, 120; blood pressure, 140/92; temperature, 98.6° F.; weight, 183 pounds, normal weight 196 pounds. The patient looked tired. The tonsils were small and buried and one anterior pillar was red. There was a palpable nodular remnant of the thyroid gland on the right side. The cardiac dulness was 9 cm. to the left of the midsternal line, the cardiac rhythm was regular except for an occasional extrasystole; and the heart sounds were normal.

A tentative diagnosis of hyperthyroidism was made by the examining physician and the surgeon.

Special Examinations and Laboratory Data: Repeated urinalyses gave normal findings; the blood count and the blood sugar were normal. A blood Wassermann and a Kahn test gave negative findings. An electrocardiogram was normal. The patient was placed in the hospital and the pulse rate remained at 80 while she was at rest. The basal metabolism estimations made on two successive days with the patient in bed were plus 25 per cent, and plus 2 per cent respectively.

Complete rest and mild sedatives were prescribed. The patient was seen a month later when she was found to have regained her weight and to show improvement in the other symptoms. The nervousness recurred following discontinuance of the sedatives, and subsequently supraclavicular pains developed with paresthesia of the hands and feet; all these symptoms of hypothyroidism, dryness of the skin, and a poor memory, disappeared following the administration of desiccated thyroid.

Discussion: It seems reasonable to assume that in this case operation was performed for the relief of symptoms which were not due to hyperthyroidism, since they persisted following the thyroidectomy up to and including a period during which the patient appeared to have hypothyroidism.

Neurocirculatory Asthenia.—Of all the neuroses which may lead to difficulties in the differential diagnosis of hyperthyroidism that one

which we choose to designate neurocirculatory asthenia, but which has also been called "nervous exhaustion," and "irritable heart," is by all odds the most bothersome.

Neurocirculatory asthenia is frequently mistaken for hyperthyroidism because it may present excitability, fatigue, tachycardia, tremor, sweating and weight loss, and because the condition often occurs in persons with a distinct enlargement of the thyroid gland. The differentiation may be still more confusing when several metabolism estimations show a value of from 12 to 18 per cent above the expected normal. Peculiarly enough, many patients who present almost identical physical findings with those found in patients with a high basal rate, may have a basal metabolism as low as 18 per cent below normal.

Neurocirculatory asthenia is a disorder of young people, occurring usually in individuals under thirty years of age. It most commonly occurs in individuals between puberty and twenty years of age. There are many differentiating features between this disease and hyperthyroidism but most of them are easily overlooked.

The histories differ in the following manner. The mental attitude of the patient with hyperthyroidism tends to be optimistic and he complains very little, while the patient with neurocirculatory asthenia is discouraged and complains of many vague symptoms. The one is inclined to be bold and ambitious, beginning the day's work eagerly only to be forced to stop by fatigue; the other is constantly exhausted and feels too weak to accomplish any work, and yet in spite of this, may have carried on considerable activity for a long time. Previous attacks may have occurred in both diseases. If Lugol's solution has been given, the patient with neurocirculatory asthenia will have received no benefit. Any loss of weight in the patient with hyperthyroidism is associated with normal or increased appetite while in neurocirculatory asthenia the appetite is poor.

In hyperthyroidism tachycardia is noticed by the patient chiefly on exertion and a forceful beat is a prominent feature, while in neurocirculatory asthenia palpitation may occur frequently on excitement or during rest. Tendency to faint and to constipation occurs relatively infrequently in hyperthyroidism, and a choking sensation is more frequently complained of in neurocirculatory asthenia.

Examination usually reveals many differentiating points. The general appearance of the patients with hyperthyroidism and with neurocirculatory asthenia differs, patients with the first disease mov-

ing quickly and appearing to be stimulated, while in the other disease they become tired with less vigorous movements. In the first disease the skin is warm, moist, and pink and of unusually fine texture, while in the other disease there is coldness and moisture of the hands and feet, and a tendency to acrocyanosis and mottling of the skin, and in some cases dermatographia occurs. In true hyperthyroidism the tremor tends to be finer, more regular and more forceful than in neurocirculatory asthenia.

Tachycardia occurs in both diseases but in hyperthyroidism it is more persistent than in neurocirculatory asthenia, in which it is usually variable, quickly falling to nearly the normal rate when the patient is recumbent, while it may rise to 160 or even higher when the patient rises to a standing position.

In neurocirculatory asthenia the cardiorespiratory reflex tends to be exaggerated, slow deep breathing causing a considerable variation in the pulse rate. In hyperthyroidism the oculocardiac reflex is not present but in neurocirculatory asthenia ocular pressure may cause a distinct slowing of the pulse rate. Erben's phenomenon is usually absent in hyperthyroidism while in neurocirculatory asthenia forceful flexure of the trunk may cause a slowing of the pulse from 150 to nearly normal. In neurocirculatory asthenia the heart itself does not have a forceful thrust, there is usually no widening of cardiac dulness on percussion and a systolic murmur is absent or, if present, is more likely to be in the pulmonic area than at the apex. In neurocirculatory asthenia the systolic pressure is normal or lowered and the pulse pressure is not elevated.

In neurocirculatory asthenia the pupils are often dilated and show hippus. Firm epigastric pressure may produce an obvious pupillary dilatation (viscero-ocular reflex).

If a goiter is present in a patient with neurocirculatory asthenia it is ordinarily diffuse and soft.

In short, in the case of a young patient, in whom fatigue is a prominent symptom, the complaints many, the patient's appetite poor and the appearance suggestive of exhaustion, the pulse variable and the hands cold, the diagnosis of hyperthyroidism must be made with the greatest caution. This is equally true in the presence of goiter, tremor, weight loss, and slight elevation of the basal metabolism. In such cases hyperthyroidism is usually absent, or if present at all, its control will not lead to a symptomatic cure. It should always be borne in mind, however, that in a patient with distinct neurocirculatory as-

thenia, hyperthyroidism may be developing. The following case illustrates this point.

Illustrative Case.—A young woman, twenty-two years of age, came to the clinic in December, 1929. The salient points of her history were as follows: She had been entirely well until two years before admission to the clinic. Since that time there had been occasional gastric distress and pain in the lower abdomen, which was not related to meals. In May, 1929, the patient noticed that she was more easily excited than previously, and that she had some slight vertigo, which was transient, and occasionally there was a sense of dyspnea on exertion or even at rest. The symptoms abated somewhat from July until November. Since the latter date she had noticed increased nervousness and dizziness, and that she perspired rather more readily than previously, the hands and feet being usually cold and moist. Twelve pounds of weight, which had been lost during the period in which she had had the most marked digestive disturbance, had not been regained. She had received no iodine. The family history was irrelevant. Apart from the diseases of childhood and tonsillitis she had had influenza but no other illnesses.

Examination revealed a well-developed and well-nourished young woman. Temperature, 99.4° F.; pulse rate, 92; blood pressure, 145/90. The skin and mucosa were normal with the exception of the fact that the hands were very moist and cold and the nails slightly cyanotic. The pupils were equal, regular, and reacted to light and accommodation. Examination of the nose and throat revealed no abnormalities, except a slight deviation of the septum and chronic tonsillitis. The thyroid was enlarged to about three times its normal size. It was uniformly soft in consistency. The heart was not enlarged; the rate varied considerably; there were no murmurs, and the sounds were not more forceful than normal. There was a very slight, fine irregular digital tremor. The cardiorespiratory reflex was present, the oculocardiac reflex was present to a slight degree, the pulse being slowed about twenty beats per minute. The remainder of the physical examination gave essentially normal findings.

Laboratory Data: Roentgenograms of the teeth revealed one pulpless tooth with an impaired apical membrane, *x*-ray examination of the chest revealed no evidence of any pathologic condition. A basal metabolism estimation made after one night's rest in the hospital was plus 10 per cent. The blood count and repeated urinalyses gave normal findings. Repeated blood sugar estimations and one

blood urea estimation gave normal findings as did the Wassermann and Kahn tests.

It was felt at this time that this patient had neurocirculatory asthenia which had been aggravated by chronic tonsillitis and probably by the mild apical infection of one tooth. She was advised to take further rest, to have a tonsillectomy and to have the infected tooth extracted. The patient was discharged from the hospital but returned to the clinic one month later complaining of nausea and epigastric pain which usually came on fifteen minutes after her meals and was not relieved by alkalies or by food. No abdominal tenderness could be elicited. Gastric analysis gave normal findings and roentgenograms of the stomach and large intestine presented normal pictures. Sedatives, a smooth diet, alkaline powders, petrolagar and feedings between meals were prescribed for the relief of the gastric distress.

The patient was seen once each month until August, 1930. During this time the amount of perspiration and the force of the heart beat increased and dyspnea on exertion developed. The appetite gradually increased, but the patient neither gained nor lost weight. The digital tremor gradually became more marked, the hands became slightly warmer, the pulse rate increased to above 100, being usually about 120 when the patient was in the office. The systolic blood pressure was usually from 148 to 155 and the diastolic pressure was 80 or below. There was a staring expression. In August the basal metabolism was plus 24 per cent.

A thyroidectomy was performed on September 3d. Pathologic examination of the removed tissue showed slight hyperplasia.

The most recent observation was made on December 3, 1930, at which time the patient had gained 10 pounds in weight and was eating a great deal less than before. The staring expression had lessened and the eyes appeared to be less prominent than they had been. The tremor had disappeared, but the hands were still cold and wet. The cardiorespiratory and oculocardiac reflexes were present. The blood pressure was 136/85, the pulse rate 86. The infected tonsils and infected tooth had not been removed.

Discussion: The record in this case illustrates the fact that hyperthyroidism and neurocirculatory asthenia, two conditions which are frequently mistaken for each other, may occur in the same patient. In this case neurocirculatory asthenia was diagnosed first. Later the presence of hyperthyroidism was recognized. Thyroidectomy

relieved the symptoms due to hyperthyroidism, but did not relieve those which were due to the neurocirculatory asthenia. In such a case operation is necessary but, because of the residual symptoms due to the irritable sympathetic nervous system, the symptomatic relief is never as complete as in uncomplicated cases of hyperthyroidism.

Means and Richardson[1] state that the neurotic patient shows a metabolic rate falling with each successive reading until the normal zone is reached, while "the truly thyrotoxic person without treatment will show a maintained elevation." It has been true, however, in our practice, that in the case of a patient who receives no treatment except rest in bed, the basal metabolism may fall to within normal limits, and the patient may still have hyperthyroidism, as in the case cited above.

Syphilis of the Central Nervous System.—Of the organic diseases which affect the central nervous system the one which is probably most commonly mistaken for hyperthyroidism is syphilis. The resemblance is usually superficial and a correct diagnosis will finally follow repeated basal metabolic and serological tests. (See Chapter XIX.)

Illustrative Case.—A man thirty-three years of age was seen January 7, 1930. The outstanding features of his history were as follows: While hunting in October, 1929, he noticed excessive perspiration and pounding of the heart. On any exertion since that time he had perspired profusely, the heart had beat very forcibly and fast and he had quickly become exhausted. His appetite had been good, not excessive. He had lost no weight. There had been a slight tremor which was more marked when he was excited as he frequently had been especially just prior to his admission to the Cleveland Clinic. During the preceding few months his face had been more flushed than usual. He had used iodized salt for years but had received no other form of iodine medication. During the preceding summer he had had peculiar yellowish-red spots on the palms of the hands which had completely disappeared.

Physical examinations revealed slight nystagmoid jerks but no true nystagmus. The tonsils and anterior pillars were slightly reddened. There was a slight thyroid enlargement with increased solidity of the gland. The temperature was 98.6° F.; blood pressure, 136/78; pulse rate, 90. The ocular reflexes were normal. The deep reflexes in the arms and legs were slightly hyperactive but equal.

The superficial, abdominal, and cremasteric reflexes were normal. The patient had a slight staring expression of the eyes and his general appearance suggested stimulation. The remainder of the physical examination gave normal findings.

Because of the history of the skin lesions, although there was no history of anything which suggested a specific primary luetic lesion, syphilis was suspected. It was felt that a quiescent stage of hyperthyroidism should also be considered.

Laboratory Data.—Erythrocyte and leukocyte counts were entirely normal; hemoglobin estimation, 80 per cent. The differential leukocyte count was normal. Blood sugar and urea estimations gave normal findings, a blood Wassermann test was 4 plus to 3 antigens and a Kahn test gave a positive result. Basal metabolism estimations were plus 4 per cent and minus 7 per cent respectively on two occasions. A spinal fluid Wassermann test gave a negative result. The colloidal gold test gave normal findings. The Pandy test gave a negative result. Antisyphilitic treatment was instituted.

This patient was seen again in January, 1931. The excessive perspiration, palpitation, fatigue, flushing of the face, and staring expression all had disappeared entirely. No nystagmoid jerks were observed. There was a slight digital tremor. There was no redness of the throat and the thyroid was the same as on previous examination.

Discussion.—This case illustrates the superficial resemblance which syphilis may bear to hyperthyroidism. It is not at all improbable, however, that many cases of syphilis would be diagnosed as cases of hyperthyroidism unless careful basal metabolism estimations alone or in conjunction with blood Wassermann examinations were made. Could it be possible that some cases reported in the literature as cases in which Basedow's disease was cured by antiluetic treatment were similar to the case just cited?

Encephalitis.—Encephalitis may cause a high rate of metabolism associated with weight loss, nervousness, and tachycardia and may be mistaken for hyperthyroidism. A careful neurological examination, however, will usually reveal some changes relative to the central nervous system. It has been our experience that in such cases iodine fails to reduce the metabolic rate materially and that the symptoms suggestive of hyperthyroidism are not aggravated following its withdrawal.

The following case will serve to illustrate the above points:

Illustrative Case.—A man fifty-nine years of age was seen at the

Cleveland Clinic on December 2, 1930. His history included the following data: In January, 1930, following a severe dental infection the patient noticed that he was easily excited. He felt stimulated and found it difficult to concentrate on his work. He began to lose weight in spite of a good appetite. Slight digital tremor developed and he experienced slight shortness of breath on exertion. He also noticed a high pitched tinnitus which seemed to be synchronous with the pulse. There were transient periods of dysarthria.

Between January and September, 1930, the patient lost 30 pounds in weight and in September his basal metabolism was found to be plus 35 per cent. A diganosis of hyperthyroidism was made and the patient was given large doses of Lugol's solution, which did not improve the symptoms at all.

Neurological examination at this time showed abnormal findings similar to those described below.

General physical examination on December 2d showed the pulse rate to be 92; blood pressure, 120/65; temperature, 98.6° F. The patient was poorly nourished and appeared to be stimulated. There was no evidence of exophthalmos or of lid-lag. Dental examination showed badly infected gums. The thyroid gland was slightly but diffusely enlarged, was soft in consistency; and there was no thrill or bruit. Examination of the heart, chest, and abdomen gave normal findings. Examination of the genitalia, rectum, bones and joints revealed no abnormality. Examination of the nose and throat gave normal findings except for chronically infected tonsils. Examination of the eyes revealed old, inactive chorioretinitis of infectious origin. A roentgenogram of the chest showed a normal picture. An Ewald test meal, a complete blood count, blood sugar and blood urea estimations and urinalysis gave normal findings.

Neurological examination showed sensation to be normal to touch, pin prick, vibration, and temperature. The sense of position of the joints was preserved, and coordination was good. The heel-to-knee and finger-to-nose test gave normal results. Examination of the motor system showed that the tongue protruded to the left of the midline, that the facial muscles lacked tone, and that the eyes moved freely in all directions. Gait was slow but essentially normal. Examination of the reflexes showed that the right pupil was fixed for light and responded slightly to distance. The corneal and conjunctival reflexes were active. The patellar reflexes were very sluggish and on the right side were elicited with difficulty. Plantar reflexes

were hyperactive with some fanning of the toes but no definite Babinski reflex could be elicited. The cremasteric reflex was absent on the right side and the abdominal reflexes were absent. Examination of the special senses showed air conduction to be greater than bone conduction on both sides. The left eye showed an absence of perception for red. The sense of taste in the posterior one-third of the tongue was diminished.

The spinal fluid was clear, showing four cells per high power field; Pandy's test gave a normal result and the colloidal gold curve was normal. The Queckenstedt test also gave a normal result. The basal metabolism was plus 9 per cent.

Discussion.—In view of the above-cited symptoms plus the high rate of basal metabolism the condition could readily be mistaken for hyperthyroidism. The poor response to iodine, however, was distinctly against such a diagnosis. The neurological findings could not be explained as due to hyperthyroidism and we felt that encephalitis most probably explained the high metabolism and the loss of weight together with the other symptoms.

We believe that this is an example of cases in which an irritative lesion of the brain has caused a rise in basal metabolism with subsequent loss of weight.

Disseminated Sclerosis.—We have seen cases of disseminated sclerosis, in which the symptoms have been mistakenly considered to be due to hyperthyroidism. Occasionally a patient presents herself for examination because the symptoms, which at this time may be easily shown to be due to multiple sclerosis, have been previously diagnosed as due to hyperthyroidism.

Illustrative Case.—A young woman twenty-three years of age entered the Cleveland Clinic in October, 1928, because she had not been relieved of symptoms for which she had submitted to thyroidectomy elsewhere in March of that year. Previous to her operation she had complained of choking spells, particularly at night, of palpitation on exertion, and of increasing nervousness and goiter. At that time she had had no tremor and had not lost weight. Since her operation the nervousness had gradually increased and a slight tremor of the hands had developed. For some time following the thyroidectomy her sight had been poor but it had improved recently. The speech had become slightly slow, her memory was not as good as previously, and the tremor of the hands was most noticeable on lifting a glass or soup spoon. The gait was unsteady.

General physical examination revealed a temperature of 98.4° F., pulse rate 84, blood pressure 125/75, weight 183 pounds. There was the scar of a low collar incision and no palpable thyroid tissue. There were several crowned teeth and the tonsils were enlarged and slightly reddened. The remainder of the physical examination gave entirely normal findings with the exception of the neurological examination which showed some bilateral ataxia on finger-to-nose and heel-to-knee tests. There was lateral nystagmus to right and left. There was slight temporal pallor of the right optic disk. Abdominal reflexes were absent. Urinalyses gave normal findings. Differential blood cell counts and hemoglobin estimations gave normal results. The blood sugar content was 122 mg. per 100 cc., one-half hour postprandial. Serum calcium content was 10.1 mg. per 100 cc. Blood Wassermann and Kahn tests gave negative results. A Wassermann test of the spinal fluid gave a negative result; cell count and seroglobulin estimation gave negative findings, and the colloidal gold curve was normal. The basal metabolism on two occasions was plus 3 and minus 1 per cent. The diagnosis was disseminated sclerosis.

Discussion.—It is not known whether or not the basal metabolism was elevated at the time of the thyroidectomy. It is fairly certain, however, that the thyroidectomy was performed for the relief of symptoms which, as they have progressed, are to be accounted for as due to multiple sclerosis. It is probable that a more careful examination or repeated basal metabolism tests previous to operation would have revealed the true condition. Several cases of this kind have come to our attention during the past two or three years.

Psychoses.—Early psychoses or minor psychoses of various types will often come to the attention of the physician or consultant because of features simulating hyperthyroidism; in fact the early stages of a psychosis are frequently seen in patients with a goiter. In some such cases a great deal of stimulation of the sympathetic nervous system may be present, producing tachycardia, excessive perspiration, a digital tremor, restlessness, and a general appearance suggestive of hyperthyroidism. Due to the restlessness it may be difficult to make a satisfactory metabolism test and the results of such a test may be misleading. Cases of this type have been reported, in which thyroidectomy has appeared to be beneficial. From our experience it would seem that the symptoms are usually unimproved or aggravated.

It not infrequently happens, especially in the case of patients past middle age, that they become disorientated and drowsy immediately

after thyroidectomy. For many years in this clinic it has been the practice to administer large daily doses of desiccated thyroid gland, amounting to as much as 15 grains, for several days after operation, usually with distinct resultant benefit.

The psychoses which are sometimes concomitant with hyperthyroidism should usually be classified as toxic delirium. In extremely severe cases of hyperthyroidism during a severe postoperative reaction they are associated with a rising temperature before death. If they appear before operation they usually are associated with hyperthyroidism of such severity that it can scarcely be mistaken. As long as such a patient improves on medical management, operation is not performed. If operation becomes imperative the minimum is done and if any improvement follows, further operative treatment is not attempted for from two to three months after the mental symptoms have disappeared.

In cases of mild psychosis in which sympathetic stimulation is obviously present the diagnosis may present some difficulty, but as a rule unless the hyperthyroidism is severe it is not the cause of an existing psychosis.

Illustrative Case.—A young woman, twenty-four years of age, entered the Cleveland Clinic complaining of nervousness and difficulty in breathing. The history included the statement that six basal metabolism estimations had been made during the previous six months, the rate varying from plus 25 to plus 100 per cent. The patient was restless and irritable, a constant feeling of tension had developed, which was worse at times, and she felt unable to relax. She had an irresistible desire to be moving about and had a tendency to attempt work, which ordinarily would occupy the attention of two or three people. She had gained 18 pounds in weight during the previous ten months. She had a tendency to rather severe sudden emotional outbursts, which were directed toward the members of her family. There was no intolerance of heat. The patient perspired somewhat more profusely than before the onset of these disturbances but her hands and feet were usually cold. The patient by nature had always been of a hyperkinetic type, with a hyperemotionalized temperament, and she worked and studied intensely. She had been an excellent teacher and immediately preceding her admission to the clinic was intent upon writing a Master's thesis in addition to her usual work.

Physical examination revealed a large, rather obese young woman,

63 inches tall and weighing 188 pounds. The temperature was 98.4° F.; pulse rate, 100; blood pressure, 130/90. The pupils reacted normally. There were no abnormal findings in the nose and throat, and there was a slight diffuse enlargement of the thyroid. There was no evidence of pulmonary or cardiac disease. Nothing abnormal was found in the abdomen. Rectal and pelvic examinations were not made. The reflexes were normal and there was a very slight digital tremor.

Urinalysis gave normal findings except for a faint trace of albumin, 5 to 10 pus cells per high power field, many shreds of mucus and numerous epithelial cells. Other urinalyses gave essentially negative findings. The blood counts gave normal results. Fasting blood urea, chlorides, and sugar were normal, and the glucose tolerance test gave a normal result. Blood Wassermann and Kahn tests gave negative findings. The serum protein was 7.87 per cent, serum albumen 5.69 per cent, and serum globulin 2.18 per cent. The basal metabolism was plus 3 per cent, but on a retest on the following day it was found to be minus 1 per cent.

There were no diagnostic changes in the visual fields.

Roentgenograms of the teeth showed no periapical absorption; and a roentgenogram of the sella turcica showed it to be normal. The pulse rate was 100 at the first examination but during her stay in the hospital it was well within normal limits. We felt that the condition of this patient could be classified as mild hypomania in an essentially hyperkinetic personality.

Discussion.—A high basal metabolic rate apparently may occur in a nervous disorder such as was present in this case, and not be caused by a true hyperthyroidism. It is unusual, however, to find that repeated basal metabolism estimations show as great an elevation as in this case. It is always a question as to whether or not the metabolism estimations in these cases are truly basal.

Cases somewhat similar to this in which a thyroidectomy has been performed without resultant improvement are occasionally seen. We feel, therefore, that it is valuable to recognize this particular type of case when it appears.

Cerebral Arteriosclerosis.—When cerebral arteriosclerosis is associated with a goiter it may present symptoms which may be interpreted as due to hyperthyroidism. If operation has been performed in such cases, subsequent observations will give a distressing revelation of the true cause of the symptoms.

In the presence of *chorea*, *alcoholism*, *Parkinson's disease*, and some other conditions the diagnosis of hyperthyroidism is sometimes suggested but is usually easily ruled out.

DISORDERS OF THE CARDIOVASCULAR SYSTEM WHICH SIMULATE HYPERTHYROIDISM

There is a certain group of conditions which are characterized chiefly by cardiovascular signs which may simulate hyperthyroidism. The tachycardia which is caused by tuberculosis must be especially considered in this connection as well as that due to a focal infection or to an acute infectious process. It follows that when tachycardia exists in the presence of a goiter whether or not it is due to hyperthyroidism must be decided.

Tuberculosis in particular may present a group of symptoms which are highly suggestive of hyperthyroidism.

Illustrative Case.—A girl eleven years of age entered the hospital on March 10, 1930. For the preceding two years she had had poor general health. At first the presence of a tonsillar infection was suspected as being the cause of the symptoms and the tonsils were removed but the patient did not completely regain her health. During the preceding three months she had fainted several times. She complained of weakness and a fast pulse. When she became unconscious in a so-called "fainting spell" there was no convulsion, no stiffness and no involuntary defecation or micturition. During the few weeks preceding her admission to the clinic there had been some dyspnea. The family history was completely irrelevant. Except for childhood diseases and tonsillitis there had been no illnesses. There had been some enlargement of the neck for four or five years and recently there had been a slight, nonproductive cough. No rise in temperature had been noted and there had been no night-sweats or pain in the chest.

Physical examination revealed a slender pale girl, weighing 69½ pounds; the average normal for the age of the patient is 75 pounds. The temperature was 99° F.; the pulse rate, 130; and the blood pressure, 136/86. The thyroid gland was diffusely enlarged to twice its normal size; it was freely movable, and there was no thrill nor bruit. Examination of the nose and throat revealed no infection. The remainder of the general physical examination gave normal findings. No rectal nor pelvic examination was made.

While in the hospital the basal metabolism was plus 18 and plus

12 per cent on two occasions. Blood counts gave normal findings, the fasting blood sugar was normal; the blood Wassermann and Kahn tests gave negative findings; and blood culture after incubation for six days gave a negative result. The patient's temperature rose to 99° F., or slightly above, daily while she was at rest in the hospital. The pulse varied between 120 the first day and 95 on the fourth hospital day. A roentgenogram of the chest showed fibrous and exudative infiltration in the right upper lobe and apex and fibrosis at the hilum with extension well out into the left lung. Reexamination of the chest did not reveal any signs of activity. A diagnosis of pulmonary tuberculosis with mild activity was made, and with instructions regarding diet and rest the patient was sent home to be under the care of her physician. The patient was last seen in August, 1930. She had improved considerably but was still having a slight elevation of temperature each afternoon. She had maintained her weight, and no further signs suggesting hyperthyroidism had developed.

When tuberculosis and hyperthyroidism coexist it is necessary to perform thyroidectomy. After the hyperthyroidism is controlled the tuberculosis improves much more rapidly under the usual methods of treatment as is stated in Chapter XIII. If operation is not performed each condition usually aggravates the other.

Tachycardia of functional origin, without other obvious signs suggestive of sympathetic instability, may exist. In such a case the history usually does not suggest hyperthyroidism; the basal metabolism is ordinarily normal and no improvement follows iodine medication.

Paroxysmal tachycardia may produce a clinical picture which simulates hyperthyroidism very closely. The history usually discloses previous attacks which have appeared and disappeared with characteristic suddenness. Two cases can be recalled in which the history of previous attacks was vague, and one in which the paroxysm lasted for several days. During an attack the patient may have an anxious expression, a flushed face, a moist skin, and tremor and the basal metabolism may be elevated. In such cases, when the tachycardia stops abruptly and the appearance of the patient quickly becomes normal, the diagnosis is apparent. It has been our experience that thyroidectomy has no effect upon paroxysmal tachycardia.

Arterial Hypertension.—Early arterial hypertension especially when it is accompanied by a forceful cardiac pulsation and tendency to tachycardia, an increasing excitability, slight tremor and a sug-

gestive appearance may suggest the possibility that hyperthyroidism is present. If a goiter is present the problem becomes more difficult. If the goiter is solid in consistency but the metabolism is essentially normal, the question frequently arises as to whether or not this solidity may be the result of recent iodine medication.

Auricular Fibrillation.—Hyperthyroidism should always be suspected as a possible cause of auricular fibrillation.[2, 3] Sturgis and Levine have emphasized the point that a mistaken diagnosis of organic heart disease is frequently made in cases of hyperthyroidism. In such cases the careful history is of the greatest value. The general appearance of the patient must be observed. Alertness, a tendency to a flushed moist skin, a staring expression and peculiarly loud heart sounds, if present, are helpful features.

The fact that the ventricular rate remains fast after the administration of digitalis and may be slowed on the administration of iodine is a helpful feature in some cases. There are also cases of auricular fibrillation in which none of the general symptoms of hyperthyroidism are present. A proper diagnosis is of vital importance in such cases because by proper management these patients may be brought from a state of almost complete cardiac failure to a life of activity, even after years of cardiac invalidism.

Organic Heart Disease.—Various writers have called attention to the fact that hyperthyroidism may be masked as organic heart disease other than fibrillation. It is also true that in some cases of rheumatic carditis the condition is called a "goiter heart" and patients are promised that they will be relieved from their cardiac symptoms by thyroidectomy when the condition is truly rheumatic in origin.

In cases in which there is an adenomatous goiter which has been present for many years there is often a history of the presence of dyspnea and palpitation for from one to five years. Some increasing nervousness is often complained of, but aside from this it may be impossible to elicit symptoms suggesting hyperthyroidism from the history or in the physical examination. In these cases cardiac damage forms the most significant part of the clinical picture and the cardiac findings are usually sufficiently consistent to warrant the opinion that such cardiac damage is due to the goiter. The metabolism is usually raised but this is by no means always the case.[4] It is our opinion, however, that in most of these cases the cardiac damage is the result of overwork from mild recurrent hyperthyroidism, which has

been present for a long period of time. The absence of a history of rheumatism is an important aid in the diagnosis.

The two most obvious cardiac findings usually are signs of enlargement of the heart with a nontransmitted apical systolic murmur. Dilatation and hypertrophy, diffuse apical impulse and loud sounds are usually associated with an increase in the amplitude of contraction.

In cases in which the cardiac condition is due to goiter, there is usually some tachycardia and there may be a systolic murmur at the base, most commonly in the aortic area. If there is any vibration it is systolic and there is never a diastolic thrill or murmur. The blood pressure is often somewhat elevated, but a diastolic pressure of over 100 mm. is seldom, if ever, due to goiter. The murmurs are usually softer in quality than those of organic valvular disease.

Cases in which an adenomatous goiter is associated with cardiac failure are sometimes seen. In such cases a slight diastolic murmur at the extreme apex may explain the heightened pulse pressure and indicate aortic regurgitation of organic origin.

Aortic regurgitation may be recognized as such in the presence of goiter or it may produce signs so suggestive of hyperthyroidism that in the presence of a goiter thyroidectomy is advised. This is especially true if the aortic disease not only causes a high pulse pressure but also a thrill and bruit in the thyroid arteries and if it is associated with a high basal metabolic rate. Such a case was seen recently in which the basal metabolism before operation was plus 31 per cent and plus 20 per cent on two occasions; the pulse varied from 100 to 120; and the blood pressure was 190/68. Cardiac and peripheral vascular signs consistent with the diagnosis of aortic regurgitation were present. The tachycardia was not reduced by Lugol's solution. A thyroidectomy was performed and a month after operation in spite of a gain of 10 pounds in weight the pulse retained the same rate as before operation; the blood pressure was 220/58 and the basal metabolic rate was plus 38 per cent.

When rheumatic carditis is associated with an adenomatous goiter, even though no hyperthyroidism is demonstrable, the safest procedure —if the operative risk is not obviously great—is usually to perform a thyroidectomy because of the tendency of such a goiter to produce additional damage to the already damaged heart, and to do this in such an insidious manner, that it may not be recognized by the patient until signs of cardiac failure are evident.

Patients are seen repeatedly in whom cardiac failure is associated with an adenomatous goiter. These patients are poor operative risks and in many cases within the preceding five or ten years they have been told by reputable physicians that the best policy is to leave the goiter alone. How much better off such a patient would have been if the adenomatous gland had been removed before the cardiac failure occurred.

Not infrequently cases are seen in which a large adenomatous goiter is present and although there is no evidence that any hyperthyroidism has ever been present, nevertheless the blood pressure is raised and there is myocardial damage with or without fibrillation. In such cases the cardiac damage is the result either of absorption of the products of degeneration from the adenomata or of obstruction to the blood flow about the neck, or of other factors rather than hyperthyroidism. In these cases distinct benefit follows thyroidectomy although the patients are likely to have some postoperative hypothyroidism.

Illustrative Case.—The patient was a man, sixty-two years of age who entered the Cleveland Clinic on February 4, 1931. He came because of a large goiter which had been present for the past forty-five years and had increased slightly in size. The patient had always been inclined to be heavy, his weight having varied during the preceding ten years between 225 and 245 pounds. He could not recollect having had any previous attacks in which he lost weight, became nervous or excitable, or had a tremor or heat intolerance. He had had no attacks which suggested hyperthyroidism. Five years before he had been told that his heart rhythm was irregular. Two years before his basal metabolism had been minus 19 per cent. During the preceding five years he had been inclined to drop asleep while reading and he had noticed that he felt the cold more than normally. The skin of the hands was dry, the nails were brittle. The patient believed that he was normally alert and his memory was good. Cardiac irregularity had been noticed frequently during the preceding five years. In February, 1930, the basal metabolism was again minus 19 per cent. For the preceding year he had been taking 5 grains of desiccated thyroid daily. On the day of his examination at the clinic the basal metabolism was plus 19 per cent.

Examination revealed a large, obese man, weighing 240 pounds, with a normal temperature, and a blood pressure of 146/100. The patient was pale and the hands and feet presented a puffy appearance.

The skin of the hands was dry and was cracked over the joints. There was a very large, soft adenomatous goiter which produced tracheal pressure as was evidenced by a brassy cough and a peculiar voice. The trachea was displaced to the left and there was a mass of the size of a large grapefruit on the right side of the trachea. The heart was irregular in volume, rate and rhythm, and an area of cardiac dulness extended 2 cm. to the left of the nipple line. The heart rate was approximately 110 with a pulse deficit; a slight systolic murmur could be heard at the apex; there were no signs of cardiac failure. The remainder of the physical examination gave no significant information.

Thyroid medication was stopped and the basal metabolism, two days later, was minus 4 per cent. An electrocardiogram showed auricular fibrillation. A roentgenogram of the chest showed a large heart with marked fibrosis extending well out to both lung areas. Urinalyses gave normal findings. The Mosenthal test showed the kidneys to have good concentrating power. Blood counts gave normal findings. Blood Wassermann and Kahn tests gave negative results. The blood sugar and blood urea were normal.

A right lobectomy was performed on the ninth hospital day and left lobectomy on the tenth day, the wound being closed on the following day.

The postoperative convalescence was uneventful. The patient received 5 grains of desiccated thyroid daily after operation, and the basal metabolism on the third day was zero. The heart did not become regular following the operation and since the patient was sensitive to quinidine this method of converting the fibrillation to a normal rhythm could not be used.

The lobes of the thyroid weighed 230 and 425 Gm. respectively. All of the tissue that was removed was made up of adenomata, which varied greatly in size, most of them being filled with deeply staining colloid and lined with flat, cuboidal cells.

The patient was discharged on the seventeenth hospital day and 3 grains of desiccated thyroid per day were prescribed. In December, 1931, the patient weighed 226 pounds. He was feeling well, was able to walk much more rapidly and farther than before without discomfort or fatigue. His heart remained irregular but there was no pulse deficit.

Discussion.—This case illustrates the facts (1) that marked cardiac damage may be associated with a large adenomatous goiter in a case

in which hypothyroidism has been present for many years and (2) that some cardiac improvement results from the removal of such a goiter.

Goiter may occasionally be associated with tachycardia without any other sign of cardiac damage and either without any history or signs suggesting hyperthyroidism, or with only vague suggestive points in the history.

Tachycardia may be due to many other causes than thyroid dysfunction but in our experience these have not given rise to any difficulty in the differential diagnosis of hyperthyroidism. The tachycardia which is due to myocarditis from various causes, or to the use of caffeine or nicotine, will not be discussed further.

Cases of hyperthyroidism are occasionally seen in which the pulse rate is normal or below. In the presence of other evidence this finding must be disregarded. Usually when a pulse rate of 68 or 72 occurs in a case of hyperthyroidism it will become much slower after thyroidectomy.

If the patient is at rest, the appearance of the pulse rate on the graphic chart has considerable significance. In hyperthyroidism the pulse varies somewhat but the lessening of the rate is progressive, a level not being reached for from two to fifteen days according to the severity of the disease. In such conditions as neurocirculatory asthenia there is great variation in the pulse rate and although it may reach a normal level during the first hour of hospital rest, it may be faster on the third or fourth day.

HIGH BASAL METABOLISM IN CONDITIONS OTHER THAN HYPERTHYROIDISM

A less important group of conditions than those described above are those in which neither symptoms nor signs would lead to the diagnosis of hyperthyroidism but in which the basal metabolism is persistently high. The two conditions in which this phenomenon is likely to cause confusion are severe arterial hypertension, and organic heart disease in cases similar to that of aortic regurgitation cited above. In both these conditions it is probable that the metabolism is never basal, although repeated readings may be plus 25 per cent or more; it may even be as high as plus 40 per cent in some cases.

In cases of cardiovascular disease of sufficient severity to be associated with a persistent elevation of metabolism, it is usually apparent that the increased cardiac activity and dyspnea may themselves

be important factors in the production of this high rate of metabolism. In cases in which a high basal metabolism is associated with hypertension of the essential type or with hypertension due to vascular or renal disease the diastolic pressure is usually above 100. The retinal vessels will probably show moderate or marked degenerative changes. The urea clearance and the phenolphthalein and other kidney tests will show reduced function or there may be urinary changes and nitrogen retention.

Elevation of the basal metabolism may occur in the presence of encephalitis as mentioned above, of lymphosarcoma, carcinoma, especially of the liver, leukemia, polycythemia, and acromegaly and in other diseases. Pernicious anemia is said to cause an elevated metabolism.[5]

WEIGHT LOSS WITHOUT OBVIOUS CAUSE

The one condition besides hyperthyroidism which is characterized by loss of weight in spite of a good appetite is diabetes mellitus. A trace of sugar in the urine or a slightly elevated blood sugar two and one-half hours after a meal should suggest not only diabetes but hyperthyroidism or perhaps some other glandular disorder as a possibility. If the glucose tolerance curve rules out diabetes but is higher than the average normal, hyperthyroidism is still suggested as Henry John has so clearly shown (Chapter XVII). If diabetes is present its frequent association with hyperthyroidism should be borne in mind.

In conclusion, let us state that with a painstaking history, careful physical examination and repeated basal metabolic estimations the diagnosis of hyperthyroidism is rarely in doubt. The differential diagnosis, however, is not infrequently difficult. It is hoped that such a review as is given above, of types of cases in which the differential diagnosis has been difficult for us, and the account of some of our own errors and of the errors of others which have come to our attention, may serve to emphasize some of the possible pitfalls in the differential diagnosis of this interesting and common disease.

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CHAPTER IX

HYPERTHYROIDISM IN CHILDREN

ROBERT S. DINSMORE

Etiology.—Formerly, it was considered that hyperthyroidism in children of fourteen years of age and under was of comparatively rare occurrence, but our experience in the past few years has led us to believe that the disease is not uncommon in children, as we are seeing cases of this kind with apparently increasing frequency.

It is not within the province of this discussion to review the various theories and hypotheses regarding the etiology of hyperthyroidism which have been presented, nor to review the history which has been so adequately covered by Helmholtz.[1]

Means[2] has discussed the two most prevalent views of Marine and Plummer very adequately and briefly, and makes the following pertinent statement: "It is evident that no one knows the primary cause of hyperthyroidism although there are those who believe that the thyroid is guilty of any one of the following disorders, or of both of the latter two: Hypofunction, dysfunction, and hyperfunction." In considering a group of children, however, it is especially interesting to consider the possible contributing factors in the production of the disease.

In reviewing the histories of a group of these children an hereditary or familial factor occasionally presents itself. Dr. Crile operated on a child fourteen years of age in whom a marked exophthalmic goiter was present, whose mother and maternal grandmother had also been operated upon by him for the same disease. I once operated on a Jewish boy fourteen years of age, who showed all the typical signs of hyperthyroidism. This lad had a brother two years younger in whom an exophthalmic goiter developed at exactly the same age, fourteen years. In three other cases, the mother of a child with exophthalmic goiter had had the disease, and in one case, that of a boy, the father also had hyperthyroidism and was operated upon later. In one case,

a mother's brother, and in another case, the sister of the mother, had an exophthalmic goiter.

The so-called "constitutional factor" is probably not very important in the case of these children, because in most instances the history is that the child was perfectly well until the onset of the disease. In certain of the cases, however, the statement has been made by the parents that the child has always been of a nervous temperament. In most instances the disease developed in apparently healthy children. In one very severe case of hyperthyroidism, the child also had a spastic paraplegia. In only one case did the child have an accompanying endocrine disorder. This girl presented all the symptoms of true hyperthyroidism together with evidence of accompanying hypopituitarism. She had a very fine soft skin, typical hyperplasia and hypertrophy of the breasts and a tendency to overweight. I have never been able to come to the conclusion that the administration of iodine as a preventive measure is a factor in the production of hyperthyroidism in children. Personally, I do not believe that iodine medication has either produced or lessened the incidence of the disease in children.

The racial factor is about the same as in adults. In our series of cases, the majority of the children were American born, of mixed parentage. Many of these children have parents of some middle European nationality. I have seen the condition in an Italian child of eight. Seven cases occurred in Jewish children. I have seen only one case in a negro child and only one in which the parents were Scandinavians.

In a few of the cases the disease followed an infection, and in the case of one child who had had scarlet fever, followed by eight months of pyelitis, hyperthyroidism developed with a very abrupt onset and a rapidly progressive clinical course. In some cases in which there had been a previous enlargement of the thyroid gland, the disease apparently developed following an attack of influenza. In one case the disease followed an attack of whooping cough. In another case, the parents were quite insistent that the disease followed tonsillectomy, and in still another, in a patient who had had a thyroid enlargement, the symptoms developed after an injury to the knee.

Geographically, our cases have come, for the most part, from the area about Cleveland, 43 having come from Ohio, Pennsylvania, and western New York, 3 from Indiana, 3 from Michigan, and single cases from West Virginia, Illinois, Louisiana, Wisconsin, and Wy-

oming. Most of Helmholtz's cases came from Minnesota, Iowa, Illinois, and Wisconsin, the remainder coming from scattered localities in other states and Canada.

Sequence of Symptoms.—In studying the onset of symptoms I find that it is very difficult to give absolute statistical percentages, owing to the confused statements made by the parents. The following figures must therefore be regarded as approximations only.

In approximately 70 per cent of our cases, either nervousness or enlargement of the gland was the first symptom noted by the parents. The incidence of each of these two symptoms as the initial symptom was about equal, namely, 35 per cent. Usually, the parent was unable to state whether the fulness of the neck or the nervousness appeared first. In seven of the histories, it was stated that the enlargement of the neck and the nervousness appeared at the same time.

In only one case was exophthalmos noted as the first symptom, although in two other cases its onset was noted at the same time as that of the enlargement of the gland.

In four cases, tachycardia was noted as the primary symptom, and in two, the first symptom that attracted the attention of the parents was shortness of breath on slight exertion. Loss of weight was the primary symptom in one case. In one case in which the disease followed whooping cough, the parents insisted that all the symptoms appeared at the same time, nervousness, enlargement of the neck, exophthalmos, tachycardia, and other signs.

Owing to the inaccuracies mentioned above, I am coming more and more to the belief that, as far as the sequence of symptoms is concerned, exact statistics will be fairly difficult to obtain. In general, however, it may be stated that usually enlargement of the gland and nervousness appear first, followed by tachycardia and exophthalmos, although sometimes the onset of these symptoms is reversed. One child of four years of age had had a rapid heart for a year, followed by the enlargement of the gland and exophthalmos.

Diagnosis and Symptomatology.—The diagnosis of hyperthyroidism in a child is extremely easy in most instances. As a matter of fact, these patients frequently come in with the diagnosis already made, and in the typical case, even the casual observer can identify the disease. It is not within the scope of this chapter to offer a detailed description of the typical symptoms presented by these children; among the most common symptoms are extreme nervousness,

easy excitability, great irritability, and the tendency to cry over the most trivial circumstances. In reviewing the symptoms presented by this group of cases, as given in the following table, I have found that they conform very closely to those listed by Helmholtz.

	Helmholtz 40 cases, per cent.	Cleveland Clinic 53 cases, per cent.
Tachycardia	100	100
Nervousness	93	91
Thyroid enlargement	93	93
Exophthalmos	83	76
Bruit	70	49
Hyperhidrosis	67	55
Tremor	57	66
Loss of weight	53	50
Polyphagia	50	40
Weakness in quadriceps	47	
General weakness	..	58
Gastro-intestinal symptoms	47	43
Dyspnea	40	55

Tachycardia was present in every case both in Helmholtz's series and in our own. The average pulse rate was 129, but the rate varied from 100 to 180. Nervousness and enlargement of the thyroid gland were present in nearly every case. It is interesting to note that the incidence of bruit in our cases is much lower than that cited by Helmholtz. In the last group of cases that I have seen, however, I have noted that this symptom was present. I attribute this relative absence of bruit in our series to the fact that these children had taken iodine, some of them for a fairly long period of time and the gland had become involuted and very firm.

In approximately two-thirds of these children, tremor had been a definite symptom, but the slight tremor which some of these children had may have been misinterpreted. Especially was this true in some of the borderline cases in which the tremor of a residual chorea had to be ruled out.

Weight loss had occurred in about half of the cases, in some instances amounting to as much as 20 pounds. The weakness of which these patients complained was often a very noticeable symptom and in some cases myasthenia was very marked. Helmholtz called attention to the presence of a weakness of the quadriceps femoris in these children. If a child with exophthalmic goiter is asked to step upon a chair, he must get a start and steps up with a quick effort, while the average child steps up without effort and raises himself slowly.

The other symptoms are those seen in the typical case of hyperthyroidism and need not be commented upon here.

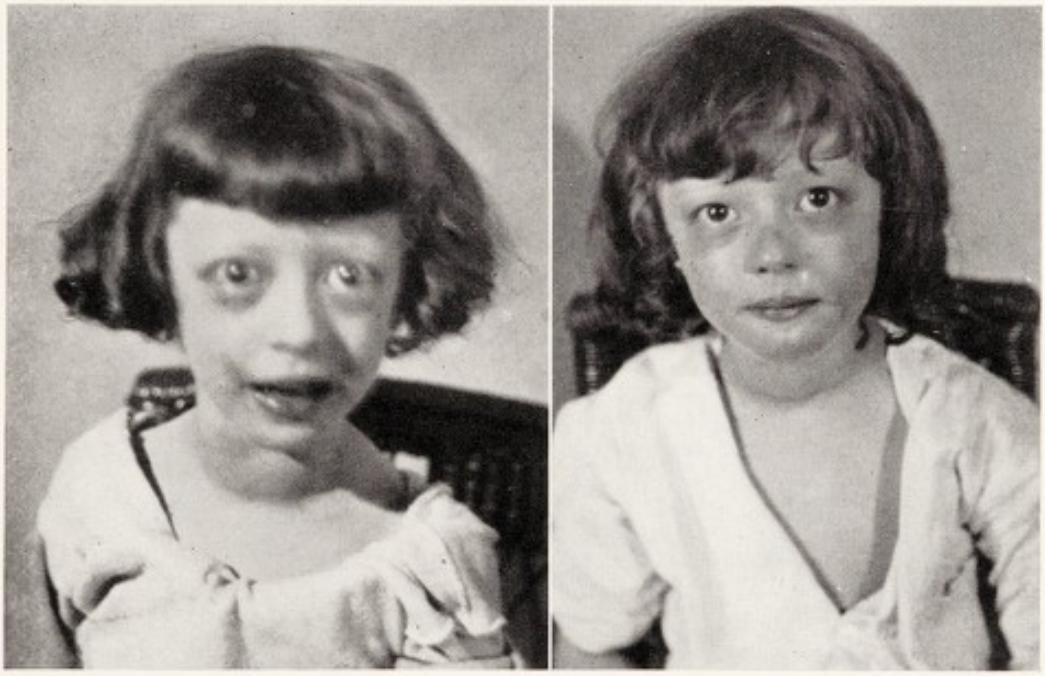
The duration of symptoms may be from a few weeks to several years. In some cases in which the disease has been present for a long time, it may be difficult to get an accurate history of the onset from the parents. Thus in one instance, it was stated by the parents that all symptoms started abruptly and appeared within a fourteen-day period. In 65 per cent of our cases, the disease appeared between the ages of twelve and fourteen years; in the other 35 per cent, it developed between the ages of four and ten years. In one case, that of a child four years of age, there was a perfectly definite history that the disease had been present since the age of two years, the clinical history forwarded with the patient verifying this statement.

We feel that in hyperthyroidism in children, operation is indicated, and the results of this treatment have been most gratifying. The preparation of these patients for operation is a distinct problem and requires a great deal of time and patience upon the part of the hospital staff, and especially of the anesthetist. The children are extremely excitable and do not take general inhalation anesthesia well. They are apt to have a rather severe reaction after deep anesthesia, even though they have been carefully prepared for it, and for this reason, we operate under local anesthesia and light nitrous oxide analgesia.

As stated above, these children are very nervous. They are therefore extremely apprehensive, and their confidence and cooperation must be obtained. The anesthetist, who must be someone who is particularly interested in children, spends much time with each child before the operation, sees him frequently, and becomes his chum and boon companion. The child is made familiar with the anesthetic mask and is put under light inhalation anesthesia. As the result of this preparation most of our children have behaved extremely well while the operation was being done.

Prioleau[3] has described in detail the routine which we use and has especially emphasized the fact that the child's fear of an operative procedure in many instances is the unfortunate result of inadvertent statements about operations made in their presence by their parents.

Treatment and Reactions.—Formerly it was the practice to perform ligations in these cases and then to send the child home for a three months' period, but in our latest series we have been able to perform a lobectomy or a thyroidectomy in practically every case.



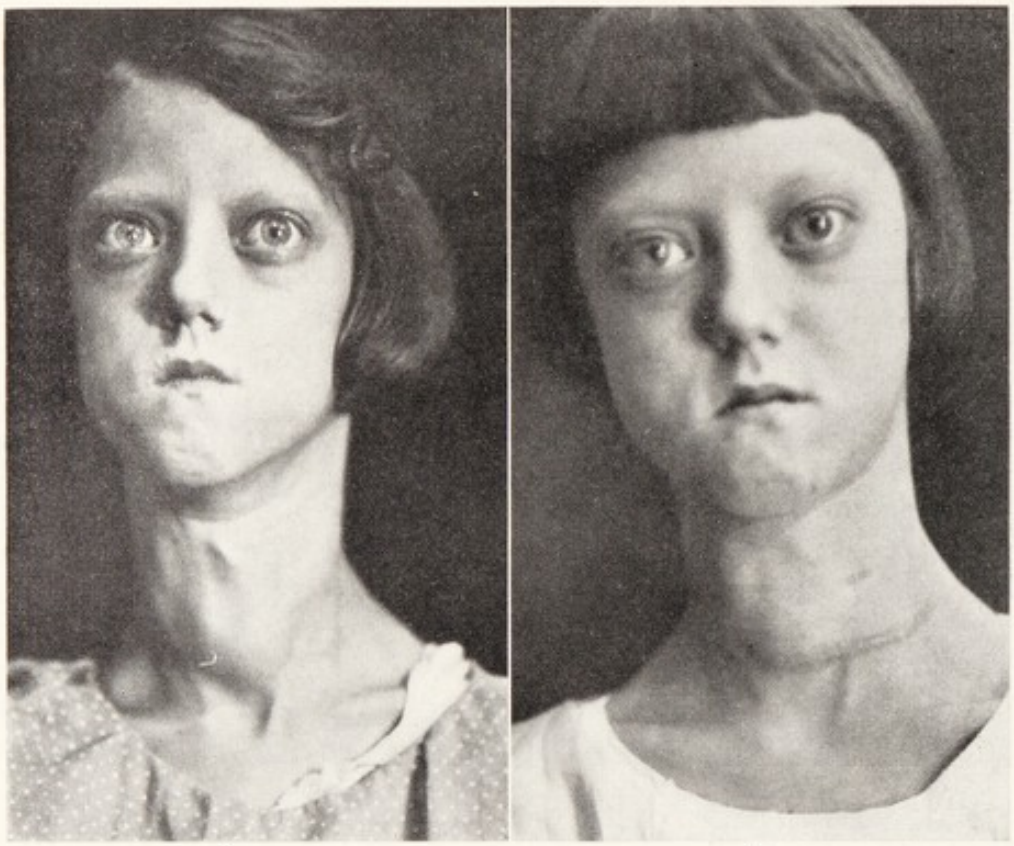
A B

Fig. 25.—Result of lobectomy in a case of hyperthyroidism in a child four years of age. An abnormally fast heart was first noted one year before photograph A was taken. Five months later exophthalmos and enlargement of the gland developed. The child had taken iodine for seven months and received six *x*-ray treatments. Photograph B was taken three months after lobectomy.

It must be remembered that for some reason, the improvement which follows ligation is very definite. I have always felt that in children this improvement is greater than that seen in the average adult. Therefore, this procedure should not be discarded in favor of a lobectomy if there is any doubt as to the wisdom of the latter as the primary operation.

The technical problems are the same as those encountered in adults with the exception that great care must be taken to leave enough tissue for the normal needs of a child for it must be remembered that

hypothyroidism is extremely likely to develop in these cases. A fairly marked reaction often occurs, that is, all the symptoms are intensified, and it is interesting to note that often these children do not appear to be as ill as the chart would indicate. Very marked tachycardia may develop, and a high temperature and flushing may appear, but still the child will say that he feels all right, and he is bright, alert, and able to take fluids without difficulty.



A B

Fig. 26.—Result of lobectomy in a case of severe hyperthyroidism in a child ten years of age. A, Photograph taken before operation. B, Photograph taken fifteen months after left lobectomy.

The immediate recovery from the operation is often astonishingly rapid, and when the patient is seen at the end of a few weeks, practically all of the symptoms with the exception of the exophthalmos, will have disappeared (Figs. 25, 26).

Ultimate Prognosis.—Although these children usually leave the hospital with a small hairline scar that can hardly be seen, within a very few weeks the scar may become red and tender and a true keloid may develop. The incidence of this sequence is very high in these cases and in the past three years, I have seen only one case in which

a keloid did not develop in the scar. This condition is best treated with Grenz ray, which is giving very satisfactory end-results. I think the general statement may safely be made that the older the patient, the better the operative scar.

We are very frequently asked what the ultimate outcome will be in the case of these children. I have followed some of these cases

Fig. 27.—Photograph of a patient eighteen years of age taken five years after lobectomy.

for years and as far as I can tell, the individuals are perfectly normal in every respect except that slight transient hypothyroidism is prone to develop from time to time.

Some of our earlier patients are now in college and are perfectly normal individuals except that they may have to take small amounts of thyroid extract from time to time (Fig. 27).

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CHAPTER X

THE BLOOD PICTURE IN HYPER- AND HYPOTHYROIDISM

E. Perry McCullagh and James H. Dunlap

The report presented in this chapter is based on a study of 1200 routine blood counts which were made in consecutive cases of hyperthyroidism seen at the Cleveland Clinic previous to January, 1930, and on the counts made by one of us (J. H. D.) in a number of smaller groups. Differential counts were made in 266 of these cases.

The average count for the whole group is as follows:

Hemoglobin	82.5
Erythrocytes	4,555,154.0
Leukocytes	7,034.0

For the 266 cases in which differential counts were made the average results were as follows:

Leukocytes	7954.7
Polymorphonuclears (relative)	62.21
Polymorphonuclears (absolute)	4948.7
Eosinophiles (relative)	0.49
Eosinophiles (absolute)	39.4
Basophiles (relative)	0.09
Basophiles (absolute)	7.5
Lymphocytes (relative)	30.3
Lymphocytes (absolute)	2412.3
Monocytes (relative)	5.7
Monocytes (absolute)	460.5
Transitionals (relative)	0.9
Transitionals (absolute)	75.5

From these results it appears that the red and white cell counts are normal. There is an absolute and relative increase both of monocytes and lymphocytes and a relative and slight absolute decrease in the number of polymorphonuclear neutrophiles and to a less degree of the eosinophiles or basophiles.

In order to study the relationship between the polymorphonuclear and lymphocyte counts two smaller groups were arranged. The fifty counts in which the number of leukocytes was greatest were grouped together. The average count was as follows:

Leukocytes	11,974.0
Polymorphonuclears (relative)	68.7
Polymorphonuclears (absolute)	8,232.4
Lymphocytes (relative)	26.0
Lymphocytes (absolute)	3,113.8
Monocytes (relative)	4.5
Monocytes (absolute)	539.8

If 5000 is considered an approximate average neutrophile count, it will be seen that the polymorphonuclears have increased by more than 3000 cells. On the other hand, the lymphocytes with a normal average in the neighborhood of 1500, have been increased in number by only slightly over 1600 cells. In this group, then, the absolute lymphocyte count is actually greater than the average for the total series. The increase in the number of polymorphonuclears, however, is so great that the relative number of lymphocytes becomes less than the average number for the whole group.

Compare the above figures with those of the averages in a group composed of the 50 lowest white cell counts.

Leukocytes	4985.0
Polymorphonuclears (relative)	57.8
Polymorphonuclears (absolute)	2861.3
Lymphocytes (relative)	36.4
Lymphocytes (absolute)	1817.5
Monocytes (relative)	4.7
Monocytes (absolute)	234.8

In this group the facts pointed out above are emphasized. The number of polymorphonuclears has fallen to more than 2000 below the normal average, while the absolute number of lymphocytes is still definitely above the usual count. Obviously then in hyperthyroidism those blood counts in which leukopenia is present will demonstrate a greater lymphocytosis than those in which no leukopenia is present. This fact is accounted for by the relatively greater fluctuation of the polymorphonuclear cells.

Since an increased number of lymphocytes has been shown to be more common when hyperthyroidism is present than in the normal

individual, it must have some diagnostic value. The frequency with which lymphocytosis may be present in hyperthyroidism is indicated by the count in a series of 266 cases as shown in the following table:

Relative small lymphocyte count, per cent.	Number of cases.	Relative number of cases, per cent.
0–15	12	4.5
15–19	13	4.8
20–24	33	12.4
25–29	48	18.0
30–39	84	31.5
40 and above	76	28.5

Thus in 78 per cent of these 266 cases the relative lymphocyte count was 25 per cent or above. In 60 per cent of the cases it was 30 per cent or above.

A few groups of cases were selected in which the average height of the basal metabolic rate varies greatly in order to determine whether or not the degree of lymphocytosis is directly related to the severity of the disease.

The first group comprised 36 cases of mild hyperthyroidism. The basal metabolic rate in these cases varied between plus 18 per cent and plus 30 per cent. This group does not include those cases in which the metabolism was below plus 18 per cent because it was felt that below this level there was a greater possibility of error in the diagnosis. It was thought that a metabolic rate of below 30 per cent would be the best index in selecting mild cases. The duration of the disease was not considered in this group. The clinical diagnosis was that of hyperthyroidism in each instance. The counts were not taken during fasting. All were done within twenty-four hours of the basal metabolism estimation.

Leukocytes	8574.0
Polymorphonuclears (relative)	68.1
Polymorphonuclears (absolute)	5836.0
Lymphocytes (relative)	26.3
Lymphocytes (absolute)	2257.0
Monocytes (relative)	4.6
Monocytes (absolute)	398.0
Transitionals (relative)	0.9
Transitionals (absolute)	88.0

Here we see a total white count which is somewhat above the average. The absolute number of lymphocytes is raised more comparatively than the polymorphonuclears. There is, however, no relative lymphocytosis.

The next group is composed of 36 cases of moderate and severe hyperthyroidism. The basal metabolic rate in these cases was plus 40 per cent and above. No cases with outstanding infection or complications were included. The blood counts are not on fasting blood and were taken the day preceding the basal metabolism estimation.

Leukocytes	7207.0
Polymorphonuclears (relative)	62.1
Polymorphonuclears (absolute)	4478.6
Lymphocytes (relative)	31.5
Lymphocytes (absolute)	2271.0
Monocytes (relative)	5.3
Monocytes (absolute)	386.0
Transitionals (relative)	0.9
Transitionals (absolute)	71.0

A comparison of the results in these severe cases with those in the previous group shows that the absolute lymphocyte count is very close to that found in the mild cases. In this group, however, there is a much lower polymorphonuclear count resulting in a lower total leukocyte count and mild relative lymphocytosis.

A third group was selected comprising 17 cases in which death resulted from hyperthyroidism before operative interference was attempted. This group includes no cases in which a complication was a contributing factor except in the case of those changes which appear immediately preceding death. The blood counts were taken from one to seven days before death.

Leukocytes	9391.0
Polymorphonuclears (relative)	73.0
Polymorphonuclears (absolute)	6861.8
Lymphocytes (relative)	19.4
Lymphocytes (absolute)	1828.3
Monocytes (relative)	6.8
Monocytes (absolute)	649.2
Transitionals (relative)	0.4
Transitionals (absolute)	45.4

Here again the low relative lymphocyte value is not so much due to any great change in the absolute number of lymphocytes as to the marked rise of polymorphonuclears.

The fourth group comprises cases of postoperative hypothyroidism. Fifty-one cases are included in which the basal metabolic rate varied between minus 15 per cent and minus 30 per cent, the average rate being minus 23.2 per cent. The blood counts in these cases were done on fasting blood on the morning of the metabolism test.

Leukocytes	8333.0
Polymorphonuclears (relative)	62.0
Polymorphonuclears (absolute)	5168.6
Lymphocytes (relative)	29.9
Lymphocytes (absolute)	2495.1
Monocytes (relative)	6.9
Monocytes (absolute)	575.4
Transitionals (relative)	0.2
Transitionals (absolute)	21.6

The same comment may be made here as in the case of the previous groups. It appears to be obvious, then, that the relative lymphocytosis bears a very close relationship to the total white count and especially to the absolute number of polymorphonuclears present. It bears little or no relationship to the severity of the disease.

Let us now examine a group of 28 cases which were selected with the purpose of determining whether or not the relative lymphocyte count bore any definite relationship to the degree of hyperthyroidism in individual cases. Cases were selected in which after one night's bed rest in the hospital the basal metabolic rate was in excess of plus 40 per cent.

	Preoperatively.	Postoperatively.
Basal metabolism	56.4	10.9
Erythrocytes	4,540,000.0	4,408,000.0
Leukocytes	6730.0	7460.0
Polymorphonuclears (relative)	63.2	70.2
Polymorphonuclears (absolute)	4253.0	5236.0
Lymphocytes (relative)	33.4	26.0
Lymphocytes (absolute)	2247.0	2039.0

In these cases a blood count was done (fasting) immediately following the metabolism test. Five days after thyroidectomy, if the wound had healed *per primam*, the basal metabolism test and blood

count were repeated as before. The results are synopsized in the table on page 148 which represents the average heights of metabolism and average counts on admission and five days postoperatively.

The relative number of lymphocytes showed an average decrease postoperatively, but there was a very slight decrease in the absolute number. There was a definite increase in the absolute and relative number of neutrophiles.

The relative number of lymphocytes was decreased postoperatively in 22 of the 28 cases or 78.5 per cent of the cases. Thus the relative number of lymphocytes may serve as some guide as to improvement in single cases.

Since the foregoing data have all been based on blood counts made in a routine manner it was felt that it would be interesting to check these results against a much smaller series made in a more painstaking way by the same individual each time. The counts in each group were all made at about the same time of day and with the same instruments each time.

The following groups were arranged: (1) Twenty unselected cases of hyperthyroidism, (2) 12 cases in which counts were made before and after thyroidectomy, (3) 20 cases of postoperative hypothyroidism, and (4) 10 cases of hyperthyroidism and 10 cases of hypothyroidism in which filament, nonfilament counts were made.

The following reports are based on the findings in these groups:

Group I. Twenty Unselected Cases of Hyperthyroidism.—The average basal metabolism was plus 42.7 per cent.

Leukocytes	6710.0
Lymphocytes (relative)	38.5
Lymphocytes (absolute)	2343.0
Polymorphonuclears (relative)	51.2
Polymorphonuclears (absolute)	3435.0
Erythrocytes	4,497,000.0
Hemoglobin (Haden-Hausser instrument)	77.3
Volume index	0.94
Color index	0.86
Saturation index	0.9

In 55 per cent of the cases the hemoglobin was below 80 per cent. In 7 cases the volume index was below 0.9 and in 3 cases it was above 1.

In 13 cases—65 per cent—the color index was below 0.9; in 2 cases it was below 0.8, and in 2 cases it was above 1.

In 7 cases—35 per cent—the saturation index was below 0.9.

A consideration of the initial differential counts in this group shows that in 18 or 90 per cent a relative lymphocytosis of 30 per cent or above was present, and that in 45 per cent a relative lymphocytosis of above 40 per cent was present. Of the latter group, in 7 there was an absolute increase in the number of lymphocytes as compared with the normal count, and as compared with the average absolute count of the series (2343). Of these 7 cases in which a relative lymphocytosis of 40 per cent or above was present, in each there was an absolute decrease in the number of polymorphonuclear cells.

In 80 per cent of this series the relative polymorphonuclear count was below 60 per cent. The average absolute polymorphonuclear count was 3435.5 which is 1334 less than the accepted average normal count.

The monocyte, eosinophile, and basophile counts were essentially normal.

Group II. Twelve Cases—Counts Made Before and After Thyroidectomy.—In this group the blood counts were made on the admission of the patient to the hospital, and repeated from four days to one and one-half months postoperatively. In all cases the basal metabolism had become greatly reduced between the time of the first and the last blood counts. In 6 cases there was an increase and in 6 there was a decrease in the absolute number of lymphocytes. The relative lymphocytosis was reduced in every case, however, obviously because of a comparable rise in the polymorphonuclear count.

Group III. Twenty Cases of Postoperative Hypothyroidism.—The average basal metabolism in 19 cases of this series was minus 23.1 per cent. The average counts were as follows:

Leukocytes	6905.0
Lymphocytes (relative)	36.5
Lymphocytes (absolute)	2453.5
Polymorphonuclears (relative)	56.2
Polymorphonuclears (absolute)	3929.5
Erythrocytes	4,611 700.0
Volume index	0.95
Color index	0.87
Saturation index	0.88
Eosinophiles, monocytes, and basophiles	Normal in all cases
Hemoglobin	80.0

In this group in only 3 cases was the erythrocyte count below 4,000,000. The hemoglobin average for the series would have been somewhat lower had it not been for one case in which there was a

slight polycythemia of 5,690,000 with a hemoglobin of 104 per cent. In 50 per cent of the counts in cases of hypothyroidism the hemoglobin was below 80 per cent.

In this group the average color index, volume index, and saturation index were all slightly below normal as was the case in the group of cases of hyperthyroidism.

In 5 cases the volume index was below 0.9; in 4 it was above 1. In 12 cases the color index was below 0.9.

Group IV. Filament, Nonfilament Counts.—A filament, nonfilament count was made in 10 cases of hypothyroidism and the average number of nonfilamented cells was found to be 19.3. In each of these cases the total leukocyte count was normal. In 10 cases of hyperthyroidism the average preoperative nonfilament count was 12.3. In these same cases the average postoperative nonfilament count was 12.1.

In one instance the total white cell count was raised to 13,850 postoperatively and the nonfilament count was 25; in the other cases the white cell counts were all within normal limits.

The counts in these selected groups when compared with the routine counts are found to be approximately the same except that in the former series of cases the total leukocyte count is slightly lower, the relative lymphocyte count is a trifle higher, and the relative polymorphonuclear count is slightly lower.

REVIEW OF THE LITERATURE

For many years investigators have sought to establish a definite and constant blood picture whereby they could be aided in the diagnosis and prognosis in cases of hyperthyroidism and hypothyroidism. In 1885, Horsley[1] stated that "marked anemia followed the loss of the thyroid gland." Since that time findings have been reported that run the gamut from marked anemia to no anemia, from lymphocytosis to no lymphocytosis, and from leukopenia to leukocytosis. The conclusions drawn from these varied findings have shown a similar variation; consequently it is difficult for one to reach any definite conclusions from the literature and it was this fact which prompted us to make the investigation here reported.

Some writers have reported normal blood findings in hypothyroidism[3, 4, 5] while others report a mild anemia[6, 7, 8, 9, 10, 24, 39] and still others reported red cell counts varying from 3,000,000 to 4,500,000[11, 12, 13, 14, 15, 16] and lower.[17, 18] Falta[20] and others[12, 21] mention

hemoglobin estimations of below 60 per cent in cases of hypothyroidism and Howard[22] reports cases with a hemoglobin of 75 per cent.

Certain writers have mentioned that in hypothyroidism leukocytosis is present.[2, 12, 21] Normal white cell counts[16, 22] and leukopenia[7, 25, 26, 27] are also reported. Schermann[38] reports that in rabbits a marked reduction in the white blood cells follows thyroidectomy.

Kocher[27] found the eosinophile count to be normal in hypothyroidism, but a few believe that the number of these cells is increased.[7, 26, 20]

Emery[19, 23, 28] states that in myxedema the blood picture is not constant and mentions reduced hemoglobin, a normal white cell count, a decrease in the polymorphonuclear count and perhaps relative or absolute lymphocytosis as frequent findings.

Plummer[43] reported the blood counts in a much larger group of cases of hyperthyroidism than had been reported before and showed that there is a tendency to lymphocytosis, that a relatively low polymorphonuclear count was a large factor in the production of this change and that the degree of lymphocytosis was a poor index as to the degree of duration of the disease.

The statements regarding the blood findings in hyperthyroidism are quite varied. Many writers believe that there is a characteristic blood picture in Basedow's disease[27, 30, 31, 36, 41] which is considered of definite diagnostic importance. Some have declared that the lymphocytosis in hyperthyroidism parallels the severity of the disease.[40] Roth[37] believes that the reduced hemoglobin, leukopenia, and lymphocytosis in hyperthyroidism is of prognostic as well as diagnostic value. Others disagree with these views and state that there is no characteristic blood picture in hyperthyroidism[29, 32, 33, 34, 35] and that the lymphocyte count is not in proportion to the severity of the disease.[42]

CONCLUSIONS

1. In hyperthyroidism, the red blood cell count is normal but there is a slight reduction of hemoglobin.

2. There is a relative lymphocytosis of 30 per cent or above in 60 per cent of the large series of cases of hyperthyroidism and in 90 per cent in the smaller series. The presence of a lymphocytosis is therefore of some diagnostic value.

3. The relative lymphocytosis is dependent on two factors in the blood: (*a*) The absolute lymphocyte rise; (*b*) the total leukocyte count.

The total leukocyte count has been found to be variable, the variation being due chiefly to the variation in the neutrophiles. There is a greater relative lymphocytosis, therefore, in the presence of leukopenia.

4. In 28 cases examined while the metabolic rate was high, and after operation, the average lymphocyte count was found to be lowered by operation. In the majority of cases there was a fall in the relative number of lymphocytes present. In the series of 20 cases counted apart from the routine counts, 50 per cent of the cases showed an absolute increase of lymphocytes postoperatively (counted anywhere from four days to one and one-half months postoperatively), and 50 per cent showed an absolute decrease. All showed a relative decrease.

5. The degree of lymphocytosis on one estimation is not an index to the severity of the hyperthyroidism.

6. The hemoglobin in hypothyroidism is reduced slightly as in hyperthyroidism. The degree of relative lymphocytosis in hypothyroidism is about as high as that in hyperthyroidism.

7. The average nonfilament count in 10 cases of hypothyroidism is higher than that in 10 cases of hyperthyroidism.

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CHAPTER XI

INFECTION AS A FACTOR IN THE PRODUCTION OF HYPERTHYROIDISM

RUSSELL L. HADEN

IN the study of patients suffering from hyperthyroidism, numerous factors in the causation of the clinical picture must be considered and evaluated. The background of the disease is often a gross anatomical change in the thyroid gland with the development of one or more adenomata. In other cases, there is an apparent constitutional disturbance involving the autonomic nervous system, usually present for years, or the engrafting of some other factor which will precipitate the clinical condition which we designate hyperthyroidism.

In considering the etiology of this disease, therefore, it is necessary to separate the background from the precipitating or activating factors. Infection can play but a small rôle in the production of any anatomical change in the thyroid, such as the development of an adenoma. Certain generalized infections, especially influenza, may, however, initiate a disturbance of the autonomic system manifested by sweating, cyanotic extremities, rapid heart action and other evidences of vasomotor instability. In this way infection may become a factor in the background of the disease although it is doubtful if this is ever the sole factor in an otherwise previously normal person. True thyroiditis is probably always the metastatic expression of a primary disease elsewhere in the body which has been carried by the blood stream to the thyroid gland. Hyperthyroidism, however, rarely occurs during the course of an acute thyroiditis and few observers attempt to relate hyperthyroidism to thyroiditis. One must conclude, then, that infection is only a minor factor in the background of the disease.

However, infection must be much more seriously considered as an activating or precipitating factor in the production of hyperthyroidism. All students of thyroid disease recognize this rôle of infection in some measure at least. Means and Richardson[1] list infection

as one of several possible factors which may play a secondary rôle in the production of hyperthyroidism. Foster[2] mentions the occasional association of infection with hyperactivity of the thyroid gland. Rienhoff[3] makes the following statement: "At times infection of the upper respiratory tract such as tonsillitis or sinusitis precedes the symptom of exophthalmic goiter with such regularity that the interrelationship of those diseases would seem to be more than a coincidence." Rienhoff cites in this connection the case of a young man, thirty years of age, in whom exophthalmic goiter immediately followed an attack of acute tonsillitis. The hyperthyroidism was relieved by operation and the patient remained perfectly well for one year. Following an attack of rheumatic fever the clinical picture of exophthalmic goiter again developed. After a course of Lugol's solution the symptoms subsided and the patient remained well. Rienhoff concludes that a generalized or a focal infection may exercise a definite although indirect influence upon the thyroid and certainly must be considered to be one of the etiologic factors in diseases of this gland.

No one of these authors mentions, however, the treatment of focal or other infections as a preoperative or postoperative procedure in the treatment of hyperthyroidism, although some writers have observed cases in which hyperthyroidism developed after an acute focal infection such as acute tonsillitis or acute alveolar abscess, in which recovery occurred spontaneously after the acute infection subsided. Brubaker[4] reports a case of marked hyperthyroidism which followed extensive restorative work on several infected teeth. Immediately after the extraction of the infected teeth the symptoms subsided and complete recovery without other treatment followed. Satke[5] describes several cases of hyperthyroidism which followed infection of the throat or teeth while other etiologic factors were lacking. These patients recovered entirely with no treatment other than the removal of the focal infection. Cases similar to these can be found in any clinic in which large numbers of cases of hyperthyroidism are seen.

If an acute focal infection can activate hyperthyroidism, the long continued absorption of bacteria or their products from a chronic focus of infection must also be a possible activating factor. Very little attention has been given to this phase of the subject.

In order more accurately to evaluate infection as a factor in the production of hyperthyroidism, Dr. H. M. Hinnant has reviewed for me 150 cases of hyperthyroidism recently seen at the Cleveland Clinic.

In 38 cases the active symptoms followed immediately after an acute infection. For the most part, these infections were in the upper respiratory tract and in most of the cases a diagnosis of influenza was made by the attending physician. Other infections recorded were mastoiditis, phlebitis, dental sepsis, and enterocolitis. Definite chronic focal infection was found in 85 cases or 56.7 per cent.

In the group in which no chronic focal infection was present, no recurrence of the hyperthyroidism was noted during a period of two years after thyroidectomy, while in 7 per cent of the patients having definite chronic focal infection the symptoms recurred and a second operation was required.

It seems apparent that the possibility that a focal infection may be present should be considered in planning the treatment of any patient with hyperthyroidism. Since influenzal infections stand out so prominently as an activating factor, patients should be cautioned regarding the care of such infections after thyroidectomy. Immediate bed rest, and proper medical care at the beginning of an influenzal infection may do much to prevent a recurrence of the thyroid disease. Much more can be done as far as chronic foci of infection are concerned. Every patient with hyperthyroidism should be studied to discover whether or not there is present any chronic infection in the teeth, tonsils, sinuses, or genito-urinary tract. It is most unwise, however, to attempt to remove chronic foci of infection before the hyperthyroidism is relieved. After thyroidectomy or the relief of the hyperthyroidism by other means the chronic foci should be removed or treated. The medical after-care of the patient is not complete until this has been done. The proper treatment of such infections should do much to prevent the recurrence of the symptoms of hyperthyroidism.

SUMMARY

Acute or chronic focal infection and generalized infection such as influenza may play a primary rôle in the production of thyroid disease by causing thyroiditis or by upsetting the equilibrium of the autonomic nervous system. However the relation of these infections to the background of hyperthyroidism is relatively unimportant.

Such infections play a much more important secondary rôle since they may activate the symptoms of the disease.

All patients with hyperthyroidism should be carefully studied to discover whether or not any focal infection is present.

A focus of infection should not be removed or treated in the pres-

ence of active hyperthyroidism because of the danger of increasing the symptoms of the disease.

The after-care of patients suffering from hyperthyroidism is not complete until focal infections are adequately cared for.

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CHAPTER XII

CARDIAC DISTURBANCES ASSOCIATED WITH HYPERTHYROIDISM

JOHN P. ANDERSON

IN hyperthyroidism the entire sympathetic nervous system is overstimulated and simple tachycardia is a constant symptom. Electrocardiograms show rapid conduction of impulses and usually an increased amplitude of all complexes. The resting phase is much diminished and may be abolished. In that case the auricular waves follow promptly the cessation of the T waves. The T waves are upright in all leads and are of normal or usually of increased amplitude.

Inspection and palpation of the precordium reveals a rapid diffuse apex impulse situated normally or a little to the left. A systolic thrill is rarely felt.

In well marked hyperthyroidism the blood pressure nearly always shows some alteration. This is demonstrated by a systolic pressure of from 135 to 150 mm. of mercury, which in rare instances may reach 190 mm., while on the other hand the diastolic pressure remains at the usual level or may be reduced to 60 or 50 mm. of mercury. This reduction in the diastolic pressure results in a considerably increased pulse pressure, 70 to 100 mm. Thrills and bruits over the thyroid vessels are very common and they may be present over the peripheral vessels, although capillary pulsation is rare.

Systolic bruits transmitted from the thyroid vessels may frequently be heard at the base of the heart. Aortic murmurs seem not to occur. No diastolic murmurs are present in uncomplicated cases.

Percussion seldom demonstrates any enlargement to the right. There often appears to be some enlargement to the left but this finding is seldom confirmed by *x*-ray examination. The mediastinal dulness is normal. If any widening is present it is not due to the hyperthyroidism, but to some other cause.

Auscultation reveals rapid sounds frequently accompanied by a systolic murmur and sometimes a reduplicated sound. The latter may suggest a mitral stenosis and, especially if accompanied by a systolic thrill, it may be difficult to differentiate this sound except by observations after the hyperthyroidism has been partially controlled.

In our series an enlarged heart was shown roentgenographically in only 6 per cent of the cases in which the heart rhythm was normal and in each instance the enlargement was associated with a diastolic blood pressure of 100 mm. of mercury or more, whereas on *x*-ray examination 60 per cent of the patients with auricular fibrillation were found to have enlarged hearts and in only 8 per cent of these was the diastolic pressure 100 mm. or more.

Endocarditis may be a complication of hyperthyroidism. In uncomplicated cases of hyperthyroidism there is rarely any difficulty in recognizing that the cardiac disturbance is secondary. If, however, the goiter is not palpable and no exophthalmos is present the condition of the heart may be thought to be due to a rheumatic endocarditis with mitral regurgitation, or to a mitral stenosis. I have seen two cases in which rheumatic endocarditis was associated with hyperthyroidism, the diagnosis in both cases being made at necropsy. In the absence of characteristic fever or arthritis there seems to be nothing to attract attention to the endocarditis. Fortunately the combination is rare.

While hyperthyroidism may cause a slight increase in temperature, it is not sustained and any continuous or recurrent fever demands a search for its cause. It is well to remember that more than one condition may be present and if hyperthyroidism be associated with a rheumatic heart it becomes necessary to evaluate the relative amount of trouble referable to the thyroid gland. When definite hyperthyroidism exists I think the thyroid gland should be removed. It is scarcely expected that this will cure all of the symptoms but it does diminish the strain on the already damaged heart.

I can recall only one case in which the usual subacute bacterial endocarditis was associated with hyperthyroidism or had to be seriously considered in the differential diagnosis.

Pulmonary tuberculosis may be associated with considerable tachycardia and when a small goiter also exists the differential diagnosis may be difficult to determine. Again one must keep in mind the possibility of the presence of two conditions and that operation may be advisable.

Sinusitis is another condition that may cause tachycardia and simulate hyperthyroidism; in fact any chronic focal infection may on rare occasions have to be considered in making the differential diagnosis.

In older persons arteriosclerosis with myocardial degeneration may be considered the cause of the tachycardia of hyperthyroidism or vice versa. In some cases it may be difficult properly to evaluate this symptom and a period of close observation will be required before the differential diagnosis can be established.

The tachycardia of neurocirculatory asthenia, or irritable heart is rather frequently encountered and it is often difficult to establish the diagnosis without prolonged observation and therapeutic tests.

In the presence of tachycardia it is well to bear in mind the following differential points:

1. The tachycardia of hyperthyroidism is persistent even when the patient is absolutely at rest while that secondary to infections lessens rather quickly with rest. The blood pressure is very seldom altered in infections or if so, the pulse pressure is not increased.

2. In neurocirculatory asthenia the pulse varies considerably with the position of the patient. The rate may be quite high (130) while the patient is standing, it is moderately increased when the patient is in the sitting posture, and is normal when he is lying down. In the patient with hyperthyroidism this variation does not occur.

3. If tachycardia is not reduced by Lugol's solution or iodine in some form it is very improbable that it is due to hyperthyroidism. The same is true of the pulse pressure and the systolic pressure.

Abnormal rhythms of different types may be associated with hyperthyroidism.

(*a*) *Cardiac extrasystoles* will be encountered in patients with hyperthyroidism with just about the same frequency as in any other patients in the same age group. They seem neither to be aggravated by the hyperthyroidism nor cured by thyroidectomy. Their presence alone is no contraindication for operation.

(*b*) *Paroxysmal tachycardia* seems to be a very rare accompaniment of hyperthyroidism. Personally I have never seen a case of hyperthyroidism in which paroxysmal tachycardia was present although one cannot say with certainty that some of the paroxysmal cardiac attacks which patients often have, may not be of this nature.

(*c*) That *paroxysmal auricular fibrillation* rather frequently occurs in cases of hyperthyroidism has been confirmed by numerous elec-

trocardiographic examinations. The paroxysms may last from a few minutes to many hours.

Inasmuch as fibrillation may last for only a few minutes or may be continuous for years it may be arbitrarily classified as follows:

1. Paroxysmal—lasting for not more than twenty-four hours.
2. Transient—lasting for not more than one week.
3. Continuous—lasting for any period of more than one week.

There is no essential difference between the paroxysmal and the continuous fibrillation except that those patients who exhibit continuous fibrillation are likely to be older or to have a more severe hyperthyroidism. Many patients will exhibit paroxysmal attacks of fibrillation for a considerable time before it becomes continuous.

Auricular fibrillation is secondary to hyperthyroidism in so many instances that when found in a routine examination its presence should at once suggest a careful examination for hyperthyroidism.

In patients past fifty years of age the occurrence of auricular fibrillation in the absence of hypertension will usually be found to be secondary to hyperthyroidism. It is well to keep in mind that in these cases there may be few other signs or symptoms of hyperthyroidism such as a palpable goiter, exophthalmos, sweating or tremors. Loss of weight and increased basal metabolic rates, however, will nearly always be found.

It is also well to keep in mind that patients with apparently simple colloid goiters may for years have a low grade hyperthyroidism or transient attacks of more pronounced hyperthyroidism that pass quite unrecognized until the onset of auricular fibrillation.

One should always keep in mind the possibility that hyperthyroidism may be the cause of cardiac disturbance. One of our patients gave a clear history of the persistence of auricular fibrillation for twenty years and yet no one had ever suggested that this condition might be due to hyperthyroidism.

Auricular flutter may be secondary to hyperthyroidism but in my experience its incidence as compared with that of auricular fibrillation is only as one to two hundred. It may be paroxysmal or continuous. It has not proved to be any more serious or any harder to control than auricular fibrillation. In no case has it persisted after operation.

In one or two cases a rather marked sinus irregularity has been encountered in a patient with an adenoma on the right side of the neck. I have felt that this might be accounted for by irritation of the vagus.

Partial heart block with a rapid rate and also complete auriculoventricular dissociation with a rapid ventricular rate have had to be considered in differential diagnosis.

Cardiac failure occurs in only 3.2 per cent of patients in whom the heart rhythm is normal as compared with 40 per cent in patients with auricular fibrillation. In the majority of these cases the cardiac symptoms disappear during the routine preoperative treatment of hyperthyroidism but when the failure is marked, either a longer preoperative period of rest and treatment is required, or special medication must be used together with treatment for the elimination of the edema.

The preoperative course of patients with anasarca, ascites, and pleural transudate can be much shortened by one or two pleural aspirations, restriction of fluids to 1200 cc. daily, and the intravenous use of novasurol or salyrgan either alone or preceded by ammonium salts. It is rarely necessary to aspirate in a case of ascites and one is often agreeably surprised to find that patients in whom the condition of cardiac failure is so advanced as to appear hopeless will gradually improve and undergo the operation satisfactorily. To accomplish this result, however, usually requires several weeks of careful preoperative treatment.

In a few cases of goiter and in the majority of instances without hyperthyroidism, progressive heart failure gradually develops and the patient may die rather suddenly. We have obtained autopsies in some of these cases and have found cardiac dilatation with marked myocardial degeneration and fibrosis. The cause of the myocardial degeneration in such cases is problematical. All these patients have been in the age period in which arteriosclerosis develops and it would therefore appear that that condition is the major cause of the myocardial degeneration. It is nevertheless impossible to state whether a prolonged mild hyperthyroidism in former years may have been a causative factor and whether the degeneration would have been arrested had the goiter been removed several years before. But certainly after viewing the hearts of such patients one feels assured that no recent operation could have benefited the patient.

There is another group of patients, usually about sixty years of age, with severe hyperthyroidism and persistent auricular fibrillation in which only ligations or a lobectomy has been possible. These patients have returned home and instead of returning at the appointed time have been delayed either by domestic reasons or some

other cause, such, for example, as an accidental fracture as happened in two cases, and have delayed the final lobectomy for approximately a year. Some of these patients withstood the final operation and made a fairly satisfactory recovery and a few did not. These patients all waited too long before applying for surgical treatment and serve to demonstrate the fact that hyperthyroidism can cause and hasten myocardial degeneration.

Angina Associated with Hyperthyroidism.—We have had a few patients who have had paroxysmal irregularity of the heart, some of whom had attacks of severe pain in the precordial area. This pain has centered in the submammary area and axilla and has extended down the left arm rather than to the substernal area. It has been associated with a cold, clammy condition of the skin and with considerable fear. One patient in whom there was no cardiac irregularity had some of these attacks while in the hospital at absolute rest. It was felt that these attacks were due to myocardial exhaustion and were different in nature from a true angina. The electrocardiogram was normal. The usual preoperative routine was carried out and a thyroidectomy was performed without any difficulty after about the usual length of preoperative preparation. There were no more attacks.

These cases are comparable to those in which precordial pain occurs with paroxysmal tachycardia not associated with hyperthyroidism and it is a debatable point whether they should be classed as cases of true angina. Apparently they do not carry the same mortality rate as cases of true angina, and I have therefore considered them separately.

We have had a few patients who had typical angina. That is, there was severe pain of a crushing or pressing type of maximum degree in the substernal area and radiating to the left arm. This pain was induced by effort. One patient in particular had attacks of this nature after entering the hospital which continued to recur until the hyperthyroidism was partially controlled. The operation was then performed and was not followed by any recurrence of the attacks. About eighteen months later the attacks recurred, but much more activity was possible.

Pericarditis with Hyperthyroidism.—There are a few patients who do not seem to respond to the preoperative treatment in whom the heart rate continues very fast in spite of absolute rest, and the use of Lugol's solution, digitalis, and sedatives. One is rather at a loss

to explain this condition until finally a precordial to-and-fro friction rub appears and then one realizes that pericarditis is present. Sometimes this condition clears up without marked pericardial effusion while at other times an effusion develops and adds to the already widened cardiac dulness. An *x*-ray examination in these cases (made with a portable machine) will also demonstrate the effusion. In our series none of these patients has been aspirated.

These patients do not get along very well and require a prolonged preoperative course of treatment so that if an immediate operation is not absolutely essential it is probably best to have them return home for a few weeks or even months. If an operation is done at once it should be only a lobectomy.

Electrocardiograms in these cases often show evidence of myocardial damage such as delayed auricular conduction or extrasystoles resulting from multiple foci. The heart remains enlarged for a long time after thyroidectomy and the cardiac reserve returns very slowly.

The preoperative treatment of cardiac failure includes the following factors:

1. Bed rest.
2. Fluid restriction to 1200 cc. daily.
3. Lugol's solution 5 to 15 minims three times daily.
4. Digitalis 3 grains in tablet form or 2 cc. of standard tincture every four hours for six doses followed by $1\frac{1}{2}$ grains or 1 cc. twice daily.
5. Ammonium chloride or nitrate, 10 to 20 grains every four hours until slight nausea is induced. This is associated with salyrgan or novasurol, 1 cc. intravenously every third or fourth day.
6. Thoracentesis if indicated.
7. Sedatives in sufficient dosage to insure rest.
8. Sometimes an oxygen tent is indicated in extreme cases especially during hot weather.
9. Special care to keep the patient comfortable and to avoid all undue excitement and manipulation.
10. In some cases quinidine may be used to good advantage for transient fibrillation or paroxysmal attacks. We do not use quinidine in cases in which there is continuous fibrillation until from the third to the sixth day after operation.

Auricular Fibrillation.—Auricular fibrillation occurs in from 6 to 9 per cent of all patients with hyperthyroidism, its incidence depend-

ing first, on the duration of the hyperthyroidism, and second, on its severity. In 1928 the incidence of auricular fibrillation in our cases of hyperthyroidism was only 5.87 per cent, but in that year there was an unusually large number of cases in which the symptoms had been present only from one to three months, so that one would expect the incidence to be lowered. In 1930 the incidence of auricular fibrillation was 8.3 per cent and in 1931, 8.9 per cent.

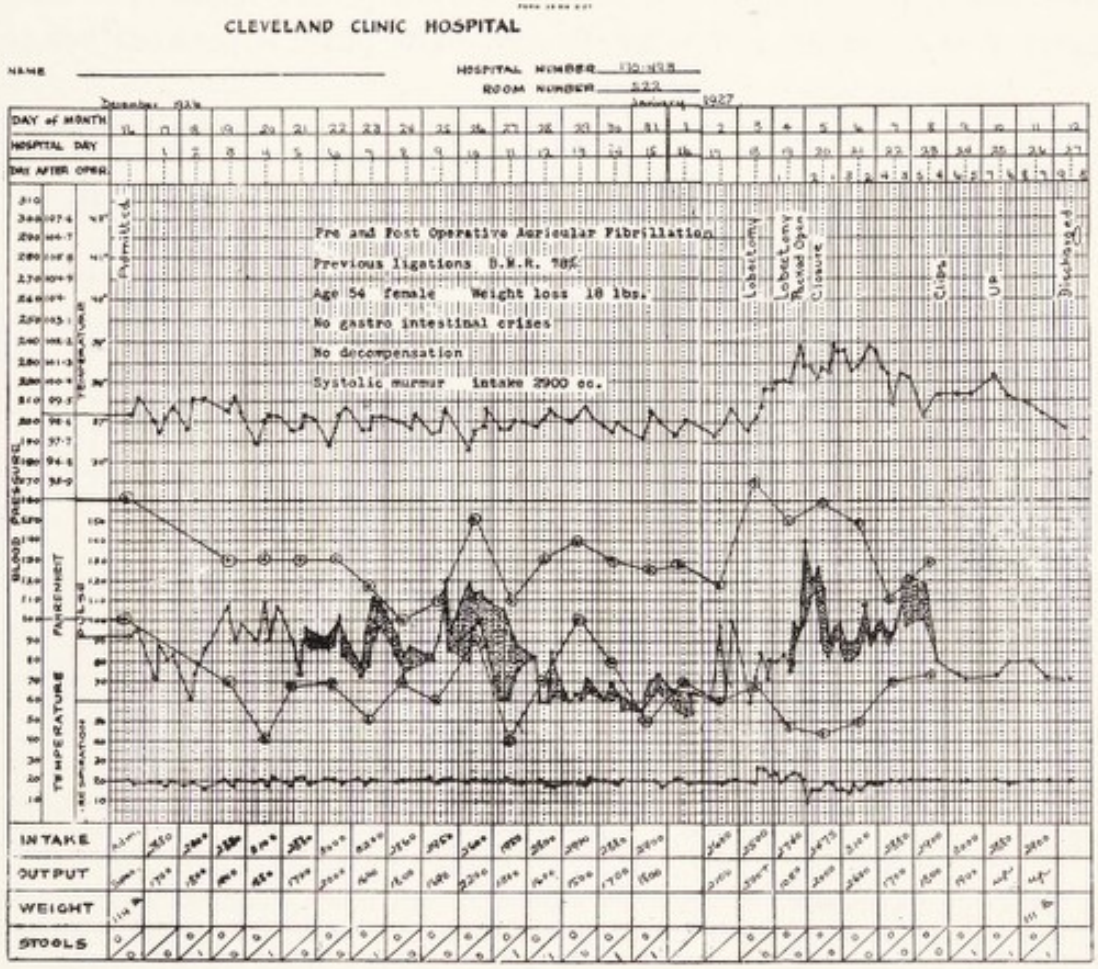

Fig. 28.—Pre- and postoperative auricular fibrillation. The shaded portions of the chart indicate the duration and degree of fibrillation.

Approximately 550 patients with auricular fibrillation secondary to hyperthyroidism have been observed; among these complete thyroidectomies were performed in 426 cases. In 45 per cent of these 426 cases a normal rhythm developed during the first three postoperative days and in an additional 15 per cent a normal rhythm in a longer period. There was no criterion, however, whereby to determine in advance in which cases the rhythm would become normal or the length of time that would be required (Figs. 28–30).

For optimum results quinidine therapy should be started during the decline of the postoperative reaction and we have therefore adopted the following schedule: Every patient in whom auricular fibrillation is present on the third postoperative day is reported and a test dose of quinidine is given on that evening. If no ill effects occur, the regular administration of quinidine is started on the following day. Five grains are administered every four hours day and night for twenty-four hours, then every three hours for twenty-four hours, and then every two hours for forty-eight hours. The pulse is counted before

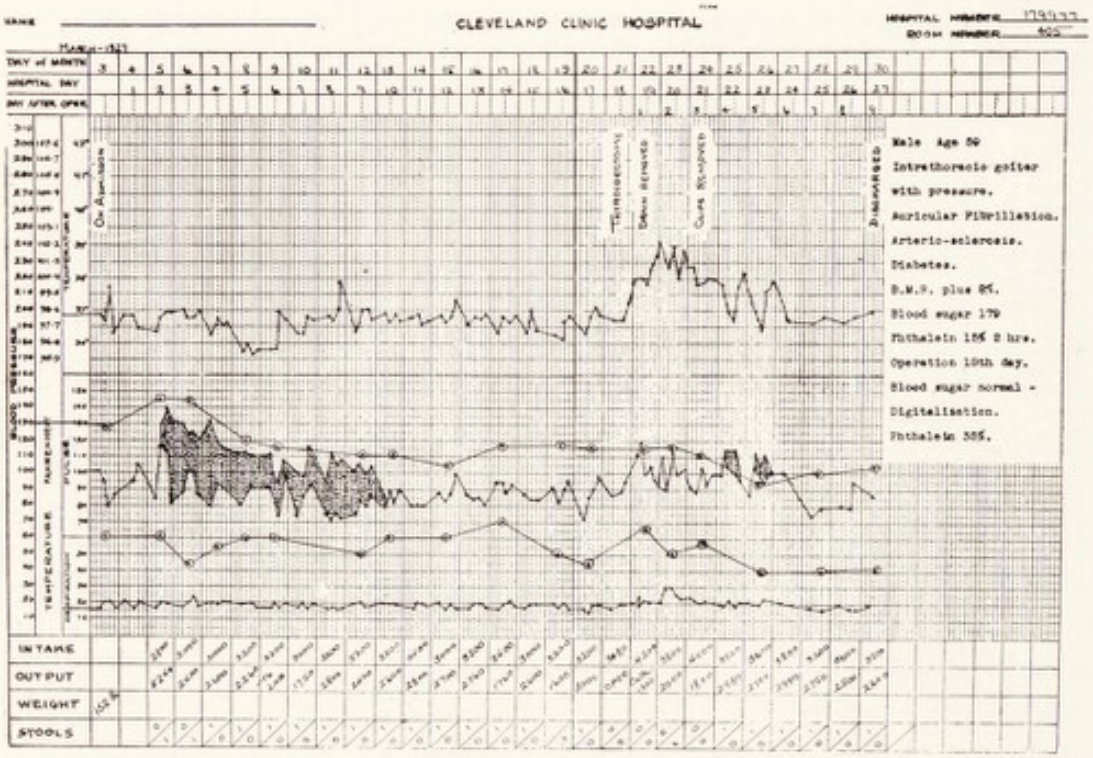

Fig. 29.—Pre- and postoperative auricular fibrillation. The shaded portions of the chart indicate the duration and degree of the fibrillation. It should be noted, however, that fibrillation was present when the patient entered the hospital but it was not charted until the second day.

each dose and if it is found to be regular no more quinidine is given. I have not found that it matters whether or not the heart is thoroughly digitalized at the beginning of the treatment with quinidine or whether digitalis is administered during this treatment, nor is it necessary to give small daily doses of quinidine after the normal rhythm is established.

When all patients who still have auricular fibrillation at the end of the third postoperative day are treated according to the above plan we can expect to establish a normal rhythm in about 90 per cent.

The operative mortality in patients with auricular fibrillation is 3.5 per cent. In 1931 in a series of 34 such cases there were no deaths.

The following question is frequently asked: Will not auricular fibrillation develop again in these patients under any special stress? I am sure that this question can be answered in the negative for I have had only occasional reports of cases in which auricular fibrillation recurred without association with a recurrent hyperthyroidism.

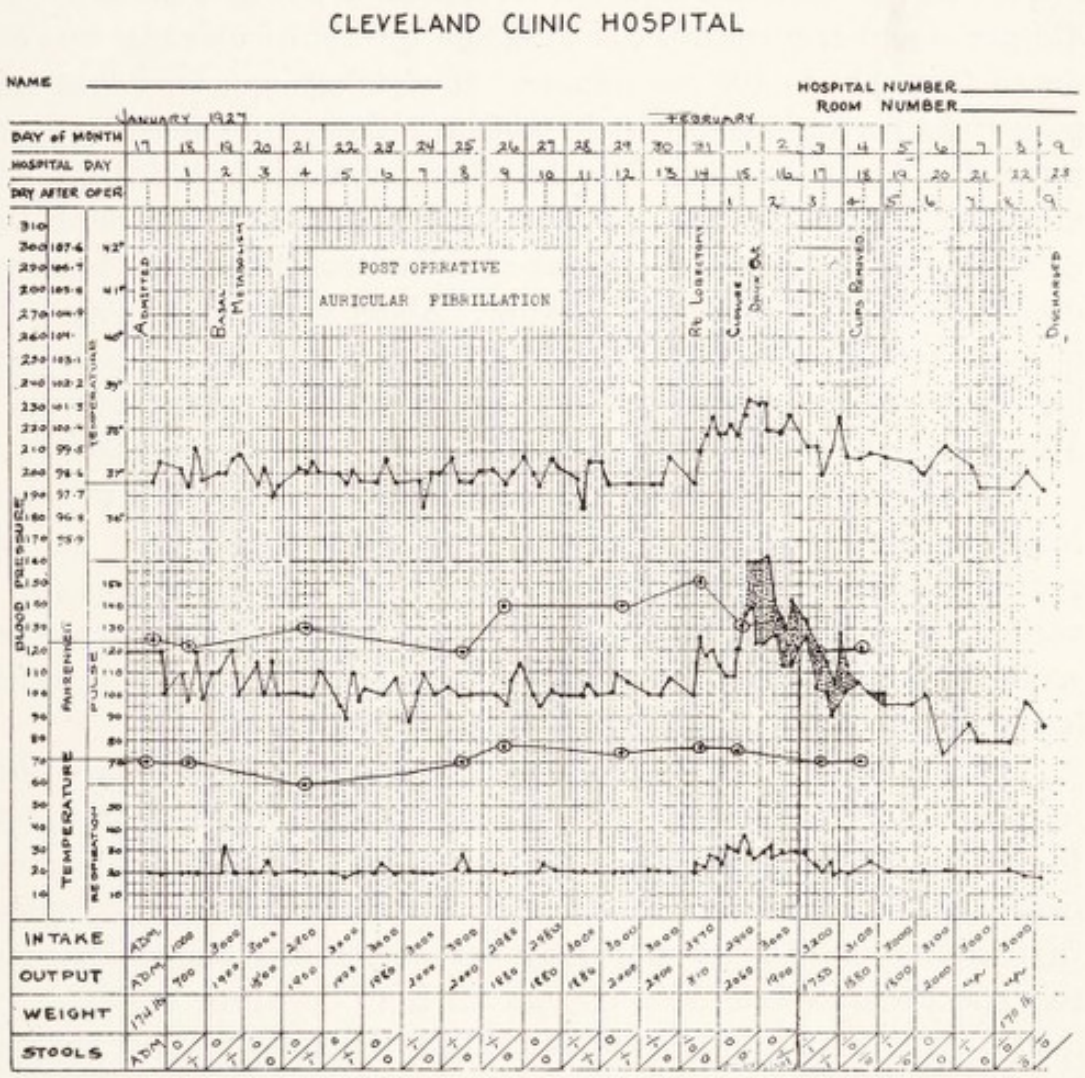

Fig 30.—Postoperative auricular fibrillation. The shaded portion of the chart indicates duration and degree of the fibrillation.

One case may be cited which illustrates very well how stable the heart may become. In this case quinidine therapy was administered and a normal rhythm was established on the third day. A few months later a large fibroid tumor was removed and the operation was followed by general peritonitis and death. For several days the temperature varied between 103° and 105.5° F. and the pulse

rate ranged from 130 to 160, but at no time was there any auricular irregularity.

In one case recurrent auricular fibrillation developed while the patient was taking thyroid extract. The patient was forty-six years of age and symptoms of hyperthyroidism had been present for two years before the thyroidectomy was performed. After the operation the patient continued to be nervous and had a basal metabolic rate of plus 23 per cent and a persistent auricular fibrillation. Digitalis did not completely control this although the ventricular rate was reduced from 130 to 100 per minute. It certainly appeared that this patient had a residual hyperthyroidism although no thyroid tissue was palpable. A course of Lugol's solution was given which did not affect the heart. The patient then received quinidine and with the development of a normal rhythm the nervousness and other symptoms disappeared and she returned to work. About a year later symptoms of hypothyroidism occurred and thyroid extract was prescribed, during the administration of which auricular fibrillation developed. This persisted for about two weeks and then stopped spontaneously.

In another case recurrent auricular fibrillation appeared to result from the administration of iodine. Several months after a normal rhythm had been acquired the patient was under treatment for a varicose ulcer for which large doses of potassium iodide were prescribed. During this treatment auricular fibrillation recurred which lasted for about ten days and then stopped spontaneously.

One patient who had only a lobectomy was given quinidine on the fourth day after operation, and acquired normal heart rhythm, but the next day, auricular fibrillation reappeared. It has been my experience that quinidine therapy is effective only after complete thyroidectomy. The rhythm may become normal temporarily but this effect seldom lasts long enough for it to be worth while.

No routine attempt has been made to obtain a normal rhythm before operation as it seldom persists and the presence of auricular fibrillation with poor compensation seems to be no contraindication to operation. On the other hand, the importance of the prompt institution of quinidine therapy after operation is very apparent.

CONCLUSIONS

In conclusion we may make the following statements:

1. Thyroidectomy is the only treatment that satisfactorily and permanently controls the tachycardia of hyperthyroidism.

2. Long-continued hyperthyroidism causes myocardial exhaustion with degeneration and progressive cardiac failure.

3. The most important point in diagnosis is to keep in mind that hyperthyroidism causes tachycardia, auricular fibrillation, and myocardial degeneration.

4. The earlier operation is performed after a definite diagnosis of hyperthyroidism has been made, the better for the heart.

CHAPTER XIII

PULMONARY TUBERCULOSIS AND HYPERTHYROIDISM

GEORGE CRILE

IN 1921 we first performed thyroidectomy on a patient who had both hyperthyroidism and tuberculosis of the lungs. We now have for study 85 such cases.

Pulmonary tuberculosis is one of the diseases, the symptoms of which so closely resemble hyperthyroidism that careful study is necessary to establish the differential diagnosis. In the early stages the clinical pictures presented by these two conditions are almost identical; they include tachycardia, flushing of the skin, sweating, nervousness, tremors, digestive disturbance, loss of weight, dilated pupils, keen intellect, exaltation of the emotions, vivid personality. Hyperthyroidism and tuberculosis are each expressions of a drive of the energy system, hence the symptoms should in many respects be identical. If one were to eliminate just a single feature of pulmonary tuberculosis, that is, the lesion in the lungs, in many cases it would not be possible to differentiate either of these conditions from the other. That is, when tuberculosis and hyperthyroidism are associated in one patient the symptoms of each overlap those of the other.

The clinical pictures are identical; what of the pathologic findings?

Before the terminal stage the pathologic findings in the brain, the kidneys, the heart, the intestinal tract, the muscular system—in every part of the body—are merely the pathologic pictures which characterize excessive activity. They are therefore identical in these two diseases.

What of the pathology of the thyroid? In tuberculosis as in hyperthyroidism in a great majority of the cases the gland is hyperplastic as the result of overwork. In such a case it is impossible to determine whether the hyperplasia is associated with the tuberculosis or with the hyperthyroidism. All that hyperplasia tells us is that the thyroid has been overworked—it does not tell us what work it has been doing. In cases in which hyperthyroidism and tuberculosis are associated, the symptoms, except for exophthalmos in one, and increased temperature in the other, perfectly overlie each other.

It is a well known fact that infectious diseases such as influenza, diphtheria, scarlet fever, etc., as well as chronic focal infection, may precipitate hyperthyroidism. Therefore, one might expect that pulmonary tuberculosis might serve as an exciting cause of hyperthyroidism.

In our series of cases of hyperthyroidism, there has been no case in which tuberculosis has appeared after hyperthyroidism was established. The sequence appears to be the other way; namely, hyperthyroidism appears in the course of tuberculosis. One must infer therefore that the energy system which is stimulated to a defense against infection, is the same as the energy system that is driven excessively in hyperthyroidism.

Now in the presence of an acute infection the wise physician takes measures to mitigate the excessive energy transformation which is manifested by the fever so as to save the patient from being killed by the excess of his response. Likewise, in the treatment of pulmonary tuberculosis, rest and nutrition are the cornerstones of treatment. Rest means a diminution of the activity of the kinetic system. Now when hyperthyroidism is superimposed on tuberculosis which is already driving the energy system continuously, the patient is suffering from a double menace. It occurred to us therefore that thyroidectomy would do for the treatment of tuberculosis what rest does. Moreover, rest is just as available after thyroidectomy, in fact it is as essential in the treatment of hyperthyroidism as is the operation. In short we believed that a patient who is fighting a battle against two serious diseases might win the more easily if we took away one of them. Therefore, during the past ten years we have performed thyroidectomies on 87 patients who had these two diseases, with the following clinical results: In the cases in which the presence of pulmonary tuberculosis was definitely confirmed by *x*-ray examination, 74.5 per cent have shown definite clinical improvement following the thyroidectomy. Of the cases in which we have been able to secure a postoperative roentgenogram, 82 per cent show improvement in the pulmonary lesions while in 35 per cent the lesion has been cured.

ILLUSTRATIVE CASES

Case I.—The patient, a woman twenty-six years of age, came to the Cleveland Clinic because of diabetes which had been discovered six months before. Examination not only confirmed this diagnosis but revealed symptoms of hyperthyroidism and pulmonary tuber-

culosis. A small goiter was present. There was marked exophthalmos and the von Graefe and Stellwag signs were elicited. The basal metabolic rate on three occasions was plus 57, plus 32, and plus 23 per cent respectively, and the patient showed other typical signs of hyperthyroidism.

The pulse rate was 110. The patient had lost 10 pounds in the preceding six weeks, and was having night-sweats and an afternoon temperature of 99.5° F. Chest resonance was poor at each apex and the breath sounds were harsh but no râles were heard except indefinitely in the right axilla. After the patient entered the hospital the afternoon temperature ranged between 99.5° and 100° F. A roentgenogram of the chest showed fibrous and exudative infiltration of both upper lobes and apices. This finding with the clinical observations indicated the diagnosis of active pulmonary tuberculosis.

The patient was subjected to the regular diabetic regimen and to the usual preparation for thyroidectomy. Thyroidectomy was performed nine days after admission to the hospital, a diffusely hyperplastic gland being removed.

Seven months after her operation the basal metabolic rate was zero and minus 2 per cent on two occasions and there were no symptoms of hyperthyroidism. The diabetic condition was under control, showing a mild prediabetic condition which under proper diet would probably disappear entirely. The weight was stationary. There were no night-sweats.

Clinical examination of the chest gave normal findings and a roentgenogram showed no evidence of active tuberculosis.

Case II.—The patient, a woman forty-three years of age, had had pneumonia thirteen years before we saw her and had experienced palpitation and fatigue ever since. Two years before she had had repeated severe colds followed by persistent pain in the chest and extreme nervousness.

On physical examination the temperature was found to be 99° F., the blood pressure was 175/75, and the pulse rate 92. The thyroid gland was enlarged and a bruit but no thrill was present. The symptoms of hyperthyroidism were not marked. The basal metabolic rate was plus 33 and plus 28 per cent on two occasions.

The lungs showed poor expansion, some dulness at the right apex and an increased murmur over the left lung. The cervical lymph glands were palpable. The mediastinum was slightly enlarged.

A roentgenogram showed opacity of the entire right chest and infiltration of the right apex.

A diagnosis of mild hyperthyroidism was made but it appeared that the condition in the chest might be sufficient to explain the symptoms of nervousness, palpitation, etc.

Because of the enlarged thyroid the patient entered the hospital for thyroidectomy and an adenomatous and colloid goiter was removed.

On her discharge from the hospital there was definite impairment of resonance over the right apex with fine, fairly dry râles indicating a slight activation of the tuberculous process.

The patient was sent home with strict directions as to a regimen of rest and diet.

One year later the patient was seen in apparently good health. All nervous and other symptoms of hyperthyroidism had disappeared and there was no clinical evidence of tuberculosis.

Case III.—The patient, a woman forty-seven years of age, had had a goiter, nervousness, palpitation, and choking for sixteen years, the onset having followed an attack of quinsy. The condition had fluctuated in intensity and had been severe during the preceding six months. The patient presented typical symptoms of severe hyperthyroidism, the thyroid gland was found to be very much enlarged, and bruit and thrills were present.

A roentgenogram of the chest showed extensive exudative infiltration over both lungs including the apices—a typical picture of advanced pulmonary tuberculosis.

A thyroidectomy was performed and pathologic examination of the gland showed marked hyperplasia.

A roentgenogram taken seven years later showed extensive fibrosis of both lungs and gave no evidence of active tuberculosis.

CHAPTER XIV

LARYNGEAL DISTURBANCES IN HYPERTHYROIDISM

WILLIAM V. MULLIN

HYPERTHYROIDISM seems to have no direct effect upon the larynx, any symptoms referable thereto being those associated with general muscular weakness, fatigue on using the voice, transient attacks of laryngitis, and hoarseness. Paralysis practically never occurs. It is conceivable that a simple adenoma might be so situated as to cause direct pressure upon the recurrent laryngeal nerve with resultant paralysis of a vocal cord, but careful clinical examinations reveal that this seldom occurs. Anatomical studies of the laryngeal nerve show that it is surrounded by so much soft tissue that serious injury from gradual pressure can hardly occur.

A large colloid goiter or an intrathoracic goiter may cause laryngeal and tracheal displacement, and sometimes the larynx may become twisted upon its own axis. In such cases, dyspnea, and stridor may be present and dysphagia is a frequent symptom. Occasionally, one recurrent laryngeal nerve may become pinched or pulled sufficiently to influence its function.

Thyroiditis and Riedel's struma are of comparatively rare occurrence so that they are not outstanding causes of laryngeal paralysis, but on account of the hard consistency of the thyroid tissue and distortion of the larynx and trachea in these diseases, involvement of the recurrent nerve is a possibility.

Because of its invasion of the surrounding tissue, a malignant tumor of the thyroid gland is a much more frequent cause of laryngeal paralysis than is simple goiter, so that when double abductor paralysis is present, together with an enlarged thyroid gland, malignancy should always be suspected.

In order to obtain accurate figures, a careful preoperative and postoperative laryngeal examination must be made in every case, and when laryngeal paralysis is found, the type of paralysis and the position of the cord should be exactly noted. It is not sufficient to as-

sume that because a goiter is present, it is the sole cause of the laryngeal paralysis, until every measure has been taken to rule out other causes of paralysis such as diseases in the chest, mediastinum, or heart.

A recent survey of 8000 cases of simple goiter, made at the Cleveland Clinic, showed the incidence of preoperative vocal cord paralysis to be only 1/10 of 1 per cent, while preoperative laryngeal examination in 153 cases of malignancy of the thyroid gland revealed vocal cord paralysis in 25 or 16.3 per cent. Bilateral abductor paralysis was present in six cases or 3.92 per cent.

During operations on the thyroid and neck, the recurrent laryngeal nerve can be injured by the injection of novocaine, by pinching with a hemostat, by stretching during overtraction on the gland, by ligation of the nerve together with the blood vessels, and by complete severance of the nerve by cutting. Cutting will produce permanent and irreparable damage, while ligation may or may not cause a permanent result, this depending on the amount of scar tissue that forms around the nerve at the site of the ligation. Recovery will finally result after lesser injuries.

Since many physicians fail to understand just what takes place in the larynx when the recurrent nerve is injured, it may be of interest to review the anatomy and physiology of the larynx and then to describe the pathologic physiology which results from injury of this important structure.

In man, the intrinsic muscles of the larynx may be divided into two groups: Those that abduct and those that adduct the vocal cords.

Abduction of the vocal cords is dependent on the posterior crico-arytenoid muscle. This muscle separates the cords, and consequently opens the glottis by rotating the arytenoid cartilages outward around a vertical axis which passes through the crico-arytenoid joints, so that the vocal processes and the vocal cords attached to them become separated.

The muscles that control adduction are the cricothyroid, the crico-arytenoid lateralis, and the thyro-arytenoid. The interarytenoid, an unpaired muscle situated between the two arytenoid cartilages, also helps in producing adduction. The lateral crico-arytenoid muscles close the glottis by rotating the arytenoid cartilage inward so as to approximate the vocal cords. The interarytenoid muscle approximates the arytenoid cartilages, and thus closes the opening of the glottis, especially of its posterior part.

The cricothyroid muscle produces tension on the vocal cords, causing elongation. This is brought about by the following movement. The thyroid cartilage is fixed by its extrinsic muscles, then the cricothyroid muscle draws the cricoid cartilage upward, depressing its posterior portion which is attached to the arytenoid, so that the cords become stretched.

The thyro-arytenoid muscle consists of two parts, each having a different attachment and direction. The action of these two parts, therefore, is rather complicated. Their main function is to approximate the arytenoid and thyroid cartilages and thereby relax the vocal cords. Owing to the connection of the inner portion of the muscle with the vocal cord, this part is supposed to modify the elasticity and tension of the cord, and the outer portion, being inserted into the anterior surface of the arytenoid cartilages, may rotate the cord inward and thus narrow the rima glottidis by bringing the cords together.

The innervation of the larynx is derived from the superior and the inferior laryngeal nerves, together with branches from the cervical sympathetic nerve. The superior laryngeal nerve divides into the external and the internal laryngeal nerves, the former of which is the motor nerve to the cricothyroid muscle, while the latter, which is mainly sensory, supplies the interior of the larynx. Some motor fibers are said to be carried to the interarytenoid muscle. The sensory branch communicates with a branch from the inferior (recurrent) laryngeal nerve, the nerve that supplies all the other muscles of the larynx. Sympathetic fibers accompany all of the laryngeal nerves, but their exact function is unknown at present.

Paralysis of either recurrent laryngeal nerve deprives all the intrinsic muscles of the larynx of their function on the side that is stricken, with the exception of the tensor muscle of the vocal cord, which is supplied by the external branch of the superior laryngeal nerve. This leads to inactivity of the vocal cord on the paralyzed side. The cadaveric or midposition is thought to result from the action of the cricothyroid muscle, which is supplied by the external branch of the superior laryngeal nerve. In slow paralysis of the recurrent nerve, the abductor muscle of the larynx is affected first.

Therefore, when the recurrent laryngeal nerve is totally injured, the vocal cord on the affected side will move up to the midline and remain there. The crico-arytenoideus posterior muscle is the one abductor muscle of the vocal cord and when it no longer receives

stimulation, the adductor muscles pull the cord to the midline, and the abductor muscle is unable to draw it away. Such a condition may produce very little laryngeal disturbance. As the cord opposite the paralyzed side has free excursion, a sufficient amount of air can enter the trachea and lungs and since good approximation is made by this cord against the cord fixed in the midline, the quality of the voice may be very little affected. In fact, the writer recalls a case in which a salaried singing position was satisfactorily held by a woman with unilateral abductor paralysis.

It seems to be too often assumed that if the recurrent nerve is injured, the vocal cord will assume the so-called "cadaveric position." Complete laryngoplegia is rare, and is due to pathologic conditions that do not concern us here.

Unless careful postoperative laryngeal examination is made in all cases, many patients with a unilateral abductor paralysis will be discharged following operation with the condition undiagnosed.

If both recurrent nerves are injured, then both cords will be fixed in the midline and the air-way will be greatly reduced. Such a condition presents a serious aspect. Dyspnea should not be permitted, as patients fail very rapidly if a sufficient air-way is not provided. No remedial measures such as steam inhalation, croup tent, or oxygen, should be tried, but a tracheotomy should be done without delay.

If a tracheotomy has been done, the question arises—when, if ever, can the patient be decannulized? Voice is a precious possession to all of us. With the tracheotomy tube *in situ*, there is good breathing and a reasonably good voice. Therefore, before any operative procedure of a plastic nature is undertaken, the patient must be apprised of the fact that the voice will not be as clear as it is with the tracheotomy.

In the majority of cases of obstructive lesions of the larynx, the patient loses the use of the voice completely when the tracheotomy tube is inserted, but this is not the case when bilateral abductor paralysis occurs, for although the cords do not move in abduction and adduction, they respond to the currents of air by vibration and will produce reasonably good tones, and they will do this just as well when a tracheotomy tube is present in the trachea.

Bilateral abductor paralysis of the vocal cords certainly presents a perplexing problem; occasionally, the cords will be fixed in a sufficiently abducted position to permit quiet breathing, but the least exertion, or slight laryngitis following an acute respiratory infection,

may bring on the characteristic "inspiratory crow" which is invariably present when the cords are in the midline.

No attempt to meet this problem has proved to be uniformly satisfactory. Cordotomy has not given permanently satisfactory results and up to the present time, anastomosis of the recurrent laryngeal with the hypoglossal or the phrenic nerve has not been uniformly successful.

In a paper offered in 1931 before the American Laryngological Association, Dr. W. B. Hoover reviewed the literature on the operative treatment of bilateral abductor paralysis and reported 4 cases in which the larynx had been opened as in laryngofissure, and the tissue between the vocal cord and the thyroid cartilage including the vocal process of the arytenoid had been removed, these procedures making possible the removal of the tracheotomy tube, but the voice was hoarse. My own feeling is that a well-fitting valve tracheotomy tube, which, if desired, can be taken to a jeweler and decorated so as to disguise its unsightly appearance, offers the patient the most satisfactory all-round comfort.

CHAPTER XV

CUTANEOUS MANIFESTATIONS ASSOCIATED WITH THYROID DYSFUNCTION

E. W. Netherton

It is well known that disturbances in the functional balance of the endocrine system may be accompanied by cutaneous manifestations. Those cutaneous abnormalities which result from dysfunction of the thyroid and adrenal glands are an integral part of certain fairly common syndromes and consequently they are more familiar to the average physician than those associated with disturbances of the function of the pituitary gland, the gonads or the pancreas.

In a healthy or normal individual there is complete correlation of function of the various glands of internal secretion. An abnormal function in one gland produces a complex disturbance in the physiologic function in general as well as the dysfunction of other endocrine glands. It follows that manifestations attributed to one gland may result in part in a secondary change in another gland. Thus, for example it is believed that the thyroid and adrenals stimulate each other; or a hypersecretion of the thyroid gland may cause a decrease in function of the pancreas with a resulting alimentary glycosuria; while in myxedema the reverse is true and the patient can tolerate larger amounts of carbohydrates.

A disturbance of the function of a gland of internal secretion may be of two types: (1) hypersecretion and (2) hyposecretion. Some observers have felt that there may be a third type of disturbance in which there is an alteration in the secretion itself; this view, however, has not been proved and is not generally accepted. It is evident, therefore, that the cutaneous manifestations associated with thyroid dysfunction are of two types, those seen in hyperthyroidism and those in hypothyroidism. As would be expected, the skin changes seen in one of these syndromes is in the main the reverse of those seen in the other.

While there are no dermatoses which are pathognomonic of hyperthyroidism, nevertheless certain skin manifestations are very fre-

quently seen in this disease. They result from the vasomotor disturbances, which are produced by the unstable vegetative nervous system, and also from the nutritional changes caused by an increase in metabolism, both of which are always present in Graves' disease.

The skin is usually smooth, thin and velvety. There is an increased surface temperature and the skin usually is moist. Because of vasomotor instability patches of hyperemia and pallor appear on the face, neck, and upper part of the sternal region. These are sometimes present simultaneously, the patches being sharply demarcated. Later there may be permanent capillary dilatation in the skin of the face and neck. Dermographia and factitious urticaria are common. Violent flushing and generalized urticaria frequently are seen and petechiae may occur. Generalized pruritus and simple dermatitis are observed at times.

Hyperhidrosis is practically constant and accounts for a diminished resistance of the skin surface to the electrical current. The hyperhidrosis is usually marked in the axillae and on the palms and soles. In some cases this is associated with a mild hyperkeratosis of the palms and soles. Jackson states that the skin may be dry in cases in which dehydration has been produced by a gastro-intestinal crisis.

Occasionally cases are seen in which there is a vesicular pustular eruption on the hands and feet, especially on the palms and soles. This eruption simulates very closely the common fungus infection of the hands and feet. It differs, however, in two respects: The skin is usually redder than in the presence of the fungus infection and negative findings result from a search for the fungus. In our cases the eruption has disappeared promptly after thyroidectomy.

Nutritional or dystrophic changes of the nails and hair are not uncommon. The nails may become flattened and spadelike with turned up ends. Alopecia is common in cases of long standing, being most marked in the axillae and on the trunk, and in many cases there is a loss of hair from the vertex and temporal regions of the scalp and occasionally from the eyebrows. The hair becomes dry and brittle. These changes have been observed in experimentally induced hyperthyroidism. Sainton and Peynet[1] repeated Zavodorsky's experiments in which hyperthyroidism was produced in hens by the administration of thyroid extract and confirmed his observation of a loss of feathers, which were replaced by white feathers. In the human a similar change in the hair may follow hyperthyroidism.

Pigmentary disturbances sometimes occur. Vitiligo, at times extensive, frequently is seen in cases of hyperthyroidism (Fig. 31). Generalized pigmentation may be a striking feature in chronic cases with cardiac decompensation. At times there is a marked degree of darkening of the skin in areas exposed to light or to irritation from clothing such as garters and waistbands (Fig. 32). In contradis-

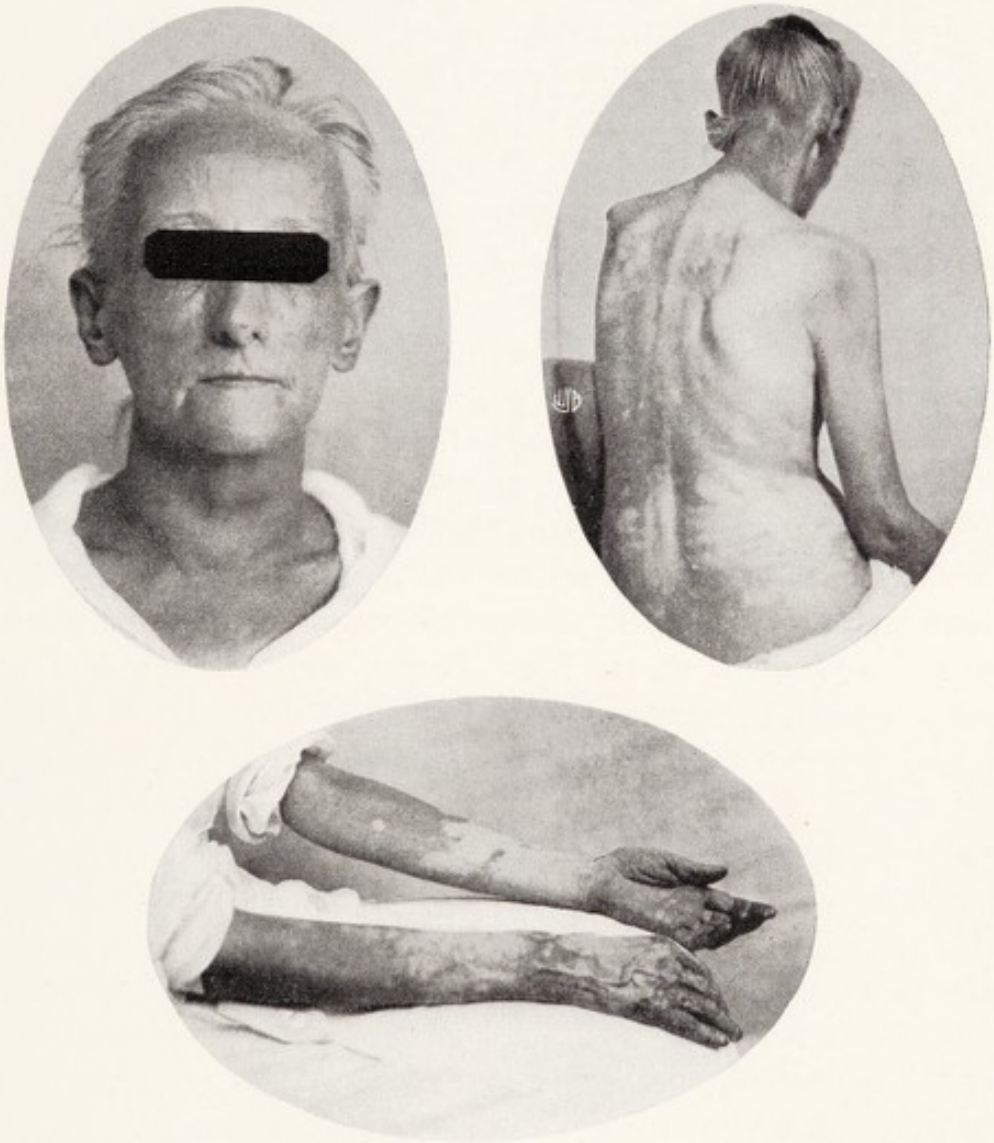

Fig. 31.—Vitiligo in a case of hyperthyroidism.

tinction to the pigmentation seen in Addison's disease, the mucous membranes are not involved. The eyelids occasionally show hyperpigmentation. The nipples, axillae, the lower portion of the abdomen, and the inner surfaces of the thighs may be darker than normal. Theoretically it may be supposed that this pigmentation is due to the effect of the excessive or abnormal thyroid secretion upon the supra-

renal glands, which seems reasonable. The pigmentation usually lessens or disappears after operation.

Jaundice may occur during a crisis of hyperthyroidism but is less frequent since the use of iodine in the preoperative treatment.

In some cases areas of edema develop which occur most commonly on the face and involve the eyelids or the extremities. Localized edema of the eyelids is usually ephemeral and is associated with urticaria. This condition may persist for days or weeks or it may appear and disappear within a few hours. It may appear again in the same location or in any other part; or it may disappear permanently.

"Histological sections which have been removed from these circumscribed areas are quite different from similar sections made in cases suffering from myxedema. The tissue in the former is thickened because of the presence of water; in the latter because of infiltration with a mucoid substance" (Ochsner).

A chronic trophic edema of the so-called "solid type" has been observed. It does not pit on pressure and has been regarded as akin to the characteristic swelling of myxedema. It appears on the wrists, on the calves of the legs or around the ankles.

O'Leary,[2] in an excellent article, has recently reviewed the literature and reported cases of hyperthyroidism which presented localized plaques of myxedema on the legs. Biopsy sections made in 2 cases showed a mucinous degeneration in the cutis. Pillsbury and Stokes[3] have also reported a case with the same condition which developed following an operation for hyperthyroidism. The condition does not respond to treatment.

We have observed the following case which is an example of this condition.

The patient, a woman forty-six years of age, was first seen on July 22, 1924. At that time she consulted Dr. Crile because of a goiter. The patient was obviously suffering from recurrent hyperthyroidism. A lobectomy was done by Dr. Crile on July 29, 1924. A few months later the skin on the anterior surface of the legs became thickened and rough. This condition gradually became worse until two-thirds of both legs were involved the condition extending from just above the ankles upward (Fig. 33). There was slight itching.

On the lower portion of each leg, large thickened, noninflammatory, waxy colored plaques were present. They appeared to be edematous but did not pit on pressure. The lower third of each leg was involved but on the lateral and posterior surfaces the plaques were especially

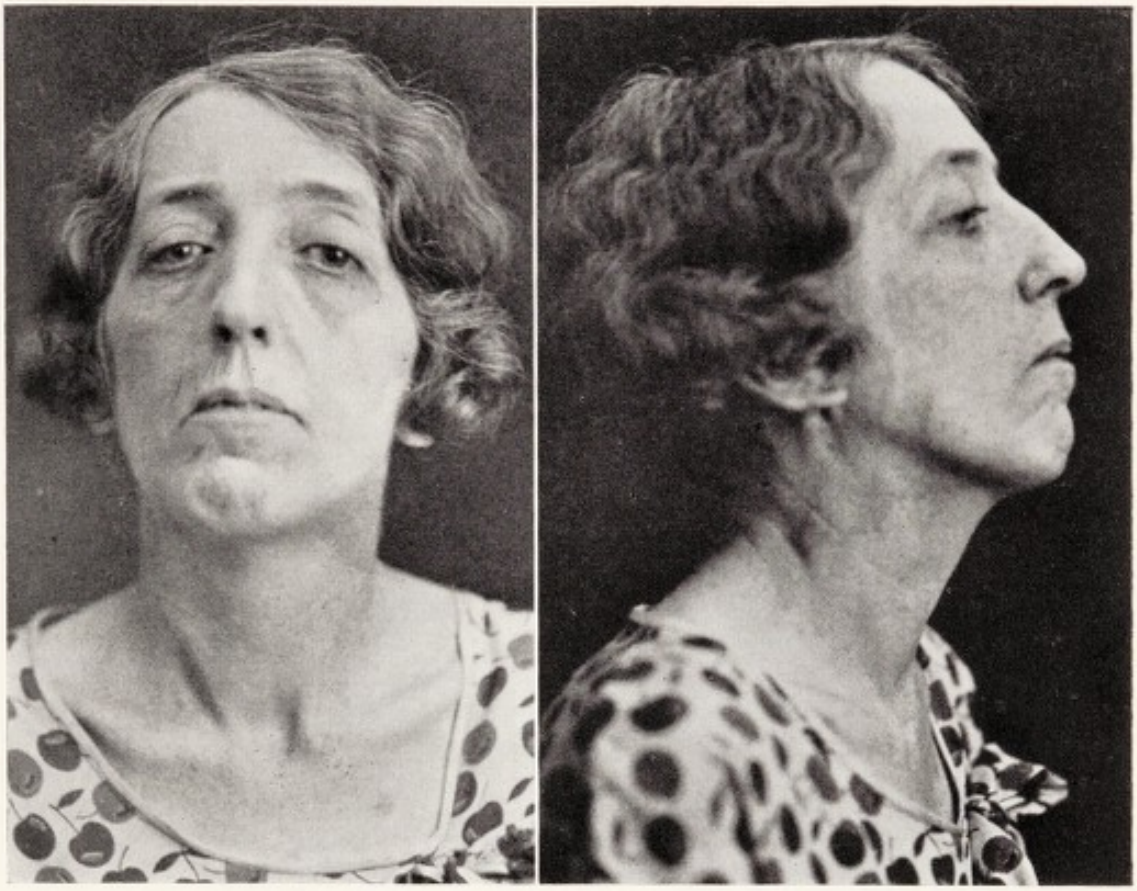

Fig. 32.—Pigmentation of face and neck of a patient with hyperthyroidism.

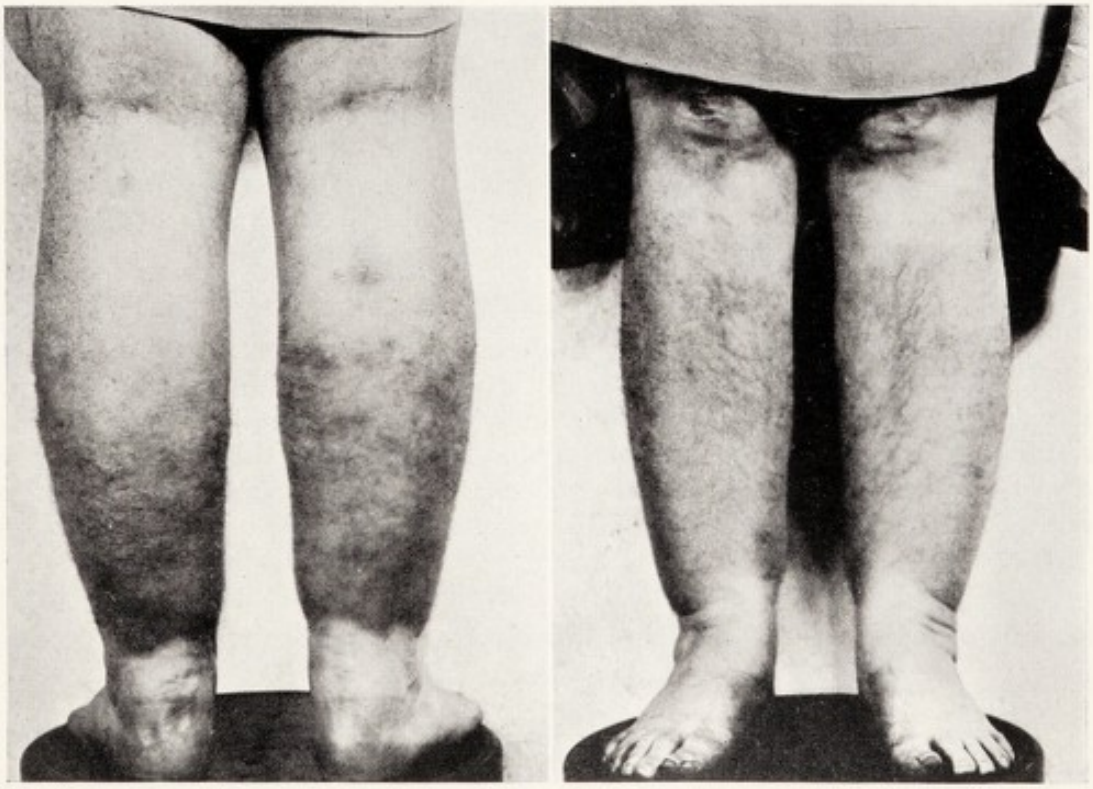

Fig. 33.—Localized myxedema.

thick. There was a fairly abrupt lower margin to the condition. The skin of the ankles and feet was normal. The hair on these plaques was coarser than normal and the follicles were the site of small dimples giving a pig-skin appearance. The skin over the whole body was dry.

At the onset of this condition the patient's physician prescribed thyroid extract as the basal metabolic rate was found to be low, but

Fig. 34.—Mucinoid degeneration in the cutis. Pathologic report: "The superficial layers of the dermis consist of loosely arranged, collagenous fibrous tissue. In the dermis and hypodermis there are irregular, scattered masses of poorly staining, collagenous connective tissue and throughout this area, the tissue seems diffusely edematous but there is no well defined myxomatous tissue. Tissue fixed in bichloride and stained with thionin shows large quantities of mucoid material in the dermis."

no improvement followed the administration of thyroid extract and iodides.

Histologic studies of the skin demonstrated a mucinous degeneration in the corium similar to that reported by O'Leary, and by Pillsbury and Stokes (Fig. 34).

Youmans[4] studied the absorption time of intradermal injections of salt solution in cases of hyperthyroidism and found it increased. The absorption time returned to normal following treatment of the thyrotoxicosis. However, Mora[5] had previously noted an increase in the absorption time in similar cases.

Although the pathogenesis of scleroderma is obscure many authors have expressed the opinion that some alteration in the endocrine system is a factor in its causation. It has been observed to appear at the menopause or in association with some dysfunction of the thyroid gland. It has been seen in association with hyperthyroidism as well as in cases of hypothyroidism. In some cases improvement follows the administration of thyroid extract while in others no benefit follows treatment. These observations seem to be too numerous to be adequately explained as coincidental, but nevertheless the relationship between scleroderma and the thyroid gland is not understood but it is probably of an indirect type.

Hektoen and Wells[6] observed a case of diffuse scleroderma in which there was atrophy and sclerosis of the thyroid gland, and hypertrophy of the pituitary gland; there was an extensive endarteritis of the thyroid vessels, and diminished iodine content of the gland.

Natthofft (quoted by Foerster[7]) reported a case in which diffuse scleroderma was accompanied by an atrophied thyroid gland. However, he felt that there was no causal connection between the two conditions as extensive thyroid changes may be seen without the development of scleroderma.

In 1903 Hyde and McEwen[8] reviewed 111 cases of hyperthyroidism in which there were cutaneous manifestations and found scleroderma in 5 of them.

Morawiecka[9] observed a case of Basedow's disease associated with scleroderma and osteomalacia. He stated that prior to 1928, 37 cases in which scleroderma was associated with Basedow's disease had been reported and 23 in which Basedow's and osteomalacia were associated. These did not include a case reported by Mäbius and Hirsche in which the syndrome of Basedow's was associated with osteomalacia and myxedema. He claimed that his case was the first one reported in which scleroderma and osteomalacia have occurred simultaneously in association with hyperthyroidism. Morawiecka was of the opinion that an alteration in the sympathetic nervous system was responsible for the production of these three conditions.

Vallery-Radot, Hillemand, and Chomereau-Lamotte[10] observed an interesting case in which hyperthyroidism responded to treatment with radiotherapy and hemothyroidin. Four years later characteristic myxedema developed which two years later developed into scleroderma. The palate was involved and there was also an ovarian insufficiency which was evidenced by a scarce and irregular menstruation which began at the age of sixteen. This case is of interest because there is a close clinical resemblance between the early edematous stages of scleroderma and myxedema.

It has been suggested that there is some relationship between dysthyroidism and **Dercum's disease** or **adiposis dolorosa.** Foerster[7] stated that in five out of six autopsies made in fatal cases of this disease pathologic changes were found in the thyroid. Price[11] reported necropsy findings in two cases, in one of which there was a colloid goiter while in the other there was a small atrophic and sclerotic right lobe of the thyroid gland. Price also reviewed six other cases reported in the literature, in five of which there was either hypertrophy, sclerosis, or atrophy of the thyroid gland.

Sainton and Veran[12] stated that **erythromelalgia** is a syndrome which is rarely associated with hyperthyroidism. They also cited a case reported by Engelen, that of a young man, twenty years of age, who had Basedow's disease and painful paresthesia of the hands which came on sometimes spontaneously, sometimes under the influence of heat. In the interval between the crises the hands remained red and palmar and facial hyperhidrosis was present.

Sainton and Veran also reported a case they had studied in which this rare association occurred in a woman, forty-two years of age. Erythromelalgia involving the hands appeared five months after the onset of hyperthyroidism accompanied by amenorrhea. In this case the reaction to temperature was paradoxical. Heat gave relief while cold produced intensified redness and pain. Besides the associated amenorrhea, aortitis was present, but the serological findings were negative and the patient presented no other signs of syphilis. As the symptoms of hyperthyroidism decreased the erythromelalgia improved. However, as these regressed cardiac insufficiency developed. This was improved by treatment for six weeks in a hospital. No further observation was made after the patient's discharge from the hospital.

These authors felt that erythromelalgia resulted from disturbance in the sympathetic nervous system, probably with lesions in the vaso-

motor sympathetics. They were doubtful as to the relation between the thyroid disease and the erythromelalgia in their case. It was possible that latent syphilis was present, an association which is frequently seen in cases of erythromelalgia, as there was an aortitis that could not be explained on any infectious or rheumatic basis. They also considered the possibility of ovarian insufficiency as a causal factor of the erythromelalgia in their case. Both the spontaneous and induced types of this condition have been observed to develop during the menopause.

Very little is definitely known concerning the relationship that exists between diseases of the thyroid gland and scleroderma, adiposis dolorosa, erythromelalgia, osteomalacia, and other comparatively rare conditions whose etiology is obscure; however, the frequency with which pathologic changes of the thyroid gland have been noted in these conditions is probably high enough to be of some significance. The association of a disease such as scleroderma, sometimes with hyperthyroidism and sometimes with hypothyroidism or myxedema, and the improvement in some cases following the administration of thyroid extract and the lack of improvement in other cases after the same medication are contradictory observations which allow for no conclusions. A more comprehensive understanding of these cases must await the advancement of our knowledge of endocrinology as well as more exact information regarding other possible factors in the etiology of these diseases. The theoretical assumption that they are due to an alteration of the secretion of an endocrine gland cannot be accepted as there is no proof that this occurs.

Drug eruptions, although not a part of the clinical picture, are frequently seen in cases of hyperthyroidism. The preoperative treatment usually includes the administration of bromides and iodides and consequently an acneform eruption develops in a large percentage of the cases. We have observed other types of bromide and iodide eruptions in these cases but they are uncommon. In our hospital luminal dermatitis is not uncommon especially in cases of hyperthyroidism. Frequently this is accompanied by an elevation of temperature, sometimes as high as 103° F., thereby making it necessary to consider the exanthemata in the differential diagnosis. That a fever may accompany a luminal eruption is not a new observation but it is a fairly constant occurrence in cases of hyperthyroidism. As we know the slightest disturbance in a marked case of hyperthyroidism is frequently followed by an elevation of temperature.

In 1926 I reported a case of a rare condition known as **Fox-Fordyce disease**[13] which was associated with hyperthyroidism. The manifestations of this disease consist of a discrete papular eruption involving the axillae, pubic region, and areolae of the nipples. Itching is of the paroxysmal type and is very intense. There is a loss of hair from the axillae and pubic regions. In this case the intensity of the itching paralleled the severity of the hyperthyroidism and the eruption and subjective symptoms disappeared after thyroidectomy. No other case in which this disease has been associated with hyperthyroidism has been reported, but in several reported cases evidence of endocrine disturbances has been noted. We do not think the hyperthyroidism was the cause of the Fox-Fordyce disease in our case but believe this observation is of sufficient interest to warrant its inclusion here.

Records appear in the literature of cases in which **psoriasis** has been improved following the administration of thyroid extract. We have seen several cases of psoriasis associated with hyperthyroidism in which the eruption has been the same in character as in ordinary cases and no change has followed thyroidectomy. The same may be said of many of the more common skin diseases.

Of the cutaneous manifestations associated with thyroid disturbances those which are the most characteristic and consequently of most diagnostic importance are those seen in myxedema. These skin changes are in the main the reverse of those seen in hyperthyroidism.

In **myxedema** the skin is thickened, cold, dry, scaly, and at times wrinkled and pigmented. Usually the skin has a sallow or yellow color. Small follicular hyperkeratotic papules may be seen on the extremities. The thickening of the skin is due to a peculiar infiltration which gives the sensation of edema and does not pit on pressure. The infiltration consists of a mucinous degeneration or deposit in the corium. This is associated with a mild cellular infiltration around the hair follicles, sebaceous glands, and sweat glands.

Swelling or thickening usually appears first on the face, around the eyes, or on the chin and cheeks. In early cases nephritis may be suspected. Local tumefactions may be present, especially in the supraclavicular regions.

The malar regions and nose frequently are flushed or cyanotic. The skin of the wrists, hands, and feet is thickened, rough, and scaly. The dryness of the skin is the result of the marked reduction or al-

most complete absence of perspiration and a decreased activity of the sebaceous glands. As noted above, scleroderma has been observed to develop in myxedema. As a result of the changes in the skin the lips and ears became thickened or swollen making the features coarse. The infiltration of the skin of the hands makes them larger and impairs the movement of the fingers. The palms and soles are dry, thickened, and sometimes fissured. Engman[14] states, "A scurfiness of the elbows and knees, when accompanied by palmar and plantar changes, is characteristic of hypothyroidism in those past thirty."

The hair becomes dry, sparse, and alopecia develops which is more marked than that seen in hyperthyroidism. The alopecia is especially marked on the lateral and frontal portions of the scalp. The eyebrows become thin and other hairy portions show a loss of hair. The nails become dry and brittle and may show longitudinal or transverse ridges. Definite mental inertia is associated with these cutaneous changes.

In a well-developed case of myxedema the diagnosis is not difficult, but in many patients who suffer from hypothyroidism myxedema does not develop, but both cutaneous and systemic symptoms do occur which are relieved by the administration of thyroid extract. Alopecia associated with dry coarse hair and with moderate xeroderma not infrequently results from hypothyroidism. General pruritus which is not associated with dermatitis and is not caused by scabies or other parasites or by soap, rough undergarments or too frequent bathing in hot water or which cannot be explained as due to diabetes, jaundice, leukemia, senility, or any other disease such as urticaria is probably due to hypothyroidism. We have seen several such cases and have obtained good results from the administration of thyroid extract.

We have observed several cases in which chronic **eczema** or **dermatitis** was associated with a low basal metabolic rate and occasionally with achlorhydria. In these cases dermatitis usually involved the face, neck, upper portion of the trunk, and the cubital and popliteal fossae. This is the type of case in which an allergy is thought to be the cause of the dermatitis, but we were unable to demonstrate a sensitization in most of these cases. These patients were usually benefited by the administration of thyroid extract. Thyroid extract should not be employed unless the basal rate is low and should be given only in amounts necessary to induce and maintain a normal metabolic rate. Engman, Morris, and others reported similar cases in which good results followed medication with thyroid extract.

Ichthyosis is an hereditary malady. Some authors are of the opinion that decreased thyroid function may be a factor in its etiology. Improvement of this condition has been observed to follow the administration of the thyroid extract but we have tried this medication in a few cases without securing any apparent improvement. In adults who have developed a dry, scaly skin suggestive of mild ichthyosis the basal metabolic rate is frequently low. In such cases the patient is benefited by thyroid extract. Such cases, however, should not be confused with ichthyosis.

Winfield[15] has reported a case of congenital ichthyosis in an infant without a thyroid gland. Nothing was found at autopsy to show that the gland had ever been present. The relationship of these two conditions was obscure. However, the observation is of interest. Congenital ichthyosis should not be confused with simple ichthyosis which is not an uncommon disease.

Foerster[7] stated that in cases of **chronic tetany** due to decreased parathyroid secretion changes may occur in the ectodermal structures. The hair may cease growing or alopecia may develop. Dystrophic changes of the nails and teeth may be present, and at times chronic ulcerations of the skin may occur. We have observed some of these manifestations.

Although excellent articles[16, 17, 18, 19] have been written concerning the dermatoses associated with dysfunction of the thyroid gland, it can safely be stated that with the exception of the changes seen in myxedema there are no dermatoses which are specifically the result of dysthyroidism. Such conditions are significant only when they are considered as a part of the whole clinical picture. Caution must be used in basing conclusions concerning the etiology of a dermatosis upon improvement following the administration of a glandular extract as this does not necessarily signify that the disease in question is the result of a hypofunction of that particular gland. The physiologic effect of such an extract is complex and in some instances the result may be of secondary nature. As our knowledge concerning the correlation of function of the endocrine glands increases it is possible that some of the dermatoses, the etiology of which is obscure may be found to be related to endocrinopathy.

The lack of correlation between various dermatoses and dysfunction of the thyroid gland is well illustrated by the following table which presents an analysis of 142 cases of hyperthyroidism, 105 cases of hypothyroidism and 31 cases of simple goiter which I have seen be-

TABLE SHOWING THE LACK OF RELATIONSHIP BETWEEN VARIOUS DERMATOSES AND THYROID DYSFUNCTION

Dermatosis.	Number of cases.		
	Hyperthyroidism.	Hypothyroidism.	Simple goiter.
Acne	28	1	11
Alopecia	1	3	
Dermatitis venenata	25	50	2
Drug eruption	13		
Eczema	13	12	
Erythema, toxic	7	3	2
Erythema nodosum	1		
Herpes simplex	3	3	
Hypertrichosis	1	1	
Lichen planus	3	3	1
Lupus erythematosus	2		
Pityriasis rosea	5	3	1
Psoriasis	4	4	5
Pruritus, generalized	10	9	
Miliaria	1		
Rosacea	1	1	1
Seborrhea	6	3	4
Scleroderma	1		
Tinea versicolor	5	..	1
Urticaria	6	7	2
Vitiligo	5	..	1
Chloasma	..	1	
Fox-Fordyce disease	1		
Localized myxedema	..	1	
Total	142	105	31

cause of the presence of some skin condition. This table is not presented in an attempt to determine the frequency with which any dermatosis occurs in association with thyroid dysfunction as the avail-

able material is not complete enough for such conclusions to be drawn. Many other skin conditions such as scabies, epidermophytosis, and impetigo which occur not infrequently in such cases are not included. Although the number of cases in this analysis is small, it is sufficient to indicate that there is no etiologic relationship between thyroid dysfunction and these common dermatoses.

Our experience is in accord with the observation of others that with the exception of the cutaneous manifestations of myxedema there are no dermatoses which are pathognomonic of thyroid disease.

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CHAPTER XVI

OCULAR CHANGES ASSOCIATED WITH HYPERTHYROIDISM

A. D. Ruedemann

In 1786, Parry described a case in which an enlargement of the thyroid gland was accompanied by enlargement and palpitation of the heart. He described the appearance of the patient as follows: "The eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress especially in any muscular movement." In 1835, Graves[1] was the first to appreciate the symptomatology of hyperthyroidism and in 1840, Basedow[2] described the disease again. All the early writers as well as many later authors lay particular stress on the exophthalmos which is associated with thyroid disturbance. The reason for this emphasis can readily be explained as the position and relative physiologic actions of the lids and eyeball were not understood.

To too many physicians, exophthalmos still represents the only ocular change associated with hyperthyroidism. Altogether there are about twenty eye signs of hyperthyroidism, but their presence and significance are apt to be overlooked. On the other hand, these eye changes are often recognized by the oculist who has not sufficient appreciation of their relation to the underlying diseases and is surprised when attempts to correct the ocular change by glasses or operation prove ineffective.

The most important ocular changes associated with hyperthyroidism are widening of the palpebral fissures, exophthalmos, muscle weakness and paralyses. But such conditions as spasm of the levator palpebrae, lack of coordination, poor convergence, disturbances of accommodation and corneal ulcers are significant and when present their possible association with hyperthyroidism should be investigated.

Widening of the Palpebral Fissure.—Dalrymple first described this condition and Stellwag called attention to the frequency with which it occurs. This sign gives the most terrifying aspect to the pa-

tient with a toxic thyroid and probably sends more people to the surgeon than does true exophthalmos. The widening gives the appearance of exophthalmos; it comes on earlier than exophthalmos and is readily corrected by thyroidectomy. The most brilliant results of thyroidectomy occur in cases in which widening of the fissure is associated with beginning exophthalmos. It is necessary to measure the anterior-posterior diameter of the eyeball in order to understand that widening of the fissures usually precedes the exophthalmos, frequently by

Fig. 35.—Unequal widening of the palpebral fissures simulating unilateral exophthalmos. Anterior-posterior measurements: O. D. 20 mm. O. S. 19 mm. (Hertel's). Fissures O. D. 15 mm. O. S. 10 mm.

as much as a month—in a recent case the latter did not appear until more than eighteen months after the appearance of the former symptom.

From a review of a large series of cases of hyperthyroidism it becomes evident, not only that widening of the fissures appears before exophthalmos and is next to the latter in diagnostic importance, but that it may occur with or without proptosis although it is worse when proptosis is present.

To measure the width of the fissures the patient is made to fix his gaze on an object on a horizontal level with the eyes so that the center of the cornea is in the midline.

In cases in which extreme widening is present lagophthalmic ulcers may occur which are best corrected either by tarsoplasty (Wheeler[3]) or by suturing with a purse string suture (Spaeth[4]).

Proptosis does not occur in the eyes when the fissures are extremely wide unless postocular edema is present. A Bullar shield of

Fig. 36.—Unequal widening of the palpebral fissures simulating unilateral exophthalmos. Anterior-posterior measurements: O. D. 19 mm. O. S. 19 mm. (Hertel's). Fissures O. D. 11 mm. O. S. 8 mm.

glass or cellophane works admirably if it is not used over too long a period of time.

Although the widening of the fissures is easily simulated and is found in many conditions, its presence is sufficient to warrant further ocular study and to consider whether or not it is due to thyroid toxicity or to overstimulation of the sympathetic nervous system.

Widening of the fissure is more commonly encountered than is exophthalmos and can be ascertained more easily. Whenever the cornea is completely uncovered the eyes should be examined to discover whether other eye changes are present (Figs. 35, 36).

Spasm of Levator Palpebrae.—Spasm of the levator palpebrae is responsible for the photophobia and indirectly, therefore, for the lacrimation which is frequently seen in patients with hyperthyroidism. The spasm of the levator muscle may be unilateral and the conscious effort to bring the lid down may give a pseudoptosis to the other side. When it is bilateral the spasm is frequently unequal. It bears a more direct relationship to the degree of toxicity than does exophthalmos. The degree of widening varies greatly and is very inconstant and like

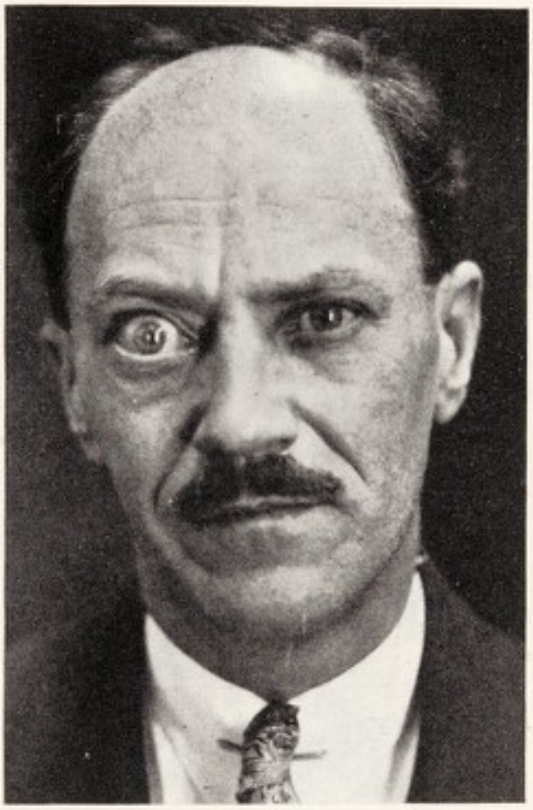

Fig. 37.—Unilateral exophthalmos which became bilateral in about three months. Anterior-posterior measurements: O. D. 22 mm. O. S. 17 mm. (Hertel's).

true exophthalmos, if allowed to remain too long, it will not be corrected after thyroidectomy.

Lid-lag.—Von Graefe[5] first drew attention to the sign best described as lid-lag. I believe that this sign is a manifestation of spasm of the levator palpebrae. Sometimes there is also a widening of the fissure but this sign may be absent because of an associated spasm of the orbicularis oculi.

Exophthalmos is considered one of the most striking symptoms in the syndrome of hyperthyroidism. No other disorder of the thyroid gland causes proptosis except postoperative hypothyroidism or the hypothyroidism which occurs in a certain group of patients in whom

a low-grade edema is present. Many of these patients are confined to bed and therefore the instrument must be applicable to these individuals who frequently exhibit more bizarre changes than do ambulatory patients.

Hertel's exophthalmometer is the instrument of choice for the anterior-posterior measurement as it is accurate, simple, portable and inexpensive. The measurements made with this instrument are accurate because it rests on the lateral orbital ridge which is ex-

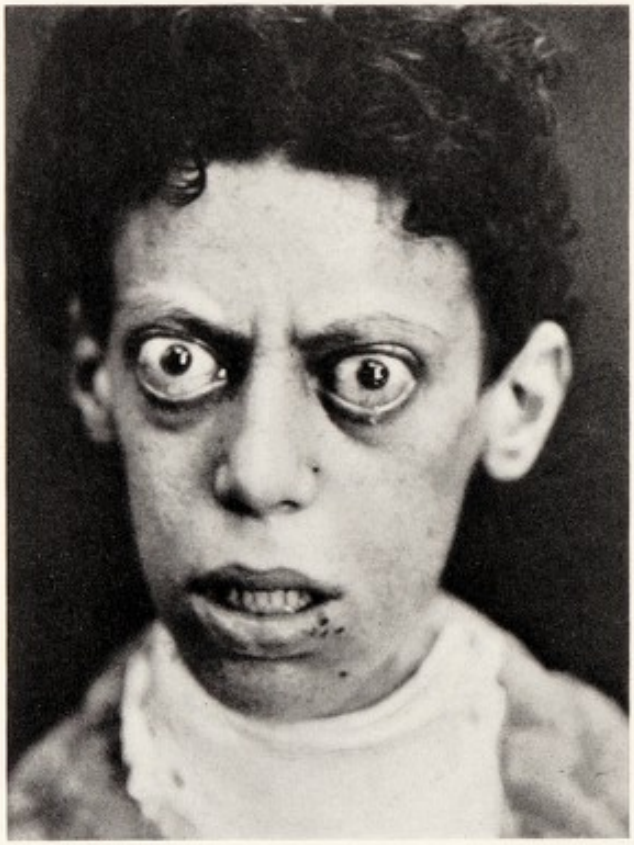

Fig. 38.—Exophthalmos with widening of the palebral fissures and corneal ulcers. Anterior-posterior measurements: O. D. 33 mm. O. S. 33 mm. (Hertel's). Fissures O. D. 18 mm. O. S. 18 mm.

tremely constant in its position. After measuring the position of the eyeball in over 1500 normal individuals we concluded that any anterior-posterior measurement, from 14 cm. to 20 mm. could be considered as within normal limits.

This eye sign has been bilateral in our series of cases of hyperthyroidism; no cases of actual persistent unilateral exophthalmos have been seen (Fig. 37). There are many cases in which the degree of exophthalmos is unequal, but the difference rarely amounts to more than 2 mm., the largest difference in our series was 5 mm.

However, this inequality may be relative rather than actual because the widening of the fissures is more commonly unequal or unilateral.

The exophthalmos frequently occurs without any accompanying widening of the palpebral fissures and in a certain number of cases the fissures are in the low normal range, because of spasm of the orbicularis oculi. This is not an unusual finding which may account for the absence of the Dalrymple sign in some cases.

The degree of exophthalmos is not an indication of the severity of the hyperthyroidism and may range from a nearly normal position

Fig. 39.—Postoperative exophthalmos with edema of the lids. This is a type which is sometimes seen in postoperative hyperthyroidism. Anterior-posterior measurements: O. D. 34 mm. O. S. 30 mm. (Hertel's). Fissures O. D. 14 mm. O. S. 12 mm.

which is found in many cases to luxation anteriorly to the lids (Fig. 38). This is a most serious complication as spasm of the orbicularis oculi often prevents the replacing of the lids. A canthoplasty may be done after which the lids are sutured by a purse string suture (Spaeth). In one case, that of a woman with a high degree of exophthalmos and no widening of the fissures the patient can at will protrude the eyeball and replace it without difficulty.

Progressive exophthalmos in association with other signs of hyperthyroidism requires earlier surgery than those cases in which

the exophthalmos is stationary, since the eye changes have a tendency to remain constant instead of returning to normal after operation. On the other hand thyroidectomy is definitely more beneficial in progressive cases than is rest or general treatment. No local eye treatment is beneficial in cases of exophthalmos due to hyperthyroidism.

Posey[6] states that the degree of exophthalmos may vary from day to day, it also varies from morning to evening and the position of the head varies the anterior-posterior position of the eyes.

Early edema of the orbit is readily corrected by thyroidectomy and exophthalmic eyes usually return to normal limits within two or three months after operation. However, in those cases in which fibrosis and lymphocytic infiltration has taken place because of a long-standing edema there is but a slight return toward the normal, the average recession in all of our cases amounting to 2 mm. (Figs. 39, 40).

In many cases the overcoming of the lid retraction and of its accompanying signs is the only improvement noted but this actually is more important cosmetically than is the recession of the eyes. It is the retraction of the lids more than the exophthalmos that gives the characteristic appearance to the patient with hyperthyroidism. The possibility of a recurrence of the exophthalmos should always be borne in mind and a guarded prognosis should be given for the possibility of recession is not nearly as definite as is recovery from tremor and tachycardia.

Exophthalmos and widening of the palpebral fissures is best treated by a thyroidectomy by a surgeon who has the ability to ascertain the amount of gland to remove and the cases in which to operate. On the part of too many surgeons there is a tendency to operate upon every patient with true or simulated exophthalmos.

Photographs and notes relating to cases of hyperthyroidism with exophthalmos should be accompanied by actual measurements with the name of the instrument used, as is done in reporting cases of glaucoma. Photographs are misleading and are of no value unless accompanied by this information.

The degree of exophthalmos is not so much a guide to the severity of hyperthyroidism as to its duration. Widening of the fissures more nearly indicates the degree of severity of the hyperthyroidism while muscle paralysis is a sign of its long duration.

Lack of Coordination.—The fact must be borne in mind that co-

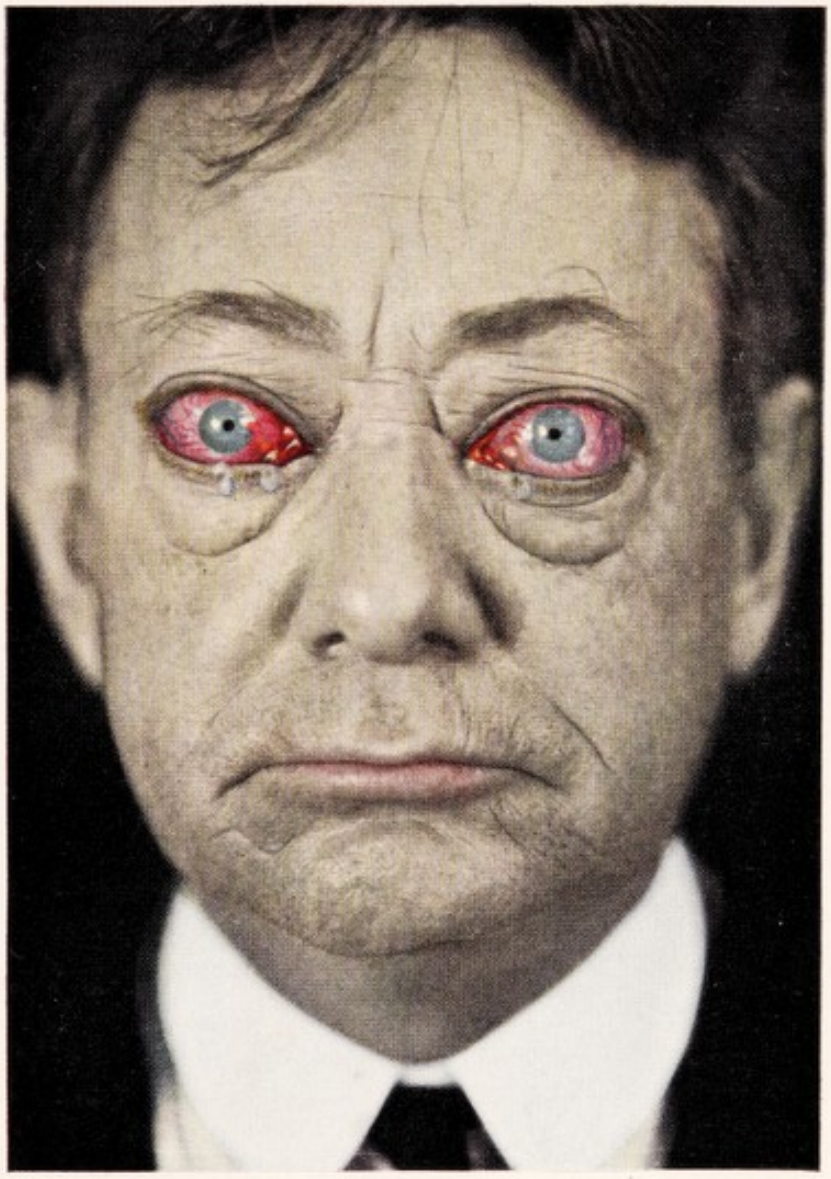

Fig. 40.—Postoperative exophthalmos with congestive type of conjunctivitis.

ordination is not perfect in eyes affected by thyroid disease. This is best attested by the absence of all convergence and the fairly common solitary paralysis. This is not a dependable sign of hyperthyroidism, as it occurs, recurs, and disappears during the course of an untreated case and may also be elicited in other general conditions, and may be simulated by the instillation of cocaine (Kocher and Jessup[7]).

Weakness of Convergence.—The force of convergence is definitely depressed in many cases of hyperthyroidism and is present in many of the conditions which involve the nuclei at the base of the brain, such as encephalitis, basilar meningitis, etc. Undoubtedly it is associated with the profound general debility which accompanies hyperthyroidism but it cannot be classed as a true sign of hyperthyroidism. When present it is very annoying and unquestionably leads many patients to seek relief from the oculist because of inability to use the eyes over a period of time. That this is a fact is easily shown, for in over 60 per cent of the cases in which surgery is required refraction has been determined within too short a period of time before the admission of the patient to the hospital for operation. The ocular stimulation contributes to the general nervousness and the effort to read is too great, so that reading should be restricted, especially in cases in which weakness of convergence is manifested, although there is a large group of patients in whom latent weakness is present.

Disturbance of Accommodation.—In association with the actual weakness of convergence there are a number of cases in which accommodation is definitely disturbed. A comparison with previous prescription will show a wide variance, a change of one and a half diopters not being unusual. The weakness of convergence and the disturbance of accommodation in these cases warrant the warning that glasses should only be prescribed with the understanding that they may have to be changed and it should be borne in mind that muscle exercises or even prisms may be indicated later. We usually do not prescribe glasses until six months after thyroidectomy. Recovery from these conditions of the eyes is very slow and the ability to use the eyes over a prolonged period of time may never become normal in these cases. It may be necessary to recommend that the patient change his employment as the condition of the eyes may sometimes delay an otherwise complete recovery, and must be investigated in all cases in which nervousness and fatigue continue after operation.

Tremor of the lids on closing, known as the "Rosenbach" sign, is due to spasm of the levator palpebrae. An associated spasm of the orbicularis is not constantly present. This sign is not dependable and must be classified as a secondary eye sign.

Gifford's Sign.—The difficulty of eversion of the upper lids—Gifford's sign—is worse in cases of exophthalmos in which the lids are retracted but it is very marked in those cases in which the upper lid is edematous and the fold is filled by edematous tissue. This fold may become almost solid and remain permanently edematous. Edema of the lower lids is less common.

Muscle Paralyses.—Muscle paralyses are rarely seen unless there is some exophthalmos but the paralysis is not due to the exophthalmos but to infiltration of the orbit by secondary fibrosis and lymphocytic invasion. The involvement of the muscles varies from weakness of a solitary muscle and transitory diplopia to complete bilateral external ophthalmoplegia. When the last of these is seen it means that the patient is in a serious condition. In all the cases we have seen there was a fatal termination.

The muscle most commonly involved is the right external rectus; involvement of the right superior rectus being next in order of frequency (Fig. 41). There is no muscle which may not be involved and it is not possible to classify these paralyses. There are certain interesting observations, however, that should be cited.

In cases of hyperthyroidism in which correcting operations for squint have been performed, the eyes return to the primarily manifested position. Recovery from muscle paralysis is not rapid and an operation may be required, but before resorting to operation one should procrastinate as long as possible or for at least six to nine months, because the surgical results are generally unsatisfactory. The discomfort which results from muscle instability or paralysis may delay convalescence and for this reason it may be necessary to resort to operative treatment in less than nine months.

Muscle fatigue is common and distressing and the use of the eyes increases the tendency to diplopia and naturally the nervousness is increased.

Paralysis of associated muscles may occur, of both superior recti as has been seen in six cases, or of an oblique and associated superior rectus. It is rather difficult to regard these paralyses of associated muscles as coincidental and I believe the facts do not justify such a conclusion. In so toxic a condition as hyperthyroidism it is not in-

conceivable that the nervous elements may be directly involved and that some of the muscle paralyses are central rather than peripheral in origin.

Although cases in which ptosis has been associated with toxic goiter are reported, in our series here not a solitary case was observed though, as already stated, cases of pseudoptosis are not uncommon. The muscle changes present a difficult problem. The fact that they are most frequently seen in late cases is another argument in favor of early surgery in cases in which the diagnosis of hyperthyroidism is made.

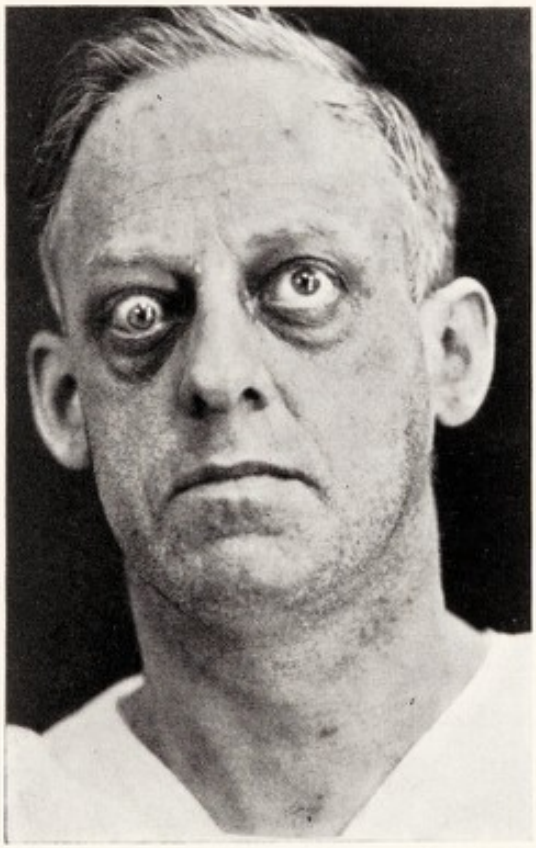

Fig. 41.—Paralysis of superior rectus muscle of the right eye.

As has already been stated there are some twenty eye signs of hyperthyroidism. It is rather superfluous to describe them all, as only widening of the fissures, exophthalmos, and muscle paralyses occur independently, but certain other conditions of the eye which are associated with hyperthyroidism should be noted.

Lacrimation is associated with hyperthyroidism in early cases of lid retraction in which the cornea is still sensitive especially when it is associated with photophobia which is probably due to the complete exposure of the pupillary area and iris to light, the protecting reflex

of the orbicularis being overcome by the overstimulated levator palpebrae. Later in the disease lacrimation diminishes, but whether this is due to decreasing sensitivity of the cornea or to decreasing activity of the thyroid has not as yet been determined. The faulty positions of the puncta and the stretching of the lids may account for the tendency of the tears to flow on to the cheek. Protecting the eyes by tinted lenses and the use of cold compresses often gives some relief from this difficulty.

The **cornea** itself may be involved in a low-grade superficial infiltration due either to the constant exposure, to lack of tears and consequent drying or perhaps to some central trophic disturbance as is suggested by two cases in which ulceration occurred for which no other cause could be assigned. However, the most common cause of corneal ulcer is lagophthalmos, in the presence of which the cornea becomes affected by the drying out that occurs during resting hours.

These ulcers get much worse during the night unless they are carefully treated during this time. They usually occur in cases in which spasm of the levator palpebrae is associated with exophthalmos. They are similar in character to those ulcers which are due to postganglion trophic changes and are best treated by early thyroidectomy and a Bullar shield plus the frequent instillation of any bland ointment especially at night. These ulcers are very annoying occurring as they do in patients who are as apprehensive regarding their appearance and the condition of their eyes, as are patients with hyperthyroidism. These ulcers should never be treated casually; they have a tendency to become deeply infiltrated and to form early and permanent scars; they may perforate by nature of their position and prolapse of the iris may occur. Ulceration of the cornea as the result of anterior luxation is only excusable in cases in which the patient refuses early thyroidectomy. If an early thyroidectomy is performed anterior luxation should never develop in a case of hyperthyroidism.

There are no diagnostic changes in the **fundus.** In certain cases hyperemia occurs which it is difficult to evaluate unless it is secondary to the exposure. However, although a low-grade retinitis might be present in certain cases, one cannot make the diagnosis of hyperthyroidism from ophthalmoscopic examination, which in nearly 2000 cases has not revealed a single sign in the fundus. Cases of choked disk are associated with thyroid disease but are not due to it. The muscle infiltration and orbital involvement may cause retrobulbar

inflammation and edema of the nerve head. In cases in which this condition is known to be of long standing it is probably a sequela of the hyperthyroidism.

Since there is no change in the fundus one naturally would not expect to find any changes in the visual field. Although the work of Holloway[8] shows some scotoma and other field changes we do not feel that they are of any diagnostic value as far as hyperthyroidism is concerned. These patients are poor subjects for study of the visual field because of their inability to cooperate and their rapid fatigue. It is an interesting observation that visual acuity is usually increased and a very common statement made by these patients is that their vision has become sharpened and more clear.

Eleven cases of **glaucoma** or rather of a transitory increased tension have been noted. The high tension ranged (Schiotz-Gradle) from 35 to 100 and was not associated with vision loss or field changes except in one case, with a high degree of myopia in which glaucoma continued after operation until the patient failed to return for further observation. In the other ten cases, the increased pressure disappeared immediately after thyroidectomy and later observations revealed normal pressure. In all of these cases the patients suffered from severe headaches which did not recur after thyroidectomy. Among these ten cases not one showed any fundus change such as is characteristic of glaucoma. Corneal anesthesia and shallowing of the anterior chamber were present and both of these signs are absent at the present time.

Pigmentary changes are not constant in hyperthyroidism and are a poor diagnostic aid. Injection of the ocular conjunctiva is directly related to the amount of exposure and of external irritation. Continued use of the eyes, especially when the muscles are affected, causes an irritation of both the ocular and palpebral conjunctivae. The application of zinc sulphate ($\frac{1}{4}$–$\frac{1}{2}$ grains) or of adrenalin (1 drachm of 1 : 1000 solution in 1 ounce of aqua distillata) is usually sufficient to give relief.

In dealing with cases of hyperthyroidism the oculist very frequently is confronted by a query on the part of the patient as to whether or not the operation was a success because of a failure to recover cosmetically. One cannot be too careful or guarded in replying to these patients as they are very irritable and hard to handle. Before the operation is performed they should never be led to believe that the local condition will right itself quickly or completely. They

must be instructed as to the proper use of their eyes and the necessity for local rest. Early thyroidectomy is indicated in the progressive cases, and in cases of ulceration. Continued paralyses may be due to residual weakness of the ocular muscles.

Postoperative exophthalmos is usually due to hypothyroidism. Care must be taken not to perform a second operation in these cases because of a suspected recurrent hyperthyroidism. In this form of exophthalmos there is usually no widening of the fissures but edema of both the upper and lower lids is present; it is progressive and is difficult to handle. Thyroid extract should be administered to these patients and the eyes should be examined repeatedly so that further proptosis may be prevented. In this type of exophthalmos the eyes recede very little. It presents a most serious problem.

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CHAPTER XVII

CARBOHYDRATE METABOLISM IN HYPERTHYROIDISM

HENRY J. JOHN

THE presence of glycosuria in a case of hyperthyroidism is not an uncommon occurrence. For several decades writers in this country and abroad have reported the coincident presence of this finding. Joslin and Lahey[1] in their recent study of 500 cases of disease of the thyroid report the occurrence of glycosuria in 38.6 per cent of 228 cases of primary hyperthyroidism and in 27.7 per cent of 83 cases of adenomatous goiter with secondary hyperthyroidism, as compared with only 14.8 per cent of 189 cases of nontoxic goiter and 13.6 per cent of patients without diabetes or any disease of the thyroid gland (Table 1). In a series of 100 glucose tolerance tests which I made

TABLE 1

GLYCOSURIA IN HYPERTHYROIDISM

Author.	Number of cases.	Percentage of cases showing glycosuria.
Marsh[2]	...	2.0
Joslin and Lahey[1]: Primary hyperthyroidism	228	38.6
Secondary hyperthyroidism	83	27.7
Nontoxic goiter	189	14.8
Schulze[3]	16	25.0
John, present publication	100	19.0
Bryan[4]: Toxic adenoma	244	3.2
Nontoxic adenoma	982	1.0
Exophthalmic goiter	361	1.1

in 82 cases of hyperthyroidism and 10 cases of colloid goiter there was a fasting glycosuria in 19 per cent.[5] In Table 1 are given the reports

of various authors as to the incidence of glycosuria in cases of hyperthyroidism.

When chemical blood analyses began to be used generally, hyperglycemia, either with or without glycosuria was demonstrated in sporadic cases of hyperthyroidism. A review of the literature showing the incidence of hyperglycemia in hyperthyroidism (Table 2) shows a very great discrepancy in the findings of different investigators.

TABLE 2

THE INCIDENCE OF HYPERGLYCEMIA IN HYPERTHYROIDISM

Author.	Number of cases.	Per cent of cases showing hyperglycemia.
Fitz[6]	1800 exophth.	0.5
Wilder[7]	2340 exophth.	0.6
von Noorden and Isaac[8]	1000	0.6
Wilder[7]	1131 toxic aden.	2.0
Sattler[9]	....	3.0
Lund and Richardson[10]	29	3.4
John, present publication	9000	6.88
John, 1928[11]	3335	8.5
Mojarova[12]	84	25.3
Flesch[13]	....	60.7
Geyelin[14]	27	90.0
Total 18,746	Average 18.31	

Experimental studies on animals made to determine the relation of the thyroid gland to the blood sugar content, showed that extirpation of the thyroid gland leads to a lower blood sugar level, while on the other hand, the injection of thyroxin or the feeding of hashed thyroid gland to animals, or the injection of thyroid extract produces hyperglycemia. In other words, various workers tried to duplicate the clinical finding of hyperglycemia in the syndrome of hyperthyroidism. Many observations regarding the thyroid blood sugar relation in humans are recorded.

The incidence of hyperthyroidism among cases of diabetes is comparatively low as can be gleaned from Table 3, the average being

TABLE 3

THE INCIDENCE OF HYPERTHYROIDISM IN DIABETES

Author.	Number of cases of diabetes.	Number of cases with hyperth.	Per cent.
Greeley[15]	614	6	0.97
Joslin and Lahey[1]	4917		
Primary hyperthyroidism	....	43	0.87
Toxic adenoma	....	28	0.57
Simple goiter	....	4	0.08
Wilder[7]	1249		
Primary hyperthyroidism	....	14	1.1
Toxic adenoma	....	22	1.8
Rabinowitch[16]	3000	24	0.8
von Noorden[8]	1000	30	3.0
Murphy and Moxon[17]	827	8	0.96
		Average	1.68

1.68 per cent. A diabetic patient is of course subject to the same ailments as is a nondiabetic individual. The incidence of diabetes among cases of hyperthyroidism, on the other hand, is a fairly consistent figure as can be gleaned from Table 4, and is nearly twice as high as the general incidence of diabetes.

TABLE 4

INCIDENCE OF DIABETES IN HYPERTHYRIODISM

Author.	Thyroid disease.	Diabetes.	Per cent.
Joslin and Lahey[1]:			
Total hyperthyroidism	5908	75	1.26
Primary hyperthyroidism	1751	43	2.5
Secondary hyperthyroidism	....	28	4.3
Sattler[9]	1866	56	3.0
O'Day[18]	....	4	
Fitz[6]	1800	9	0.5
John, all thyroid diseases[19]	9000	207	2.3
		Average	2.31

The present study comprises clinical and laboratory observations made over a period of ten years including an intensive study made during the period from January 1, 1925 to October 1, 1931. During this time, about 9000 cases of thyroid disease have been seen at the Cleveland Clinic, most of which were cases of hyperthyroidism (exophthalmic goiter, Basedow's disease, adenoma with hyperthyroidism). Of this group 620 cases or 6.88 per cent showed some degree of nonphysiologic hyperglycemia (fasting or two and one-half hours or more postprandial) either with or without glycosuria. During these years it has been our practice to make a routine blood sugar estimation in every new case, as this gave much information about many unsuspected cases of diabetes which would not have been found otherwise. Most of the cases in which there was some degree of nonphysiologic hyperglycemia were then followed up and studied further for a period of ten years and the data secured from this study are offered here.

When the 620 cases showing nonphysiologic hyperglycemia were followed further, it was found that in some cases the hyperglycemia was present in only the primary examination and that in some others the hyperglycemia disappeared without any medication. Consequently these cases are not included in our consideration. In some other cases the patients have not been observed for a long enough period to be included in this series. In some cases inadequate data were available and for that reason they are not included. Intensive observations over a period of from one to ten years were made in 166 cases, all of which showed a definite disturbance in carbohydrate metabolism. These alone are included in this special study. The number of years the patients in this series have been under observation is shown in Table 5.

TABLE 5

THE LENGTH OF OBSERVATION ON 166 CASES OF HYPERTHYROIDISM AND DIABETES OVER A PERIOD OF YEARS (John)

Years of observation.	1	2	3	4	5	6	7	8	9	10
Number of cases.....	82	32	19	11	8	4	1	..	1	8

By a very conservative estimate, however, I should say that some 200 cases showed what might be called definite hyperglycemia like that of diabetes. In some of these cases the hyperglycemia was purely functional in type and therefore disappeared in a few weeks or months

after thyroidectomy, on dietary treatment alone or combined with insulin, but—as further experience taught me—the hyperglycemia would not have disappeared in all cases without such treatment. In the total 620 cases of hyperthyroidism in which hyperglycemia was present it remained in 30 per cent and it disappeared in 70 per cent. This makes the incidence of diabetes in this series of cases of thyroid disease 2.1 per cent, a figure which is close to the average incidence of diabetes in cases of hyperthyroidism as reported in the literature (2.3 per cent). Thus, out of this series, approximately 200 patients remained diabetic, had to be treated as such and 35.7 per cent of these are still taking insulin in order to control the diabetic state.

This summarizes briefly the problem and is an answer to those who try to offer an academic discussion of this subject, which interesting as it may be from the standpoint of the laboratory, cannot be fully adopted by a clinician who has to treat these patients, many of them for the rest of their lives.

This point is well illustrated by the report of Sattler[9] who in 1909 collected 56 reported cases in which diabetes was associated with hyperthyroidism. Thirty-seven of these cases had been followed for a sufficient length of time to afford positive information. Of these 37 cases, in 24 (64.8 per cent) there was a fatal termination within comparatively short periods of time and in 7 cases the patients died in coma.

The incidence of diabetes in this special series of 166 cases and its distribution, according to sex and decades, is given in Table 6. The

TABLE 6

THE INCIDENCE OF DIABETES AND HYPERTHYROIDISM AND ITS DISTRIBUTION ACCORDING TO SEX AND DECADES—166 CASES (John)

Age decade.	II.	III.	IV.	V.	VI.	VII.	Per cent.
Male	..	1	9	11	8	5	20
Female	1	4	13	37	53	23	80
Total	1	5	22	48	61	28	
Per cent	0.6	3	13.2	28.9	36.7	16.8	

Joslin and Lahey[1]; male 19, female 81 per cent.

highest incidence is in females as one would expect, since the highest incidence of hyperthyroidism occurs in females. As for the age distribution of the associated occurrence of diabetes and hyperthyroidism

I have tried to discover how it compares with the age incidence of diabetes without hyperthyroidism, and I have found that the two curves run quite parallel, as shown in Fig. 42. This suggests that hyperthyroidism does not play an important etiologic rôle as far as the age incidence is concerned. Table 7 shows clearly the priority in appearance of hyperthyroidism which occurred in 85.5 per cent of the cases of primary hyperthyroidism and in 51.9 per cent of the cases

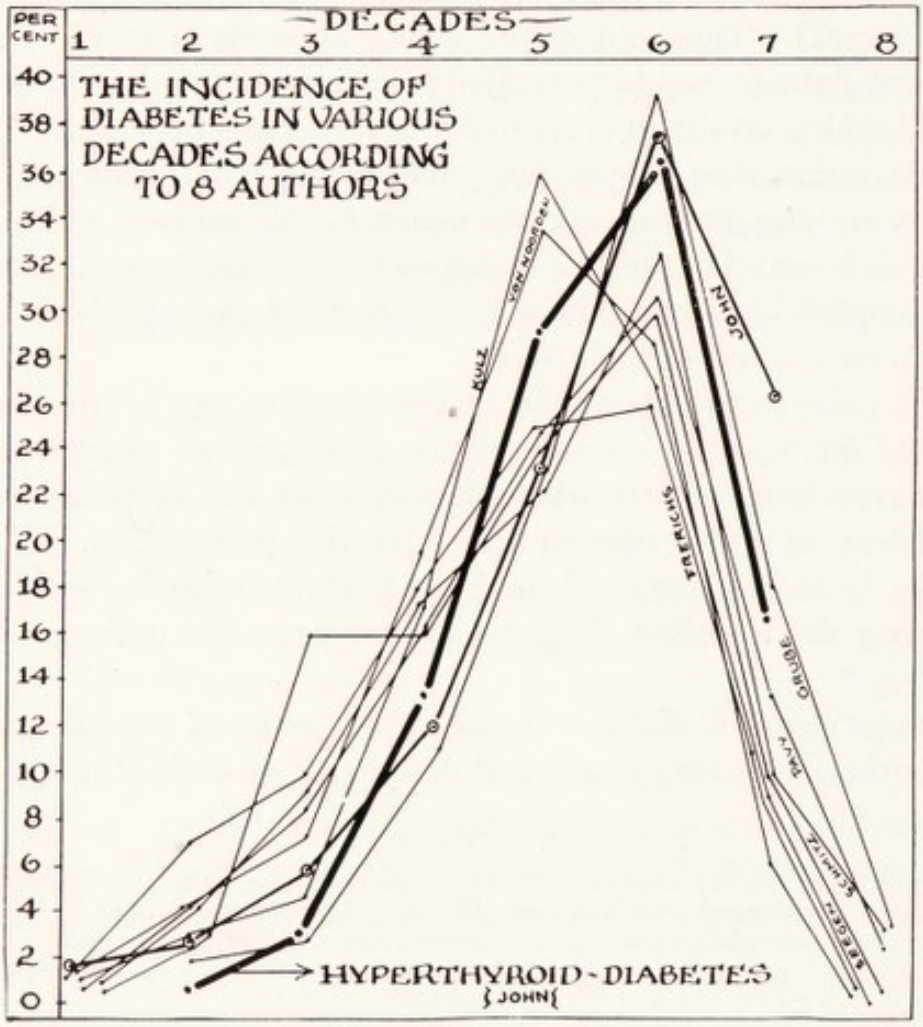


Fig. 42.—Incidence of diabetes in age decades.

of toxic adenomata, an observation which may have an important etiologic significance.

In Table 8 I offer an analysis of the 166 cases in this series in order to show the progress of these patients. After thyroidectomy 55 per cent of the patients improved as far as their diabetic status was concerned; in 15 per cent the diabetic condition remained stationary, and in 30 per cent the patients required either more insulin or if not taking insulin, insulin will have to be administered sooner or later.

TABLE 7

PRIORITY IN APPEARANCE OF HYPERTHYROIDISM OR DIABETES IN 152 THYROID DIABETICS (According to Joslin)

Condition.	Number of cases.	Hyperthyroidism precedes diabetes.	
		Number of cases.	Per cent.
Primary hyperthyroidism:			
Fitz,[6] prim. and sec. not differentiated.	22	21	95.5
Wilder[7]	12	9	75.0
Joslin-Lahey[1]	28	23	82.1
Total	62	53	85.5
Secondary hyperthyroidism:			
Toxic adenoma:			
Wilder[7]	19	9	47.4
Joslin-Lahey[1]	8	5	62.5
Total	27	14	51.9

TABLE 8

ANALYSIS OF 166 CASES OF HYPERTHYROIDISM AND DIABETES (John)

	Per cent.
Male	20
Female	80
Diabetes severe in	31
Diabetes mild in	69
Hyperthyroidism severe in	35
Hyperthyroidism mild in	65
After Thyroidectomy	
Diabetes improved in	55
Of those still taking insulin	23.5
Diabetes more severe in	30
Of those still taking insulin	46
Diabetes stationary in	15
Of those still taking insulin	62
All cases still taking insulin	35.7

As stated above, of the entire group 35.7 per cent are still taking insulin.

It is obvious that glycosuria in itself does not tell us a great deal regarding the status of the carbohydrate metabolism unless we know also the blood sugar response to the ingestion of carbohydrates and the level of the renal permeability to sugar. In a series of 100 glucose tolerance tests which I made some years ago in 82 cases of hyperthyroidism and 10 cases of colloid goiter, 66 per cent of the curves

indicated an impaired tolerance.[20] In a larger series of 239 cases of hyperthyroidism which I reported in 1930, 63.5 per cent showed an impaired tolerance. Such an incidence is as high as that found in cases of obesity (65.6 per cent). The renal threshold on the other hand as estimated in 180 cases of hyperthyroidism was low; the thresholds for sugar being below 180 mg. per 100 cc. of blood in 81.1 per cent of the cases; the average renal threshold was at 147 mg. per 100 cc. of blood. The excretion of sugar by a patient with a low renal threshold is usually of little or no significance. The measure of sugar excretion by the application of Allen's paradoxical law,* however, does throw some definite light on the differentation of glycosuria in this group of cases and is of distinct value as Rabinowitch[16] has shown. However, I should offer a caution as to any hurried diagnosis until such a case has been followed over a sufficiently long period for one to make sure of his premises, for no single laboratory functional test should ever be considered as final.

Hepatic Lesions Associated with Hyperthyroidism.—The liver in a case of hyperthyroidism is supposed to be glycogen-poor. It either does not bind glucose or else lets it go too readily, or else there is such an enormous demand for the glucose in the body that it is rapidly used and has no chance of being stored in the liver. In an editorial in the Annals of Internal Medicine,[21] regarding the hepatic lesions associated with exophthalmic goiter, the author brings out the following points: "Patients dying in exophthalmic goiter show some degree of simple or pigmented atrophy, but the most marked change was the very frequent occurrence of marked diffused fatty degenerative infiltration bearing all the earmarks of a severe toxic process (like the classic phosphorus liver). The heart and the kidneys presented a marked fatty degenerative infiltration." The author explained these changes as being the result of acute disturbances in the oxygenation of the body, resulting from or dependent upon the syndrome of Graves' disease.

"The livers further show at times a peculiar form of chronic parenchymatous hepatitis in the form of lymphocyte infiltration, bile duct proliferation, and increase in stroma of the islands of Glisson." To investigate these changes, Weller[22] studied 44 autopsies on patients who had showed no other condition than hyperthyroidism and made the following reports (Presented before the Association of American Physicians in 1930):

* The more carbohydrate that is taken by a diabetic the less is utilized.

	Hyperthyroidism.	Controls.
Number of cases showing no hepatitis	6	30
Number of cases showing slight or moderate hepatitis	16	13
Number of cases showing well-marked hepatitis	22	1

Weller summarized his findings as follows: "A well marked chronic parenchymatous hepatitis was found at autopsy in 22 of 44 selected cases of Graves' disease, while but one case of the same degree of hepatic lesions was found in a control series of the same number of autopsies. In the Graves' disease group, only 6 showed no evidence of hepatitis while in the control series 30 out of the total of 44 cases showed no hepatitis. The coincidence of hepatitis with exophthalmic goiter is therefore significant and is in accord with clinical observations of the occurrence of functional disturbance of the liver in cases of Graves' disease."

Simonds and Brandes[23] rendered dogs thyrotoxic by heavy thyroid feeding (thirty-two to one hundred days). The livers of these dogs were practically devoid of glycogen.

Asher[24] found that in animals made absolutely free of carbohydrate by thyroid feeding and phloridzin the addition of fat to the food increased the output of sugar. From this he decided that the hyperthyrotic liver possesses the ability to form glycogen but cannot fix it so that after its formation it is relinquished by the liver.

Charvăt and Gjurič[25] who studied the problem of carbohydrate metabolism in hyperthyroidism came to the conclusion that the Basedowian liver is the cause of hyperglycemia because it does not bind its glycogen in a stable manner, that its glycogen is labile and that the tissues burn glucose well, and furthermore, in order to use up as much of the circulating glucose as possible, the renal threshold in hyperthyroidism is raised.

These authors offered as an explanation that in Basedow's disease a condition of liver shock is present in which the glycogen-poor liver binds glycogen very loosely and lets it go easily, whereas the tissues in patients with hyperthyroidism need sugar badly as a ready and an excellent supply of energy; moreover, sugar does not burden the organism with any specific dynamic action as do fats and proteins. Inasmuch as the liver through the lability of its glucose causes a marked hyperglycemia, the renal threshold is easily crossed and theoretically glycosuria should result in all cases. This, however, is not

the case as Charvăt and Gjurič have shown, for the threshold rises in order to enable the tissues to use up a greater portion of the glucose.

In view of their experiments the authors studied the arterial and the venous blood sugar for a period of several hours after the injection of normal saline, in normal individuals and in patients with diabetes

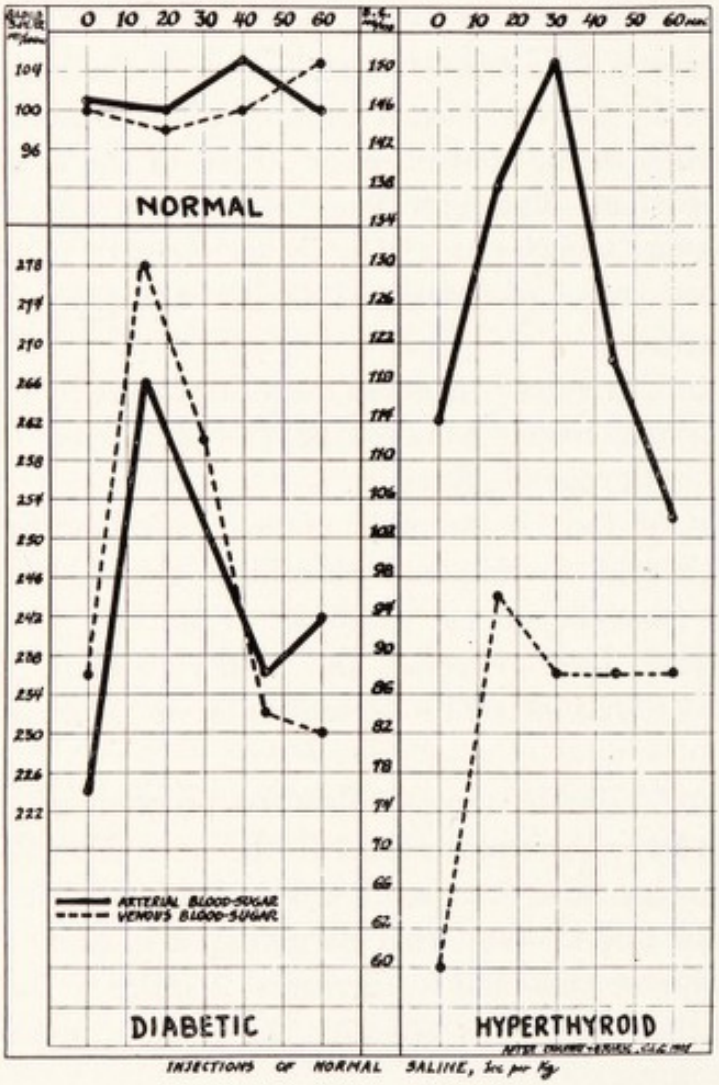


Fig. 43.—Curves showing variations in arterial and venous blood sugar after the injection of saline solution in normal and diabetic individuals and in patients with hyperthyroidism.

and again in cases of hyperthyroidism. In normal individuals they found that without the injection of saline the arterial and the venous sugar fluctuates but inappreciably. After the injection of saline in normal individuals, the discrepancy between arterial and venous blood also is slight (Fig. 43). They say that such an injection is not sufficient to mobilize the sugar, either in the tissues or in the liver.

On the other hand, the injection of saline into patients with hyperthyroidism presents a picture which is more interesting (Fig. 43). Here there is a definite dissociation between the arterial and the venous sugar. The arterial sugar rises higher than the venous sugar which rises but little or may even be decreased. Such an injection causes shock to the liver to which it answers by releasing its labile glycogen into the circulation. That this is in reality the liver sugar and not the tissue sugar is shown by the fact that the arterial blood sugar rises whereas the venous sugar is not changed. There is thus a certain surplus in the arterial blood which is caught by the tissues and does not reach the venous blood. It is a well-known fact that glucose itself is the best stimulant for the utilization of glucose by the tissues. Charvăt's former work[26] showed that the burning of glucose in the tissues of patients with hyperthyroidism is very active.

In the case of diabetic patients the picture is somewhat changed. In such a case the arterial sugar does not rise as markedly as is the case in hyperthyroidism and the curve often approaches that of normal individuals. The venous sugar on the other hand is higher than the arterial sugar (Fig. 43). According to Gjurič's view in cases of severe diabetes the tissue rather than the liver binds the sugar in a labile manner and releases it easily into the venous blood which consequently is higher than the arterial sugar. In this manner the glycoregulatory disturbance of the patient with hyperthyroidism differs markedly from that in diabetes.

That the liver is not the chief factor in the production of hyperglycemia in hyperthyroidism is suggested by the following points:

1. The incidence of hyperglycemia in hyperthyroidism is too low.

2. The incidence of hyperglycemia in hyperthyroidism is irregular; severe cases usually show no hyperglycemia, mild cases may show pronounced hyperglycemia. If the liver were the primary factor the degree of hyperglycemia would be proportionate to the severity of the hyperthyroidism.

3. In general the renal threshold in patients with hyperthyroidism is low (John) but the excretion of sugar bears no relation to the severity of the hyperthyroidism. If the storage function of the liver were at fault glycosuria would automatically disappear after thyroidectomy but this does not happen. In 35.3 per cent of the 166 cases reported here the patients have to continue to take insulin, for even though the condition of the liver has improved the pancreas still does not function sufficiently.

Ketone Bodies.—Thyrotoxic individuals who are given a carbohydrate-free diet for a few days show a marked increase of ketone bodies in the blood. In the normal individual the fasting value of ketone bodies never exceeds 3.5 mg. per 100 c.c. of aceto-acetic acid and 5.5 mg. per cent of beta-oxybutyric acid. In the thyrotoxic patient the ketone bodies rise as high as 16 mg. per 100 cc. of aceto-acetic acid and 18 mg. per 100 cc. of beta-oxybutyric acid. The patient with hyperthyroidism has a lowered glycogen reserve available for metabolism.

Levulose.—Strauss[27] first introduced the determination of alimentary levulosuria as a method for testing the liver function. Isaac and Adler[28] showed experimentally that of all the organs and cells of warm-blooded animals only the liver is capable of transforming levulose into dextrose. According to Isaac the alimentary levulosuria is dependent on the fact that the part of the levulose which is not converted into glycogen or is not burned, in cases of functional inability of the liver to convert levulose into dextrose, passes as levulose into the blood and is excreted in the urine.

Kugelmann offers the following conclusions: "We can now say with certainty that the thyrotoxic liver suffers not only severe injury in its glycogen depots but has also lost the capacity to change large amounts of levulose into dextrose and to utilize them later" (Fig. 44 represents Kugelmann's experiments along this line).

Insulin.—Ten units of Burroughs and Wellcome's insulin given intravenously in man causes a rise of blood sugar of 15 to 20 mg. per 100 cc. of blood in the first ten minutes, after which it falls. Bürger demonstrated that this primary rise of blood sugar is dependent upon the glycogen function of the liver. In cases of Graves' disease studied by the Bürger method by Kugelmann,[29] this initial hyperglycemia was seen in none. This is a further proof of poverty in glycogen in the hyperthyrotic liver.

Rathery, Kourilsky, and Laurent[30] have shown that the blood sugar in depancreatized, starved, and starved and phloridzinized dogs is distributed in the same proportions during the maximum effect of insulin as in normal animals. The discharge of glycogen from the liver is not influenced by its glycogen content. In dogs under similar experimental conditions, the hyperglycemia immediately following insulin upsets irregularly the relationship between the blood sugar in different vascular areas.

It would seem that with a little help from insulin, the liver re-

sumes gradually its capacity to bind more glucose and keep a more even blood sugar level. Were it the state of hyperthyroidism alone which brings about that functional change which manifests itself in hyperglycemia, then we would expect the degree of hyperglycemia to bear a direct relation to the severity of the hyperthyroidism, and the incidence of hyperglycemia in cases of hyperthyroidism would be greater than it is. This is not so, however, for some of the most severe derangements of carbohydrate metabolism are found in some of the

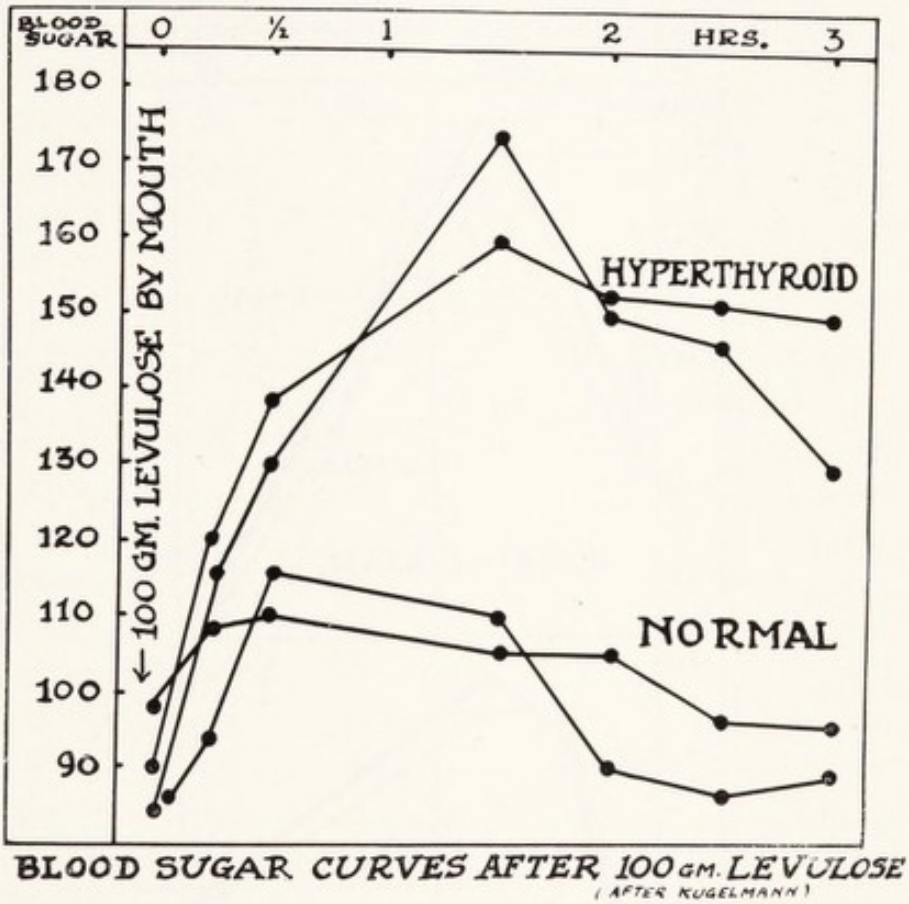


Fig. 44.—Curves showing variations in blood sugar after the injection of 100 Gm. of levulose.

mildest cases of hyperthyroidism, and many of the most severe and even toxic states of hyperthyroidism show no disturbance of carbohydrate metabolism. Insulin brings about improvement in all cases, either by its direct action, or by its protein-sparing action or through its influence on the storage of glycogen or on the diminution of the ketone bodies, or as the result of all four of these. The fact that disturbed carbohydrate metabolism rights itself in only the mild cases suggests that the protein-sparing function may play a rôle in the carbohydrate metabolism.

As for the clinical effect of insulin on hyperthyroidism, one may reason that it perhaps improves the patient's general metabolic condition, giving him a better chance to store glycogen in the liver and thus to combat acidosis; to store glycogen in the heart muscle and thus to give it a better chance to do its work; to spare protein by the increased oxidation of glucose; and to store glycogen in the muscles and thus to eliminate the instability of the organism in general. There is perhaps nothing specific about the action of insulin.

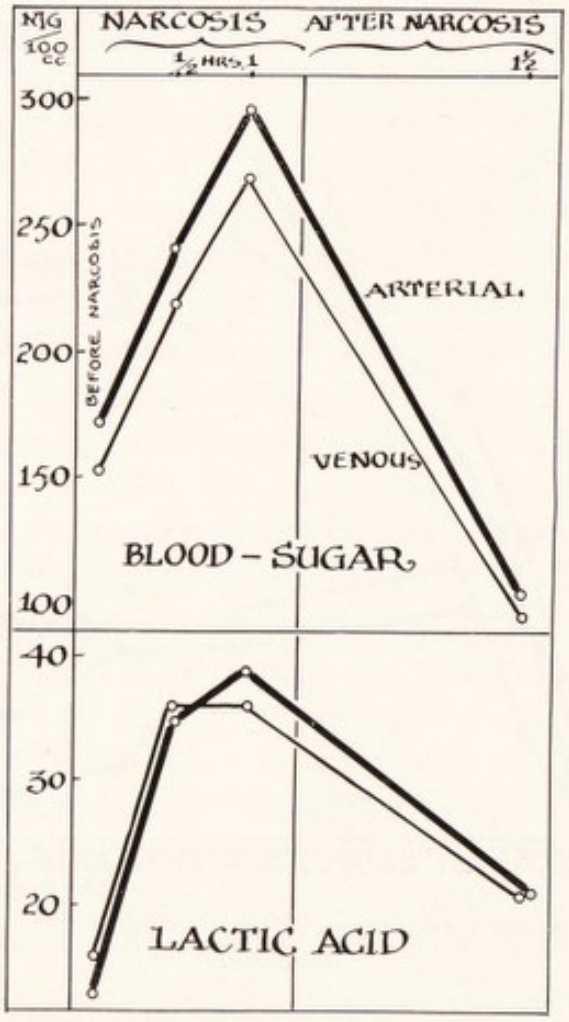


Fig. 45.—Variations in sugar and lactic acid in the blood during narcosis.

The Effect of Anesthesia on Blood Sugar.—The effects of anesthesia on the blood sugar have been studied by Dewes[31] and by Epstein and Aschner.[32] They found that hyperglycemia was produced by surgical anesthesia if the procedure was serious or prolonged. Epstein and Aschner found no change in the blood sugar in four minor operations done under local anesthesia. In five cases in which nitrous oxide-oxygen anesthesia was used there was a marked rise in the

blood sugar of over 100 mg. in some cases; a slighter rise was shown in some cases and none in only three.

Best[33] says: "Most of the anesthetics seriously diminish the efficiency of insulin. Liberation of epinephrine during the partial asphyxiation and the tendency toward an increased hydrogen-ion concentration in the blood are probable contributing factors in this effect."

Fuss[34] who used ether narcosis (closed mask) on dogs showed that there is a considerable rise of blood sugar which drops only gradually after narcosis is discontinued, the curve simulating the glucose toler-

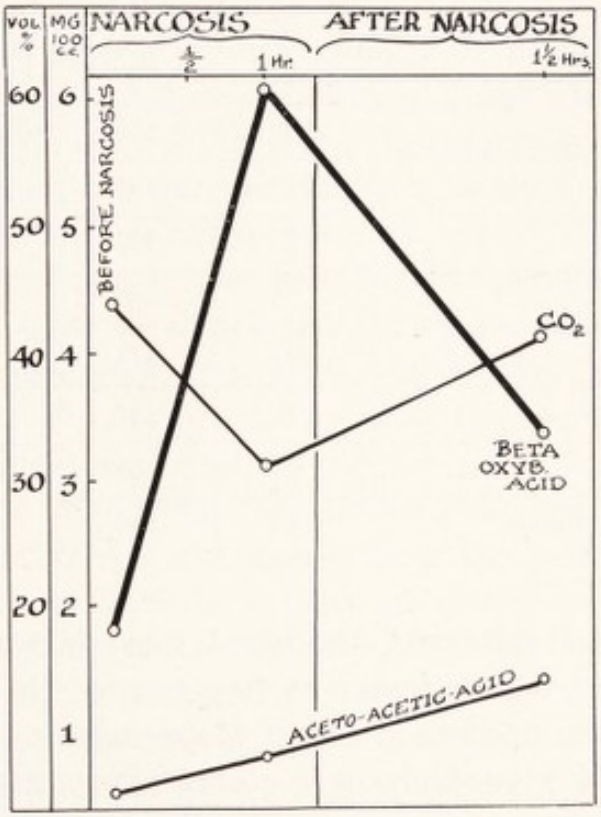


Fig. 46.—Variations in aceto-acetic acid and beta-oxybutyric acid during narcosis.

ance curve of a prediabetic. The relationship between the arterial and venous sugar is the same as in a normal waking state. The lactic acid during this time rises and falls after the discontinuation of narcosis just as does the beta-oxybutyric acid. The rise of the aceto-acetic acid, however, still continues one and one-half hours after narcosis has been discontinued. The CO_2 drops during narcosis gradually recovering its initial level after narcosis has been discontinued (Figs. 45, 46).

My own observations of the effect of anesthesia on the blood sugar content are given in Table 9. A marked discrepancy in the blood

TABLE 9

THE EFFECT OF GENERAL ANESTHESIA ON BLOOD SUGAR

Operation.	Blood sugar.		Per cent.	
	Before operation.	After operation.	Increase.	Decrease.
Massive resection of carcinoma of pancreas, colon, stomach	182	395	117	
Gallbladder drainage	131	143	9	
Lobectomy	78	147	89	
Thyroidectomy	88	98	11	
Thyroidectomy	84	109	29	
Thyroidectomy	106	118	11	
Thyroidectomy	133	168	26	
Thyroidectomy	155	193	27	
Thyroidectomy	76	89	17	
Tonsillectomy	303	434	43	
Tonsillectomy	95	89	..	6
Hemorrhoidectomy	97	68	..	42
Incision of infected thumb	150	139	..	7

sugar response will be noted, the blood sugar increasing from 9 to 117 per cent or decreasing from 6 to 46 per cent. On the basis of the previous discussion one would expect blood sugar to rise only in the cases which have a good glycogen storage and consequently a rise would be a good sign.

It would appear obvious from the above findings that in cases of hyperthyroidism in which there is a tendency to hyperglycemia the use of inhalation anesthesia should be minimized.

It is a good preoperative measure to give a patient 250 cc. of 10 per cent glucose made up in saline solution, intravenously, together with 10 to 20 units of insulin depending on the patient's condition. When the glucose is buffered with insulin, hyperglycemia does not result even in diabetic cases, as I have shown in my observations on the intravenous administration of glucose in cases of diabetes and in cases of acidosis as well as in ordinary surgical cases.[35] Such a procedure therefore is both logical and helpful, both before and after op-

eration, for the first three days following the operation is the critical period for the patient.

Postoperative Acidosis.—Acidosis is a well recognized complication of the postoperative course after thyroidectomy. The pulse rate in such cases is high and the patient can become semicomatose or stuporous immediately after operation. Is the acidosis in these cases of the same type as diabetic acidosis? Diabetic acidosis is due to the inability of the organism to burn glucose, this in turn producing an incomplete combustion of fats with the resultant accumulation of ketone bodies in the blood stream (acetone, diacetic acid, beta-oxybutyric acid) and consequent acidosis. In uncomplicated hyperthyroidism, however, there is no such inability to burn glucose, but there is rather an inability to store glycogen and a general increase of the metabolic process, so that all the available carbohydrate, including the glycogen reserve of the liver and muscles is often utilized, with resultant *hypoglycemia*. Holman[36] cites a case of hyperthyroidism in which the basal metabolic rate was plus 29 and plus 35 per cent on two occasions. After thyroidectomy, the pulse rate rose to between 180 and 250, immediately after operation, this very high rate lasting for sixty hours. Twenty-four hours after the operation the patient was in a semicomatose condition and her blood sugar at that time was found to be only 48 mg. per 100 cc. Glucose solution, 20 per cent, was administered, and immediately the patient became conscious, but six hours later the patient again went into a deep stupor. She was again given glucose, and immediately became conscious. It is clear that in this case the stupor was due to hypoglycemia, a condition similar to the hypoglycemia of an insulin reaction. This is a condition which should be borne in mind and blood sugar studies during the postoperative period are often of great value.

Basal Metabolism.—The relationship of the basal metabolic rate to the glucose tolerance in a series of cases of thyroid disease is shown in Table 10. In 60.6 per cent of the cases analyzed the glucose tolerance curve was diabetic or prediabetic in type while the basal metabolic rates ranged from minus 3 per cent to plus 90 per cent. The case in which the metabolism was minus 3, however, was one of simple goiter, not of hyperthyroidism. In 39.4 per cent of the cases the glucose tolerance curve was normal in type and the basal metabolic rate in these cases varied from minus 3 per cent to plus 80 per cent. On the basis of this study it seems evident that the height of the basal rate bears no relation to the carbohydrate

TABLE 10

THE RELATION OF BASAL METABOLIC RATE TO GLUCOSE TOLERANCE TESTS IN 66 CASES OF THYROID DISEASE (John)

	Normal BMR.	Increased basal rate, per cent.									Total.	Per cent.
		+10	+20	+30	+40	+50	+60	+70	+80	+90		
Total cases.....	3	11	8	11	10	10	4	4	4	1	66	
Type of curve: Diabetic.....	2	5	3	7	5	8	3	4	2	1	40	60.6
Normal.....	1	6	5	4	5	2	1	0	2	0	26	39.4

metabolism. The mild derangements of the carbohydrate tolerance that have been observed in this series of cases may be but functional disturbances. They may disappear only in part when hyperthyroidism is eliminated, either by operation or by other treatment, thus showing that something other than the hyperthyroidism is playing a part.

I feel that the explanation of the disturbed carbohydrate metabolism associated with hyperthyroidism is not found in the state of hyperthyroidism *per se*, but that it is due rather to some other factor which I believe is a "diabetic anlage" which was present in the patient before the hyperthyroidism developed; infection or obesity would have brought about the same disturbance. Thus Naunyn[37] in 1917 made the following statement: "I consider it justifiable to draw the conclusion that the thyroid causes glycosuria only where there exists a predisposition (anlage) to diabetes."

The following statement was made by von Noorden[8]: "Pure hyperthyroidism in the presence of a fully normal chromaffin system and a normal pancreas will very seldom produce an alimentary and spontaneous transitory glycosuria."

It is possible that in hyperthyroidism in which we are dealing with such an unstable nervous system, the nervous regulatory mechanism may also enter into the picture. But even so, the same problem is presented. Why is it that hyperglycemia occurs in some of the mildest cases of hyperthyroidism and is not present in many of the most severe?

Again one may raise the question whether in hyperthyroidism we may be dealing also with hyperadrenalism, a condition which we know produces hyperglycemia. In some of the mild cases in which the

hyperglycemia disappears after thyroidectomy, the hyperglycemia might well be due to this cause. However, were the hyperglycemia due primarily to hyperadrenalism, we would find a much higher incidence of hyperglycemia and this again would be relative to the severity of hyperthyroidism, which is not the case.

The question which is unsettled today is whether any of the factors mentioned could induce diabetes when there is no diabetic "anlage" at the start. I think not, but we do not know at present as evidence is lacking upon which to base a proper interpretation of the facts which confront us and with which we have to deal.

The incidence of diabetes in hyperthyroidism is 2.1 per cent. The incidence of diabetes at large is given as only 1 per cent. I am inclined to think that a big factor in this higher incidence in hyperthyroidism is that of overeating which is automatically brought about by the increased metabolism which demands calories and as the patient starts losing weight he automatically tries to compensate for this by eating more. This throws a great load on the insulogenic apparatus, which, if normal with a good reserve, stands it well; if the reserve be small, it easily becomes exhausted and diabetes results. The condition is similar to that in obesity due to overeating where also the incidence of diabetes is high. Also the incidence of diabetes in hyperthyroidism is high from the fifth decade on, when we have to consider the problem of arteriosclerosis and endarteritis which no doubt are contributing factors to functional changes in the insulogenic apparatus.

The medical problem involved in mild cases of disturbed carbohydrate metabolism is to protect these individuals with a decreased carbohydrate tolerance, rather than to let them drift along, unprotected, toward diabetes. They should be under surveillance until the physician has satisfied himself that stability has been established. In most of these cases, the glycosuria disappears after thyroidectomy and the carbohydrate tolerance is restored to normal; in others this does not happen. It is important, therefore, to make postoperative examinations in order to determine whether or not the carbohydrate metabolism has been restored to normal, and when this has not occurred, to institute such measures as are indicated. It is much easier to keep a diabetic patient in the mild stage of diabetes than to treat him successfully after a severe stage has developed.

Case Histories.—I shall present a few cases which will illustrate the various problems presented by the treatment of patients in whom

disturbed carbohydrate metabolism and hyperthyroidism are coincident. The usual diet prescribed for such a patient is the following: Carbohydrate, 140 Gm., protein, 80 Gm., with sufficient fat to bring the total calories from 2200 to 3000. This makes an adequate diet for a patient with increased metabolism and if we are assured that most of the 140 Gm. of carbohydrate is metabolized, then we need not worry about the keto-anti-ketogenic ratio, which quite adequately and automatically will take care of itself.

Case I.—(Fig. 47.) The patient was a woman fifty-four years of age, with hyperthyroidism. She had lost 21 pounds in weight and on

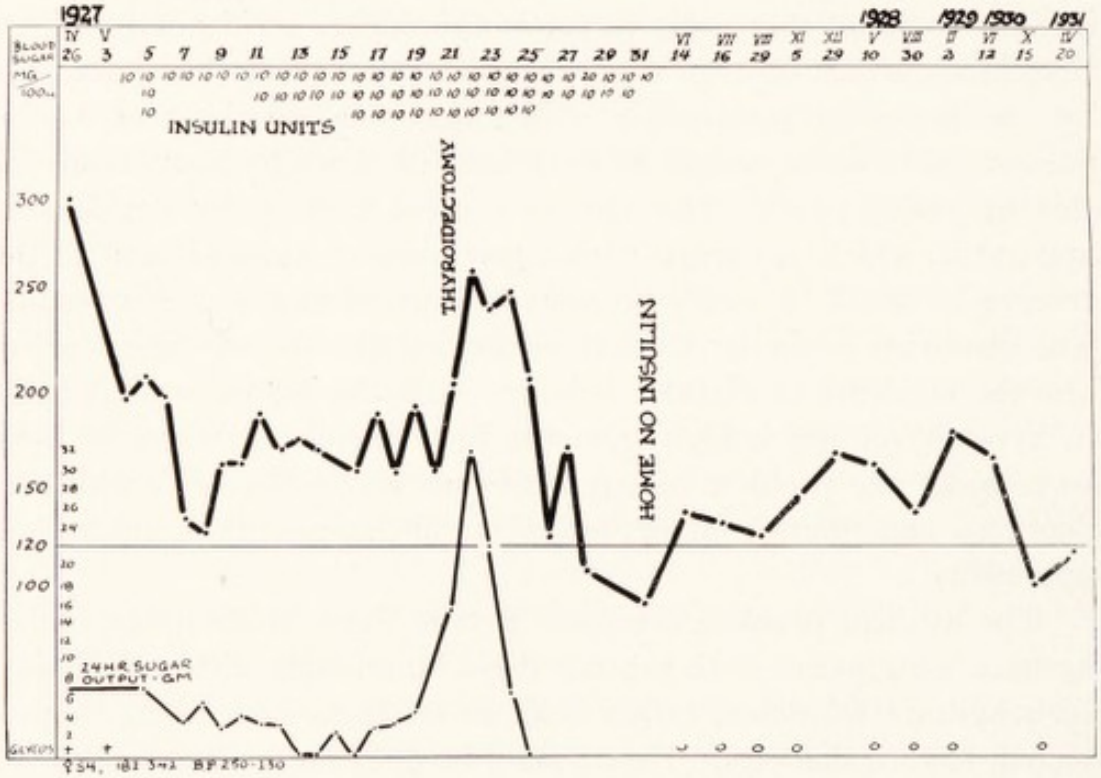


Fig. 47.—Effect of insulin and thyroidectomy on the blood sugar of a patient with diabetes and hyperthyroidism.

admission had a blood sugar of 300 mg. per 100 cc. (one hour p.c.). The urine contained sugar, 3 plus. The routine followed is clearly indicated by the chart which shows that on the prescribed diet and 10 to 30 units of insulin per day the blood sugar dropped to a level of about 170 mg. per 100 cc.; that it increased somewhat after thyroidectomy but came promptly down to the normal level, so that when the patient was discharged no insulin was needed but a special diet was continued. While there has been a slight sporadic rise in the

blood sugar, yet the blood sugar today, four years after her operation is kept within normal limits by a mildly restricted diet alone.

This patient illustrates a condition in which functional diabetes subsides completely as the result, at first of dietary treatment and insulin treatment, later of diet alone.

Case II.—(Fig. 48.) The patient was a woman sixty-three years of age, who came to the clinic with severe hyperthyroidism. The basal metabolic rate was plus 46 per cent and the blood pressure was 224/110. The blood sugar was 191 mg. per 100 cc. on entrance and the urine contained sugar, 4 plus. The chart shows the progress of

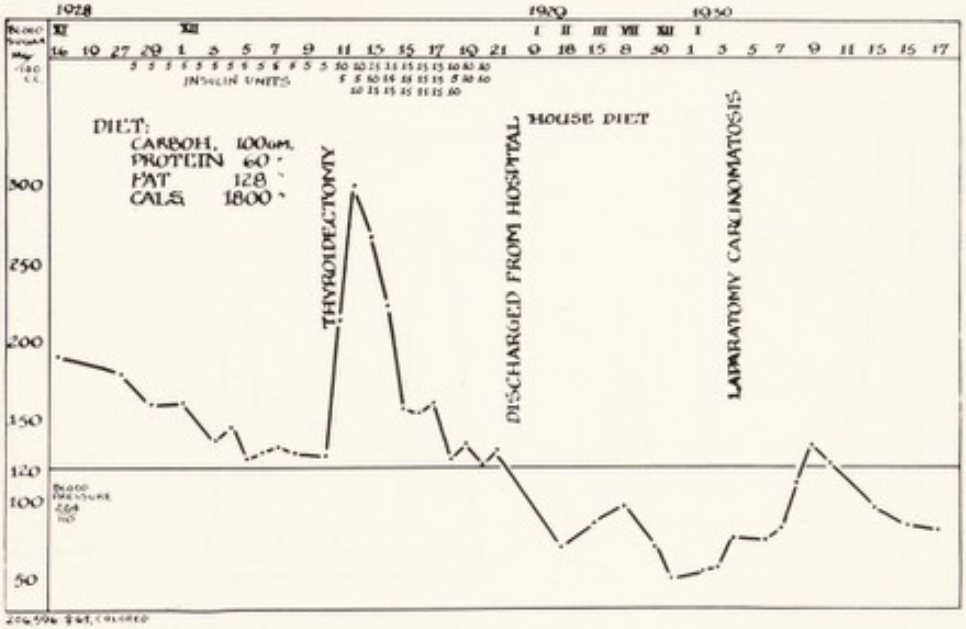


Fig. 48.—Effect of insulin and thyroidectomy on blood sugar of a patient with diabetes and hyperthyroidism.

this patient. She was placed on a diet of only 1800 calories because she was somewhat obese. She received from 5 to 45 units of insulin every day while she was in the hospital but the insulin was discontinued when she was discharged, only a prescribed diet being continued. At no time since her discharge has she shown hyperglycemia. A subsequent operation, a laparotomy, was performed because of cancer of the uterus at which time she received no insulin and there was no rise of the blood sugar. She died three months later of general carcinomatosis.

This, like Case I, was a case of mild functional diabetes which might have been handled by diet alone although it would have taken a longer time for the blood sugar to be reduced to the normal level.

Case III.—(Fig. 49.) The patient was a woman fifty years of age, who came to the clinic because of a large adenomatous goiter with hyperthyroidism. She had used iodized salt, but instead of getting better, grew steadily worse and became short of breath. In six months she had lost 20 pounds in weight. On admission the urine contained sugar, 4 plus. A glucose tolerance test was made which gave a diabetic curve although the fasting blood sugar was only 123 mg. per 100 cc. After the thyroidectomy she received a special diet and insulin and the blood sugar level was lowered. When the patient was discharged she was receiving 10 units of insulin each morning and even-

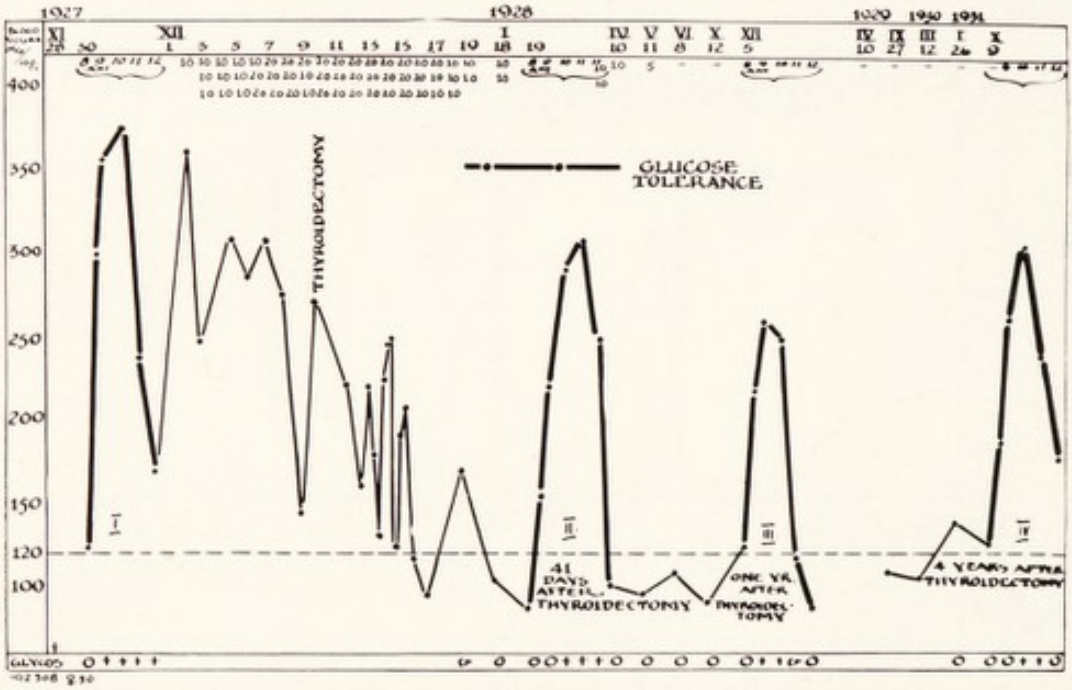
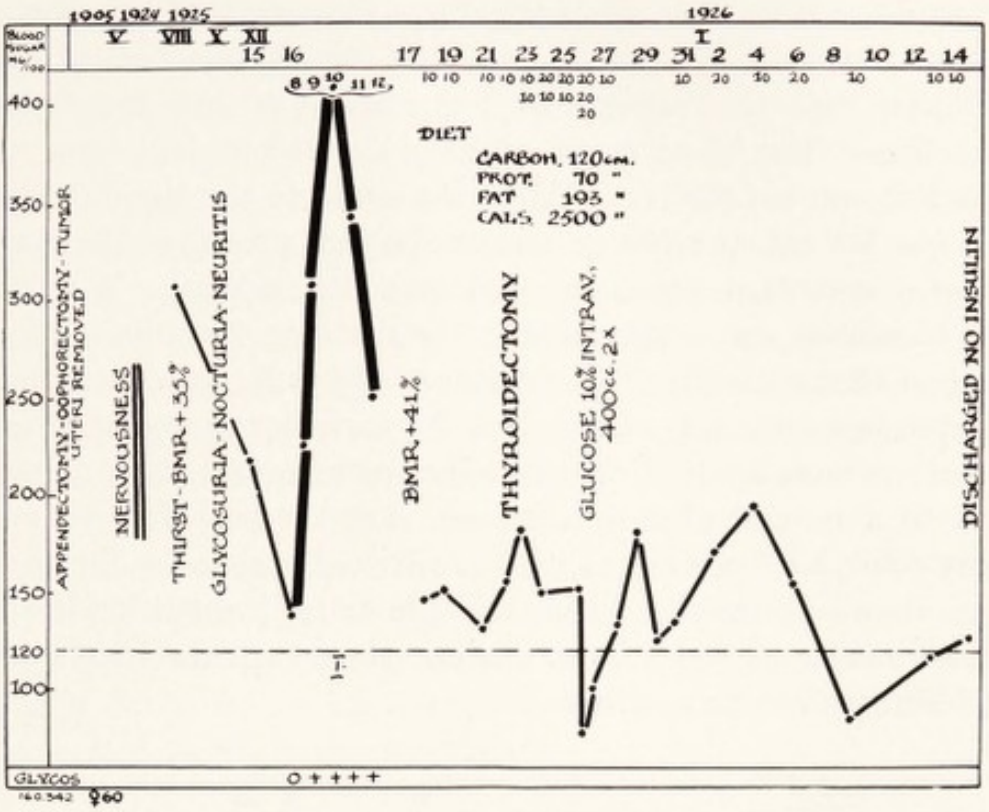


Fig. 49.—Glucose tolerance curves and blood sugar variations before and after thyroidectomy in a case of diabetes and hyperthyroidism.

ing, later this was reduced to 10 and still later to 5 units once a day and five months after her discharge the insulin was discontinued. On subsequent examination the fasting blood sugar was found to be normal and the urine was sugar-free.

As stated, the glucose tolerance test, made when the patient entered the hospital, gave a diabetic curve. Three other glucose tolerance tests, made during a period of four years, showed a lack of normal insulogenic function, which though thoroughly controlled by diet alone, without diet or in case of superimposed infection would probably have produced a true diabetic state.



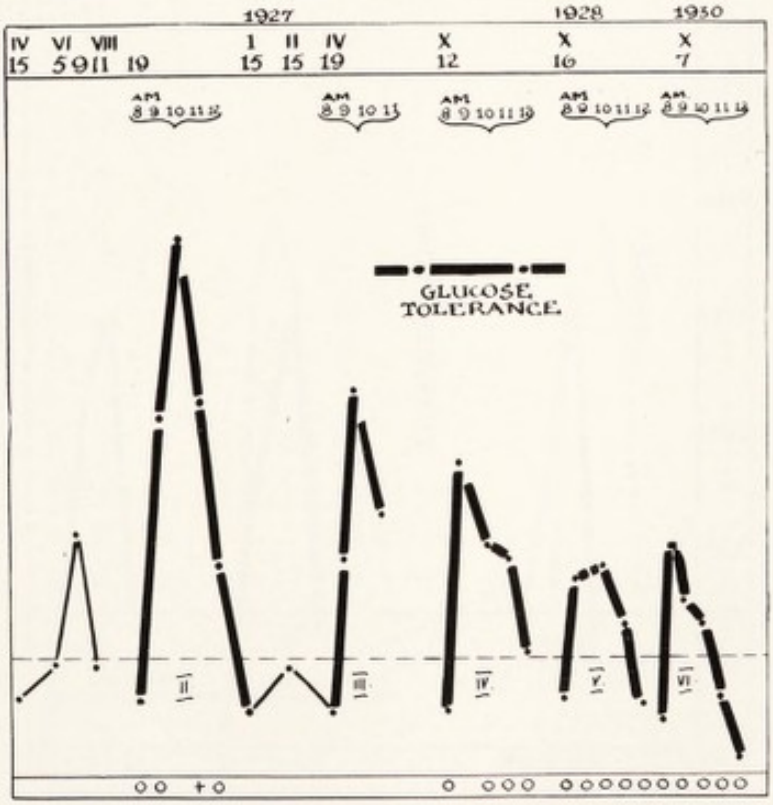


Fig. 50.—Glucose tolerance curves and blood sugar variation before and after thyroidectomy in a case of diabetes and hyperthyroidism.

Case IV.—(Fig. 50.) The patient was sixty years of age when she was first seen in 1925. The chart shows the typical onset of hyperthyroidism and the subsequent disturbance of the carbohydrate metabolism. The blood sugar estimated elsewhere had been found to be 307 mg. per 100 cc. When she came to the clinic the blood sugar was 219 mg. per 100 cc. and the patient presented the appearance of a somewhat emaciated and very sick woman. With small doses of insulin and a special diet the diabetic condition was controlled and a month after thyroidectomy all insulin was discontinued. A glucose tolerance test made when the patient was first seen and a series of five more made during the following five years, show a gradual return to a normal glucose tolerance. For the past two years the patient's diet has been only slightly restricted and today the patient is quite robust and active. This case illustrates a condition in which diet and insulin control a frank diabetic state until the effects of the thyroidectomy can be manifested.

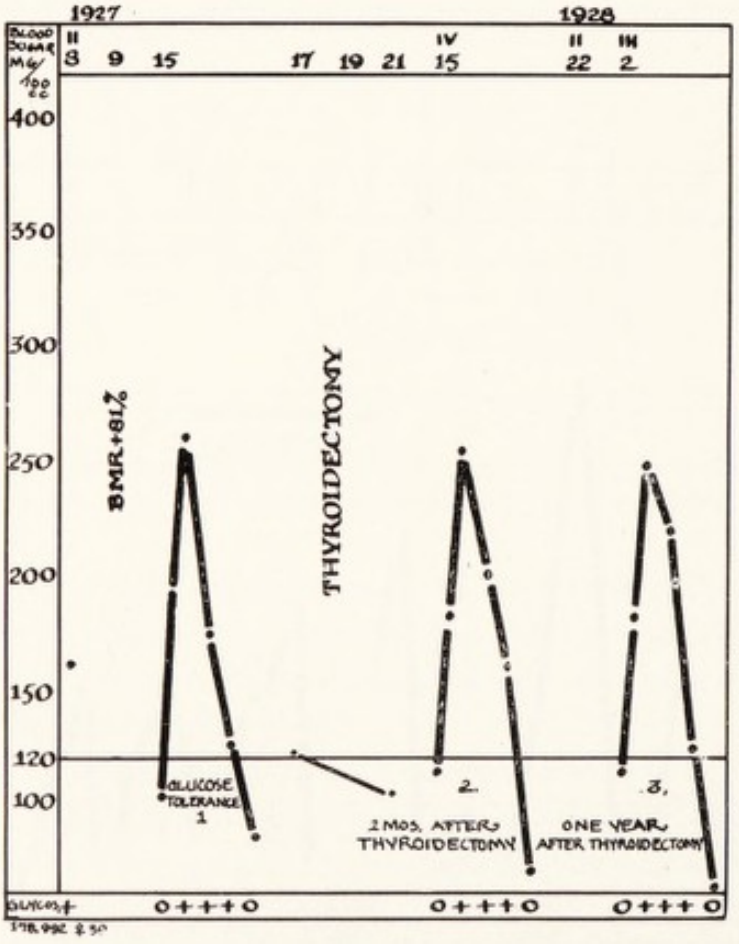


Fig. 51.—Glucose tolerance curves before and after thyroidectomy in a case of a patient with hyperthyroidism who is also a potential diabetic.

Case V.—(Fig. 51.) The patient was a woman, thirty-nine years of age, with severe hyperthyroidism. The basal metabolic rate was plus 81 per cent and the patient had lost much weight. The blood pressure was 185/48. Nearly a year before she came to the clinic the patient had had an attack of influenza with which her trouble had seemed to start. On her admission the blood sugar was 161 mg. per 100 cc. three and three-quarter hours p.c., and the urine contained sugar, 1.7 per cent. On the day after her admission the blood sugar was normal although no special diet and no insulin had been given. The glucose tolerance test gave a mild diabetic curve but on all subsequent examinations the fasting blood sugar was normal. Glucose tolerance tests made two months and one year respectively after thyroidectomy show that while this patient is apparently normal, yet the administration of glucose elicits a slightly diabetic curve.

One feels that in this case a diabetic "anlage" is present which as long as it is not stressed is quiescent, but which at some time in the future under special stress may develop into diabetes.

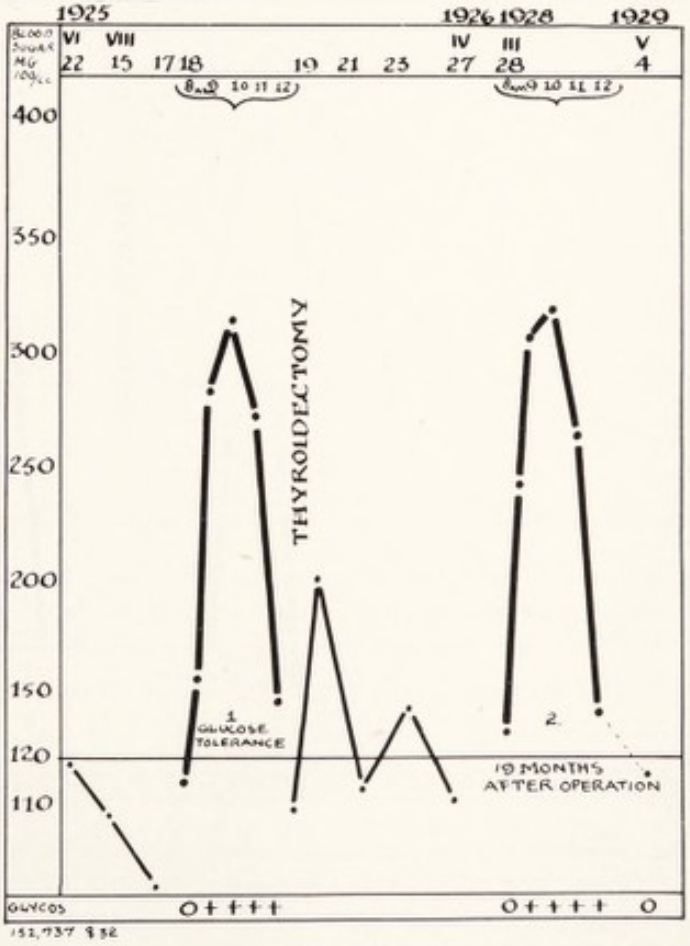


Fig. 52.—Glucose tolerance curves before and after thyroidectomy in the case of a patient with hyperthyroidism who is also a potential diabetic.

Case VI.—(Fig. 52.) The patient was a woman thirty-two years of age with hyperthyroidism. Her father had diabetes and her paternal grandmother died of diabetes. The blood sugar was normal, and the urine was sugar-free, but on account of a history of former glycosuria and the hereditary history of diabetes, a glucose tolerance test was made which gave a definitely diabetic curve. Nevertheless on a liberal diet and without insulin the blood sugar remained normal. When I repeated the glucose tolerance test one and three-quarter years after thyroidectomy the curve was practically identical with the first.

In such a case as this, I feel that the problem is that of a potential diabetic who should be under periodic observation.

Case VII.—(Fig. 53.) The patient was an obese woman fifty-seven years of age, with typical hyperthyroidism. On admission the

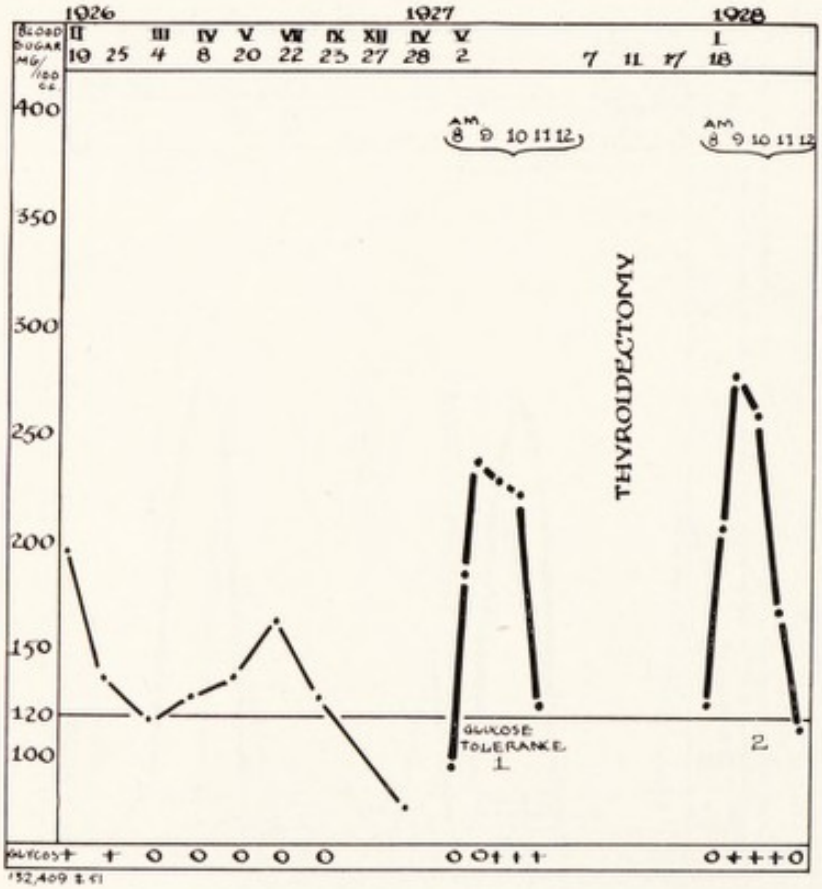


Fig. 53.—Glucose tolerance curves before and after thyroidectomy in the case of a patient who is also a potential diabetic.

blood sugar was 196 mg. per 100 cc. and she had a heavy glycosuria. The hyperglycemia was controlled without insulin. A glucose toler-

ance test gave a mild diabetic curve. When I made another glucose tolerance test eight months after thyroidectomy, the curve was almost the same as the preceding one. For practical purposes we would say that this case is virtually a duplicate of Case VI. Yet my notes show that diabetes developed later.

This case shows that a diabetic anlage is not without significance and that it behooves us to follow such patients and to protect them.

Case VIII.—(Fig. 54.) The patient was a woman, fifty-six years of age with hyperthyroidism. On two occasions she showed no glycosuria and then glycosuria appeared. The blood sugar was normal.

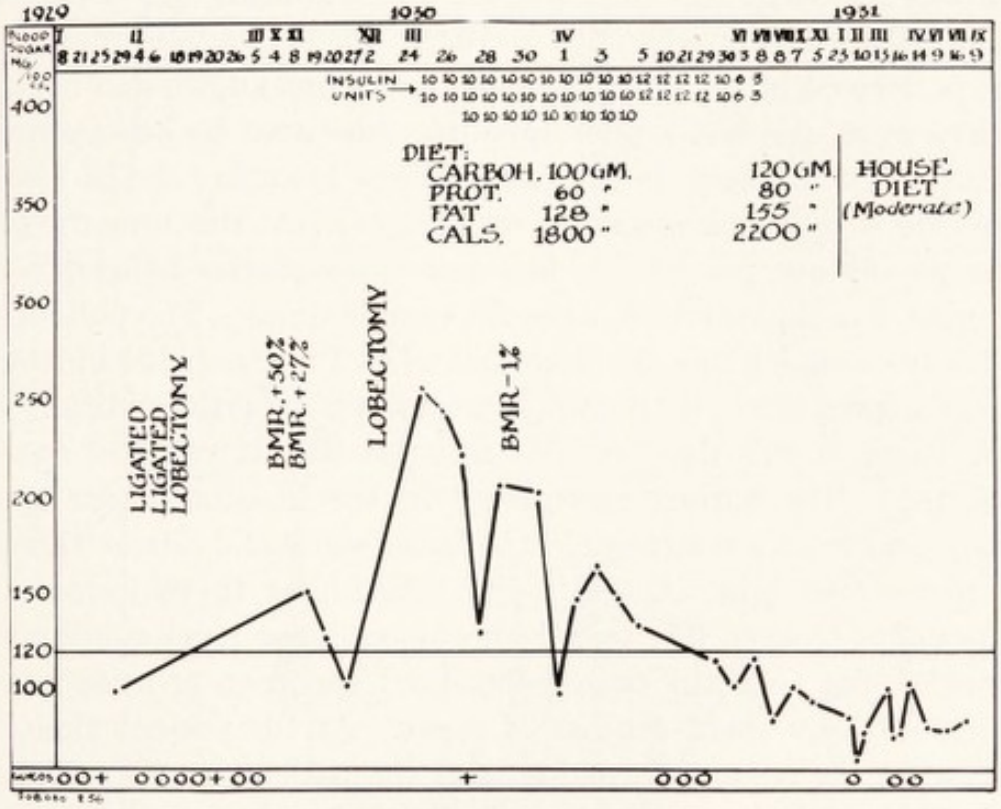


Fig. 54.—Blood sugar variations before and after lobectomy in the case of a patient who showed a slight hyperglycemia before operation.

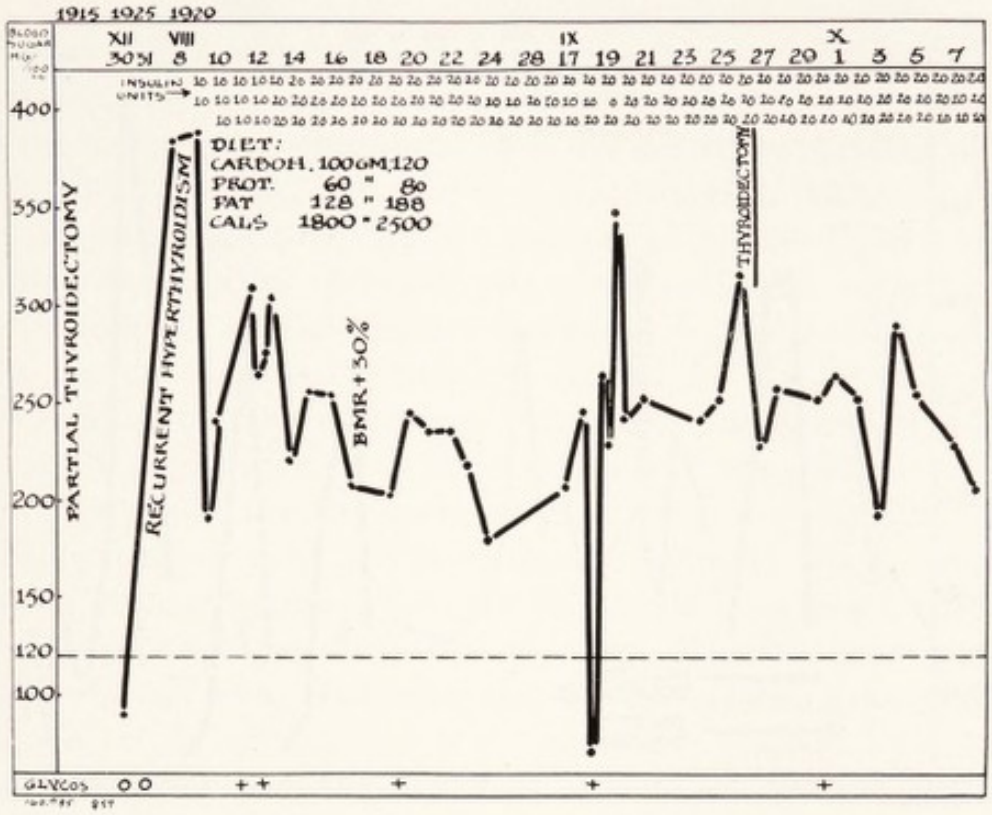
Several urine examinations made at the time of the ligations and a lobectomy, again gave normal findings. Then glycosuria appeared and on two subsequent occasions the urine again was found to be normal. The blood sugar on one occasion was 150 mg. per 100 cc. and on another it was 126 mg. per 100 cc. A second lobectomy was performed and the patient was discharged from the hospital. It would seem that two slight rises of the blood sugar and the presence of glycosuria on only two occasions could not be sufficient evi-

dence of even a prediabetic condition, but nevertheless four months after the second lobectomy this patient returned to the clinic with a blood sugar of 256 mg. per 100 cc. and had to be treated as a diabetic with special diet and insulin. However, this was an early case of diabetes in which the damage had not progressed too far, and in five months all insulin was discontinued and the patient progressed well, just as does any patient with mild diabetes.

This case shows that it is not safe to disregard slight hyperglycemia in any case without making sufficient additional investigation to classify the condition definitely.

Case IX.—(Fig. 55.) The patient was a woman, fifty-seven years of age, whom I saw originally in 1925. Partial thyroidectomy had been performed in 1915. In 1925 she had a breakdown and began to be very weak and had a poor appetite. She went to Europe, thinking that the trip might do her good. When I saw her she had lost 22 pounds in weight (she was never overweight). At this time the blood sugar was 89 mg. per 100 cc., four and three-quarter hours p.c. and the urine was sugar-free on repeated examinations. The patient was gradually becoming more nervous and when I next saw her in August, 1929, she presented the picture of recurrent hyperthyroidism. The blood sugar at this time was 384 mg. per 100 cc. two and one-half hours p.c. The patient was placed in the hospital under special dietary and insulin treatment. The basal metabolic rate at this time was plus 30 per cent. A month and a half later, thyroidectomy was performed. During this period the blood sugar level continued to be rather high, but the twenty-four-hour specimen of urine showed a comparatively small content of sugar. At the present time, two years after the second thyroidectomy, the patient is still a diabetic, having a special diet and taking 25 units of insulin daily in two doses of 10 and 15 units respectively. The carbohydrate metabolism was undisturbed during the first onset of hyperthyroidism, but when the recurrence of hyperthyroidism occurred, this broke down and the patient became diabetic.

In this case if a glucose tolerance test had been made in 1915 when the first thyroidectomy was performed it might have shown whether or not a diabetic "anlage" was present, and a slight reduction in diet might have warded off the later development of the frank diabetic state.



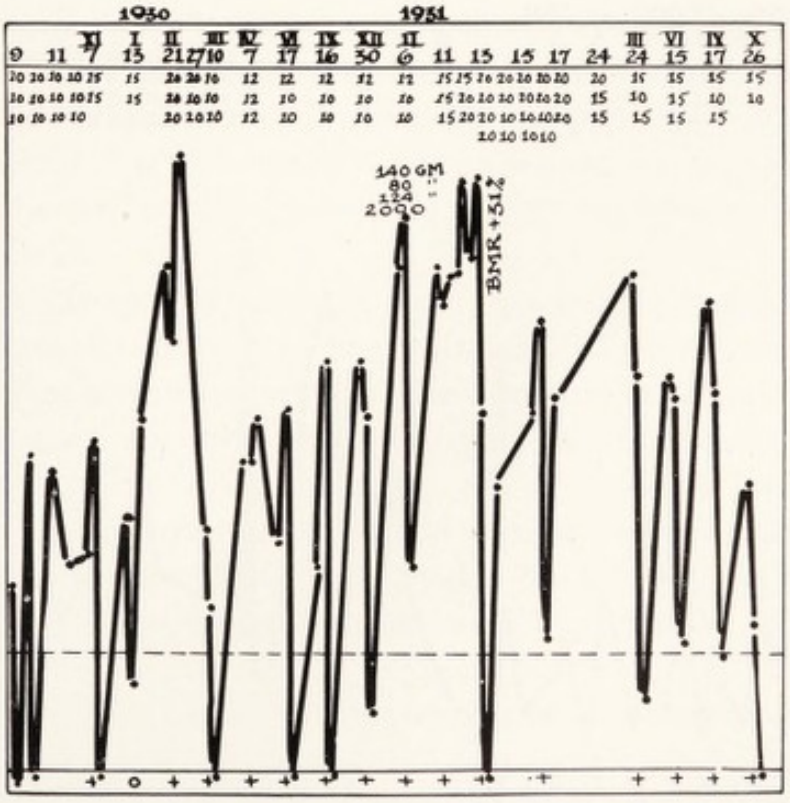


Fig. 55.—Blood sugar variations before and after a second thyroidectomy in a case of recurrent hyperthyroidism.

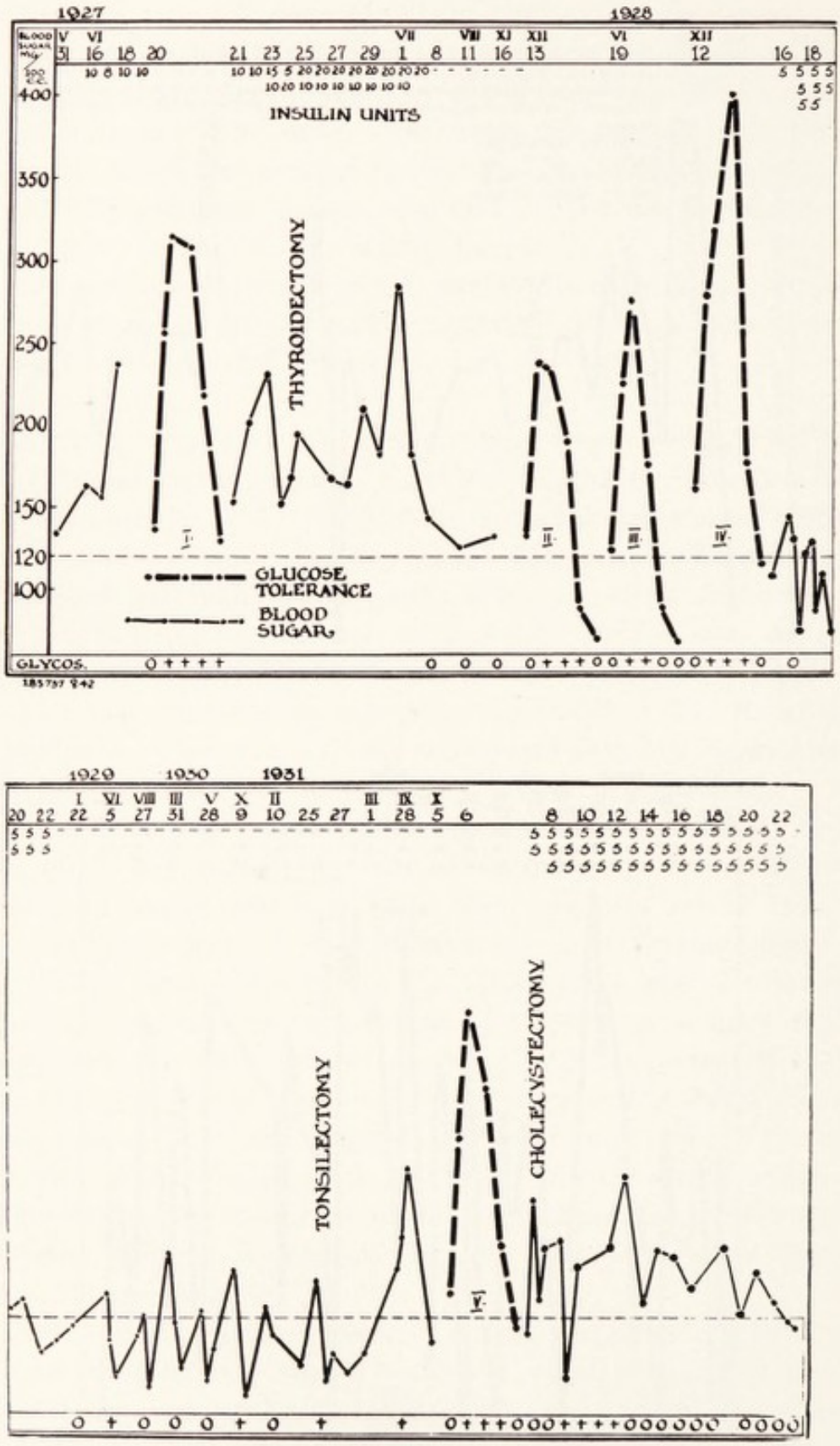


Fig. 56.—Glucose tolerance tests and blood sugar variations before and after thyroidectomy in a case of hyperthyroidism and mild diabetes.

Case X.—(Fig. 56.) The patient, a woman forty-two years of age, was quite obese, and had a mild degree of hyperthyroidism. The blood sugar was 134 mg. per 100 cc. (four and three-fourth hours p.c.) and she had a heavy glycosuria. She was placed on special diet and small doses of insulin, but the blood sugar kept on rising and a few days later a glucose tolerance test presented a typical diabetic curve. About a month after thyroidectomy the blood sugar content came down to normal, and insulin was discontinued. After this the blood sugar content remained practically normal for five months. Six months after the thyroidectomy the glucose tolerance test gave a practically normal curve. A third glucose tolerance test six months later gave practically the same curve as the preceding one. This encouraged the patient and she began to eat more freely and as a result, a glucose tolerance test, the fourth, six months later showed the presence of a frank diabetic condition. Even the fasting blood sugar level was high. Following this the patient was given a special diet and insulin and spent a few days in the hospital. The blood sugar returned quickly to normal and remained at a normal level for a period of nearly three years after insulin was discontinued. The patient had learned her lesson and was now more careful of her diet. Later a tonsillectomy was performed, after which a glucose tolerance test, the fifth, still gave a diabetic curve. A subacute gallbladder condition was found and a cholecystectomy was performed at this time. Again a special diet and insulin were prescribed but the insulin will be discontinued when the patient's improvement indicates that it will be safe to do so.

This case shows that when we have once had to deal with a mild diabetic state, it can be kept in control as long as the patient continues on a mildly restricted diabetic regimen, and that it will be manifested again whenever this is disregarded. The weakness of the insulogenic function usually persists and any adverse circumstance will promote it. There was improvement after thyroidectomy, which was overcome by overeating. Restriction of diet brought about improvement which again was overcome by the gallbladder infection.

Case XI.—(Fig. 57.) The patient was a woman, thirty-eight years of age, with severe hyperthyroidism. She had lost 50 pounds in weight. When first seen on September 29, 1925, the blood sugar was normal (136 mg. per 100 cc. one and three-quarter hours p.c.) and the urine was sugar-free. The first ligation was performed three days

after the patient's admission and the second ligation one week later. Repeated urine examinations during these ten days showed no sugar. She returned two months later for thyroidectomy. During the interim she ate heavily as patients with hyperthyroidism do, for there was no indication for restriction of the diet. When the patient returned, however, she was in a frank diabetic condition having a blood sugar content of 600 mg. per 100 cc. She was therefore given a special diet and insulin. After the thyroidectomy, the insulin was reduced and the patient progressed well. The insulin, however, could not

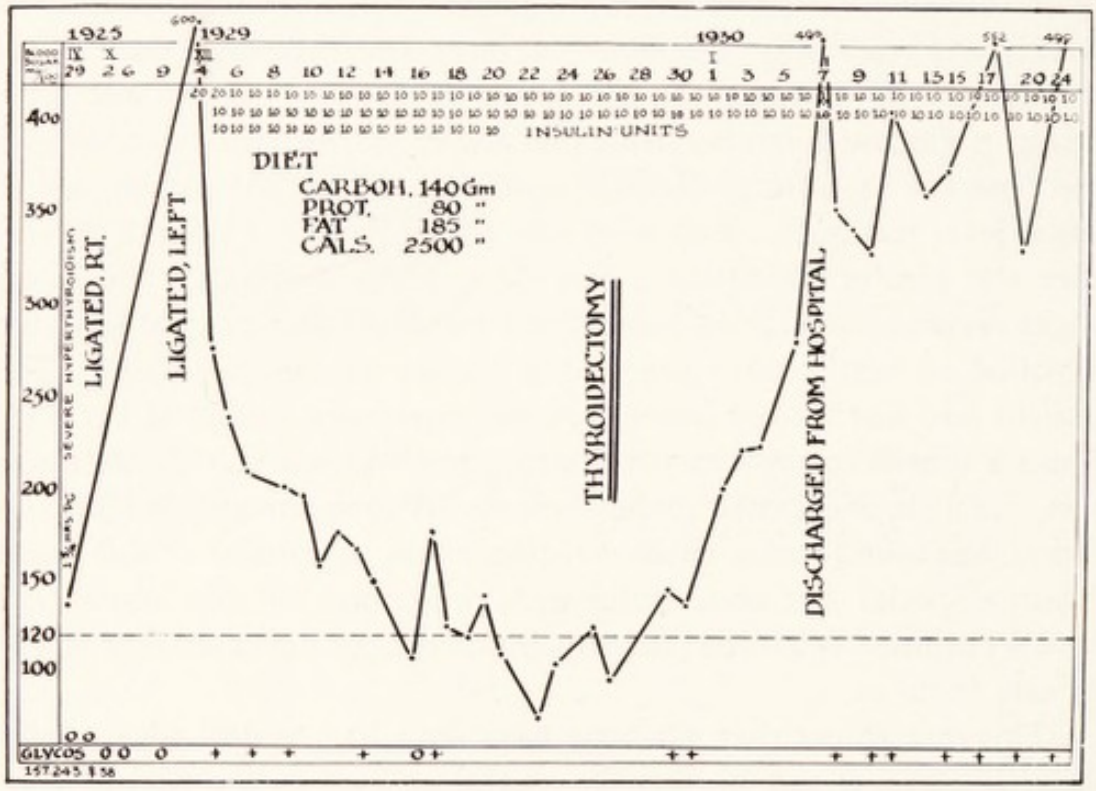


Fig. 57.—Blood sugar variations before and after thyroidectomy in the case of a patient with diabetes and hyperthyroidism.

be discontinued, for, as can be noted in Fig. 57, when in January, 1930 it was reduced to only 10 units per day, the blood sugar began to rise. When the patient was discharged she was receiving 10 units of insulin twice daily which was the amount which, with a 2500 calorie diet, had controlled her well for the previous two weeks. The patient had a low mentality and because of her ignorance, she refused to believe that she had diabetes and would not adhere to the prescribed diet although she continued to take insulin. But insulin, without a special diet, is of little avail as Fig. 57 shows.

This case illustrates the evolution of diabetes as the result of hyperthyroidism during a comparatively short period of time, and its persistence even after thyroidectomy.

Case XII.—(Fig. 58.) The patient was a woman thirty-nine years of age who gave the following history: She had four children, living and well; and had lost two in infancy; hyperthyroidism developed one month after the last childbirth which was in 1927. She went to a sanitarium where she improved somewhat but lost much weight. In March, 1930, glycosuria was discovered and a low carbohydrate diet was prescribed. I saw the patient on May 24, 1930, when she complained of urinary frequency (once each hour), nocturia (five or

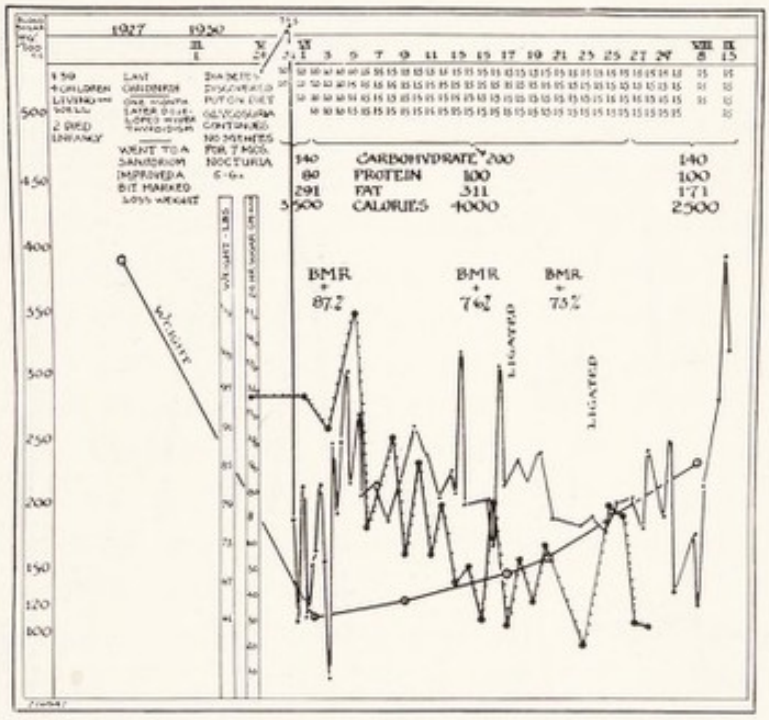


Fig. 58.—Blood and urinary sugar variations before and after ligation in the case of a patient with diabetes and hyperthyroidism.

six times); itching and burning about the genitalia; polyphagia and great thirst—all the cardinal symptoms of diabetes. She had lost much weight. The basal metabolic rate was plus 87 per cent, and the blood sugar was 535 mg. per 100 cc., four hours p.c. The urine showed a heavy glycosuria. She entered the hospital one week later when the blood sugar was 713 mg. per 100 cc. As the result of special diet and insulin the blood sugar was reduced to a reasonable level. Ligations were done and the patient was discharged with the prescription of a 2500 calorie diet and 15 units of insulin four times

daily. When two months later, she was seen again the blood sugar was at a still lower level, and she had gained weight and strength. Consequently the insulin was reduced to 15 units three times daily, but when the patient returned a month later the blood sugar again had risen to a high level and the insulin dosage had to be increased.

In this case hyperthyroidism preceded the onset of diabetes by nearly three years, during which time medical treatment had been instituted only for the hyperthyroidism without any result. One wonders whether, if the operation had been performed in 1927, the diabetic state would have been obviated and the patient spared from a severe life-long regimen.

Case XIII.—(Fig. 59.) The patient was a woman fifty-nine years of age who gave the following history: Thirteen years previously

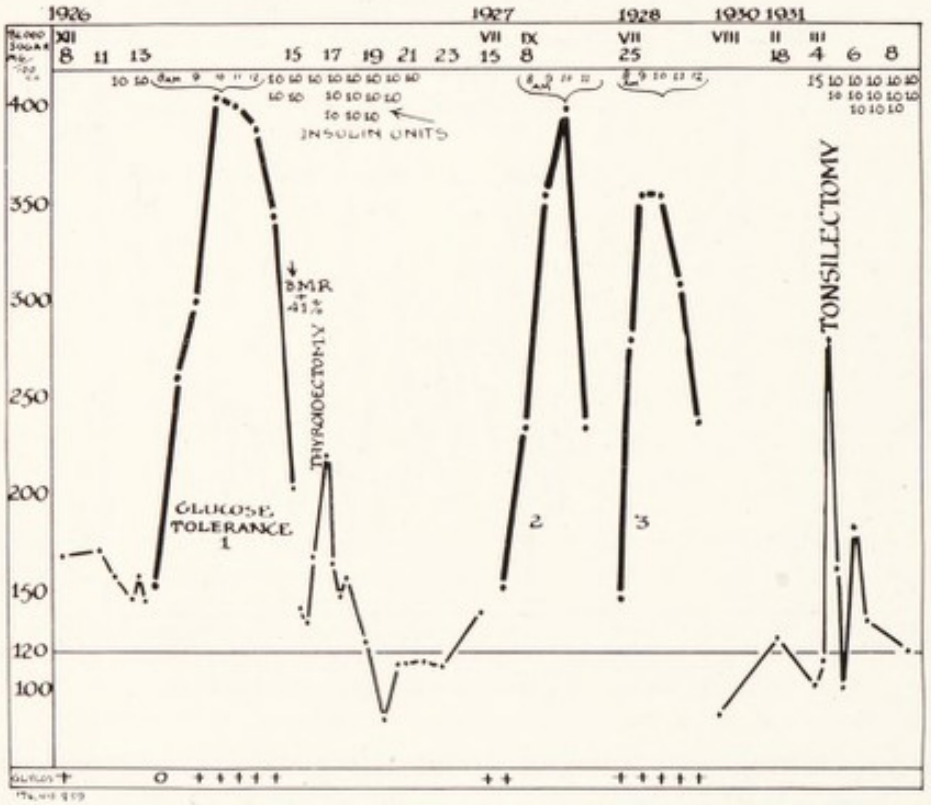


Fig. 59.—Glucose tolerance curves and blood sugar changes before and after thyroidectomy in a case of "latent diabetes" and hyperthyroidism. The blood sugar variations before and after tonsillectomy performed four years after the thyroidectomy are shown also.

hyperthyroidism had developed and eight injections of boiling water had been made into the gland, after which the symptoms disappeared and the patient had continued to be in good health until about six

months before we saw her. Since then she had been feeling quite exhausted and had lost 36 pounds in weight in four months. She had been put to bed for from ten to twelve weeks without resultant improvement.

On her admission the patient was found to have an adenoma of the thyroid gland with hyperthyroidism. The blood sugar was 169 mg. per 100 cc. three hours p.c. and the urine showed a heavy glycosuria. The basal metabolism was plus 41 per cent. Small doses of insulin and a special diet were prescribed. Thyroidectomy was performed and six days later the insulin was discontinued. She received no insulin during a period of four years after the thyroidectomy; then tonsillitis developed and a tonsillectomy was performed. This again increased the insulogenic weakness just as the hyperthyroidism had done four years before and the administration of insulin had to be resumed. I made three glucose tolerance tests at intervals of approximately a year and each test gave a definite diabetic curve, although the fasting blood sugar was near the normal level.

In such a case as this we are dealing with "latent diabetes" which can easily be controlled. As long as no emergencies arise it remains controlled, but any little mishap elicits the diabetic picture.

In order to show the importance of the early recognition of a diabetic condition accompanying hyperthyroidism, I wish to report at greater length an interesting case in which severe hyperthyroidism preceded the onset of diabetes by nearly a year and in which the diabetes was of such a severe fulminating character that the patient became extremely emaciated.

In this case hyperthyroidism and severe myocarditis persisted after both lobes of the thyroid gland had been removed, these conditions disappearing only after the removal of a little nodule of thyroid tissue which was about the size of a small marble. When I first saw him, this patient was a mere skeleton, too weak to lift his arm (Fig. 61, A). His basal metabolism was plus 70 per cent and the blood sugar 405 mg. per 100 cc. The important feature in this case was that the diabetes was masked, for though glycosuria was present, yet the fasting blood sugar was at first normal, a finding which emphasizes the fact that a fasting blood sugar estimation is not a true criterion for the early diagnosis of diabetes; a blood sugar estimation made two and one-half hours after a heavy carbohydrate meal is a far better procedure as this presents a picture comparable to that secured by a glucose tolerance test.

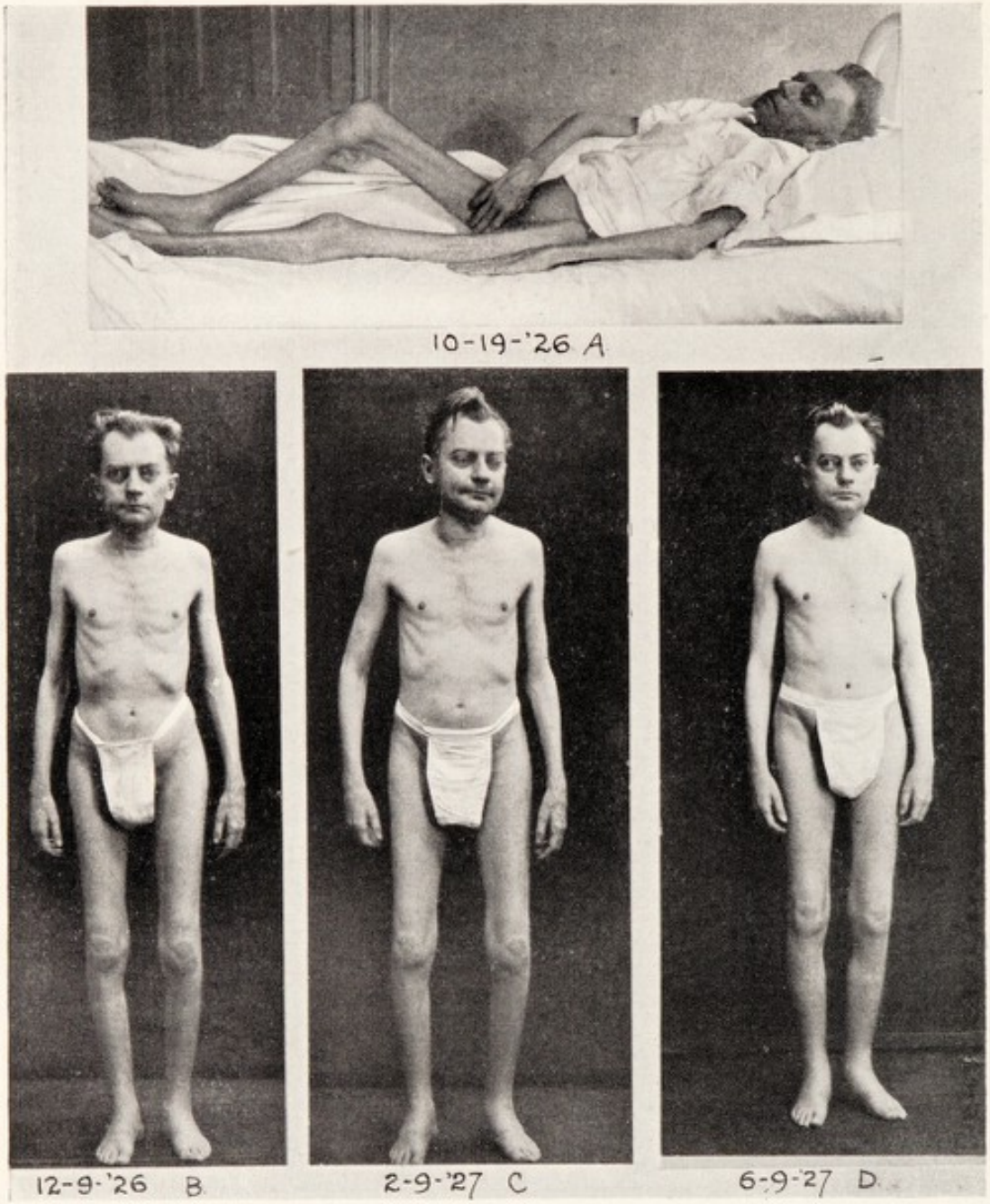
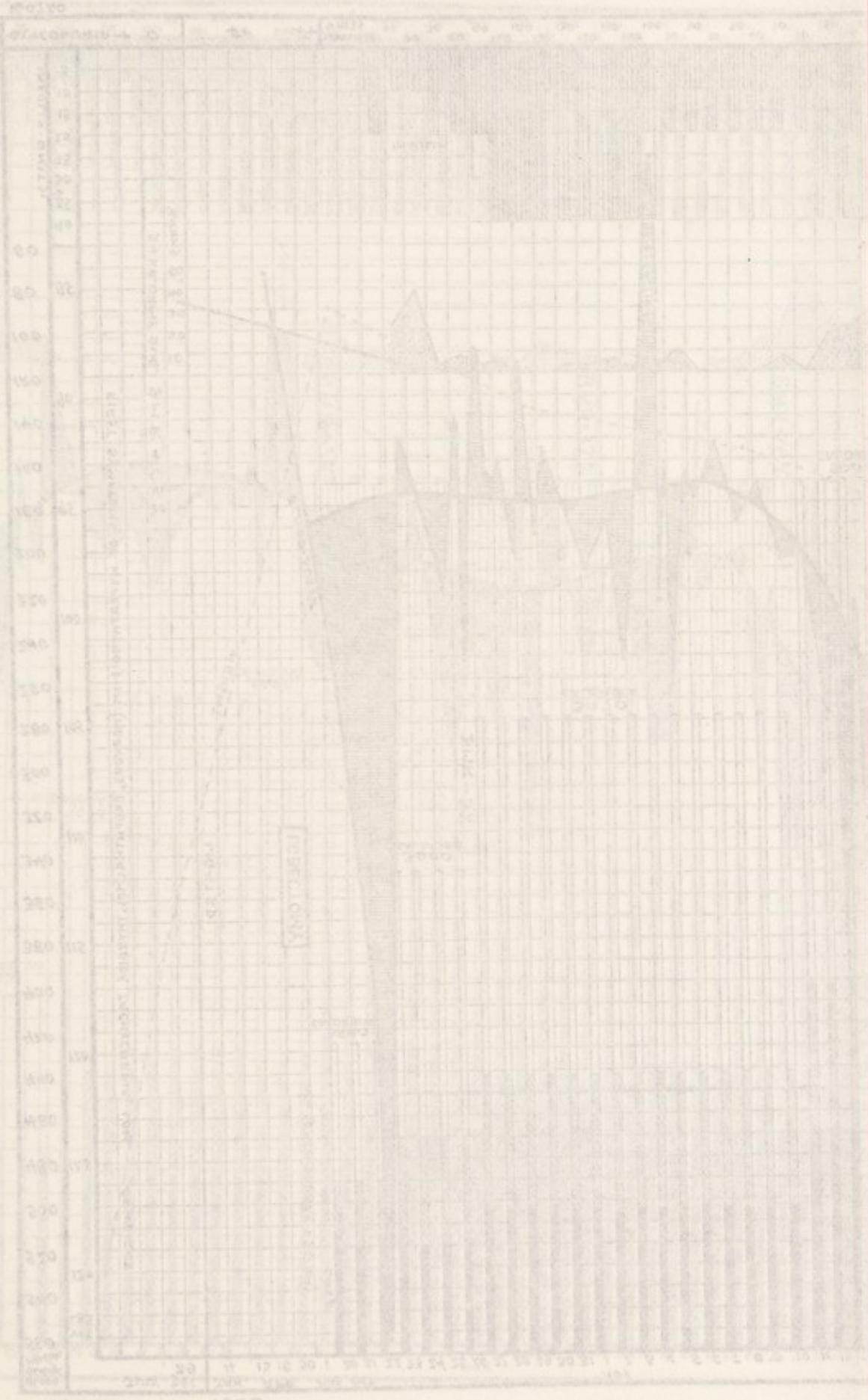


Fig. 61.—Photographs of a patient with hyperthyroidism and diabetes. A, When diabetic condition was discovered. B and C, After institution of treatment with insulin. D, One month after final operation.

Case XIV.—The patient was an unmarried man, thirty-three years of age. There was no significant item in the family history. Of the usual diseases of childhood he had had measles, mumps, whooping cough, and chickenpox. He had also had a neisserian infection. Aside from these diseases he had been in good health until the latter part of 1925, when he first noticed that he was gradually becoming increasingly nervous and later that his eyes were becoming increas-



ingly prominent. A gradual loss in weight accompanied the development of these symptoms and the neck gradually enlarged in front. The patient had some dyspnea and also tachycardia, which was increased by exertion. Two years before he came to the clinic his weight had been 130 pounds, but when first seen (December 29, 1925) his weight was 115 pounds. His pulse rate at this time was 140, blood pressure 130/60.

Physical examination revealed a thin, nervous man with a bilateral thyroid enlargement and with marked exophthalmos. He had a rapid heart which was slightly enlarged to the left, but there were no thrills, shocks, or friction rubs and no murmurs. Otherwise the physical examination revealed nothing of importance, except paralysis of the left vocal cord with great edema of the arytenoid on that side and also some affection of the right cord (false cord). The subsequent course of this patient can best be followed by an examination of Fig. 60.

In this case we were dealing with a very severe case of hyperthyroidism presenting all the cardinal symptoms. The high basal metabolic rate persisted even after a second lobectomy. At the suggestion of Dr. Marine we instituted the feeding of thymus, which was continued for nearly three months after the second lobectomy without any apparent effect. During this time, while attempting to open a window, the patient broke his left fibula. Some time after the second operation a small nodule was noted on the right side in the thyroid region. This was removed on May 2, 1927 and was found to consist of thyroid tissue. After the removal of this portion of thyroid tissue, the patient began to improve markedly; the basal metabolic rate promptly became normal and remained so, the heart quieted down and he began to gain strength.

The outstanding features in this case are the following: The hyperthyroidism preceded the onset of diabetes by nearly a year. The patient first noted the symptoms of thirst and polyuria in September, 1926. Glycosuria had been discovered five months before, in April, 1926, while he was in the hospital, just before his first lobectomy, but on the day after this discovery was made the fasting blood sugar was only 73 mg. per 100 cc. so that the presence of the glycosuria was disregarded, since this is a common finding in many cases of hyperthyroidism. Glycosuria was again found on May 1, 1926, shortly before the patient was discharged from the hospital after the first lobectomy, but was again disregarded. When the pa-

tient reentered the hospital for his second lobectomy he had had the symptoms of thirst and frequency of urination for about six weeks, he was markedly emaciated, his weight having dropped to 86 pounds (Fig. 61, A) and he was extremely weak and exhausted. The morning after his admission his fasting blood sugar was 258 and two days later it was 405 mg. per 100 cc.

The lesson one can draw from the above history is that glycosuria in hyperthyroidism cannot be disregarded, and that even a fasting blood sugar will not always tell the story, for it masked the true situation in this case. A blood sugar determination made two and one-half hours after a meal might have revealed the diabetic condition, and a glucose tolerance test certainly would have done so.

The problem which was before us in October, 1926, was twofold: (1) The diabetic condition must be controlled, and (2) the patient must be prepared for a second lobectomy. The man was given large amounts of insulin daily (Fig. 60) and began to improve immediately, as is shown in Fig. 61, B which was taken less than two months later. During this period his weight had increased from 86 to 95 pounds. He grew very hungry and his diet was increased from 1800 to 3000 calories, but this did not seem to satisfy his hunger, so that it was further increased to 5000 calories before his appetite was satisfied. Even on this high diet (carbohydrate 200 Gm., protein 140 Gm.) on many days there was but little sugar in the twenty-four-hour specimen of urine.

On one day the sugar output was 50 Gm., but most of the time it was only 5 or 6 Gm. in twenty-four hours, which indicated that the man was utilizing his food, as was shown also by his steady gain in weight. The average output did increase in 1927, when the patient was on a much lighter diet. Once the craving for food was satisfied, we were able to cut down the diet considerably until, when he was discharged, he was receiving 2200 calories (carbohydrate, 120 Gm.; protein, 80 Gm.; fat, 155 Gm.) and three daily doses of insulin of 10, 20, and 20 units, respectively. He has continued on this routine to the present day.

SUMMARY

1. No glucose tolerance curve is specific for hyperthyroidism. That is, a definite diabetic type of curve may be present in a mild case of hyperthyroidism and a normal curve may be present in a very severe case of hyperthyroidism.

2. A single blood sugar estimation made when a patient is first

seen, is no criterion for a diagnosis of diabetes. This serves only as a lead to be followed up further until the true state of the patient is determined. Even a high blood sugar estimation may be just an incidental finding which may not be repeated.

3. The diagnosis of diabetes in a case of hyperthyroidism can be made only when the patient has been studied over a sufficiently long period of time for a determination of the persistence of the defective carbohydrate metabolism. Without such a time element, many faulty diagnoses of diabetes are certain to be made.

4. Thyroidectomy lowers the total metabolism and in consequence improves the carbohydrate tolerance. In cases in which little or no improvement follows thyroidectomy this is due to the fact that lack of proper diabetic treatment or insufficient treatment has followed the operation, or else that some intercurrent infection has produced further damage to the pancreas.

5. If diabetes develops after thyroidectomy, this is due either to other extraneous factors such as produce diabetes in other cases, or to the fact that an insufficient amount of thyroid tissue has been removed and an active state of hyperthyroidism persists. In the latter case, when more of the gland is removed, the diabetes is improved.

6. Hyperthyroidism plays a fundamental etiologic rôle in the disturbances of endocrine equilibrium in patients with a diabetic anlage in which diabetes can be precipitated. The factor here may be the heavy ingestion of food which accompanies active hyperthyroidism, thus placing a heavy load on the insulogenic function.

7. Glycosuria and hyperglycemia (either fasting or, more often two and one-half hours after a meal) are not uncommonly associated with hyperthyroidism. When found they should not be disregarded, but their significance and their relationship to the carbohydrate metabolism should be determined by appropriate tests.

8. The presence of hyperglycemia two and one-half or more hours after a meal, if it persists, is usually an expression of an insufficient insulogenic function.

9. The intervention of the menopause in a case of hyperthyroidism may cause hypertrophy of the islands of Langerhans with the resultant cure of coincident diabetes. This probably, however, is of rare occurrence, for but few cases are reported in the literature (Rhodenburg[38]).

10. The glycogen depletion of the liver in hyperthyroidism increases the tendency to acidosis. This factor is aggravated in cases

in which diabetes is present. The ingestion or the intravenous administration of glucose before or after operation, with or without insulin, according to the indication in the individual case, would seem to be a logical procedure. The factors which influence the glycogen depletion are probably the following: (*a*) Toxic influences which directly affect the parenchyma of the liver cells; (*b*) a high metabolic rate which causes increased consumption of carbohydrate and depletes the insulogenic stores, with resultant depletion of the glycogen store in the liver. Such a depletion is also shown in uncomplicated cases of hyperthyroidism which do not show a high blood sugar.

11. Hyperadrenalism may also play a part in the production of hyperglycemia.

12. In cases of hyperthyroidism in which a frank diabetic condition of severe type is not present, but merely a mild degree of disturbance of the carbohydrate metabolism, there may be "functional" diabetes or these may be cases of early diabetes. If appropriate treatment is not given, a frank diabetic state may develop.

13. The administration of thyroid preparations is not without danger. It may precipitate hyperthyroidism, and may even produce diabetes.

14. In my series of 100 glucose tolerance tests in 82 cases of hyperthyroidism and 10 cases of colloid goiter, fasting glycosuria was present in 19 cases and absent in 81 cases. Sixty-six per cent of the curves indicate an impaired tolerance.

15. From the observations of these patients it would appear that the renal permeability is decreased in the active stage of hyperthyroidism. The renal threshold for glucose was below 120 mg. per 100 cc. of blood in 35.6 per cent of the patients studied. The average renal threshold in cases of hyperthyroidism was 147 mg. per 100 cc. of blood.

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CHAPTER XVIII

RELATION OF HYPERTHYROIDISM TO JOINT CONDITIONS

WALLACE S. DUNCAN

VERY few references have appeared in the literature regarding the relationship of joint conditions to hyperthyroidism. We shall not attempt here to review this sparse literature, but shall refer only to two of the earliest reports.

In the Lancet of December 26, 1908, appeared an account of a presentation by Dr. Spriggs[1] before the Royal Society of Medicine of a case of rheumatoid arthritis associated with hyperthyroidism. The exophthalmos and enlargement of the neck apparently appeared about twelve months prior to the onset of pains in various joints. These symptoms were progressive in character and apparently it was only after three years, at which time the signs of hyperthyroidism had abated, that the rheumatoid manifestations commenced to subside under medication.

In the following month, Dr. Llewelyn Jones[2] in a communication to the Editor of the Lancet reported 14 cases of complete Basedow's disease and six incomplete cases of the so-called "larval" type in which definite signs of rheumatoid arthritis were prominent. These are among the early accessible records of this association.

Curschmann[3] has reported three cases and Deutsch[4] has described two cases of the association of hyperthyroidism and rheumatoid arthritis; seven have been reported by Fink, and Herzberg[5] has reported five cases.

The patients on the services of Dr. Crile and Dr. Dinsmore whom we have observed have been seen during what one might call the florid stage of their disease. Each has been hospitalized because of the obvious manifestations of hyperthyroidism and each has been operated upon following a preparatory period. We have, therefore, had the privilege of observing 75 cases in which joint disease was apparently attributable to hyperthyroidism and as the result of our experience with these cases we are able to evaluate various therapeutic measures. In many of these cases the joint symptoms have been the most

disconcerting and trying features of the disease because of the severity and persistency of the pain, the limitation of movement, and the failure of the patient to respond to the measures ordinarily effectual in the treatment of joint lesions. We have had the opportunity of following these patients over a sufficiently long period and we have seen a sufficiently large number of cases to permit us to establish the relationship of these phenomena and the merits of certain forms of treatment. In each instance we were able to secure relatively accurate information regarding the possible etiologic relationship of trauma and the approximate time of onset of the joint difficulties in the course of the disease. From this experience, we have become convinced that this combination of disturbances exists more frequently than might be supposed.

We do not propose to enter into a discussion of all forms of so-called "endocrine arthritis" but rather to deal only with those cases which in our experience point to derangement of thyroid function. It is logical, of course, to assume that when the metabolism is so disturbed as is the case in hyperthyroidism, some associated disturbance in other sources of internal secretion would be present.

Nothing presents more gratifying proof of this assumption than the response of these patients to thyroidectomy. The history of typical cases readily demonstrates the picture which we have seen frequently.

Case I.—The patient was a woman twenty-six years of age who entered the Cleveland Clinic Hospital on November 26, 1928. She complained of an enlargement of the neck which was first noted six months prior to her examination here, and three months after the birth of a child. Two months before she came to the clinic she became extremely nervous and suffered from palpitation and diarrhea. At that time she was hospitalized and given Lugol's solution. Her basal metabolic rate was plus 18. She had improved rapidly since that time, had felt fairly well, and had gained 15 pounds in weight. She was still taking iodine.

At the time of the onset of the severe symptoms she began to notice a stiffness of the finger joints on arising in the morning. These were considerably swollen and had become increasingly tender, these symptoms showing a tendency to subside and recur.

Clinical examination disclosed the presence of a moderately severe hyperthyroidism with thickening of the proximal interphalangeal

joints of the second, third, and fourth digits of the left hand. Tenderness was present on pressure over the right sacro-iliac joint. There was no limitation of movement in the back, and no pain on straight leg raising. It is interesting to note that the patient has complained of so-called "colitis," manifested by diarrhea with no blood in the stools. There was no evidence of infection in the teeth. There was no focus of infection in the nose and throat.

Thyroidectomy was performed eight days following admission to the hospital, where the usual preoperative routine was instituted. A diffuse hyperplastic goiter was found upon pathologic examination. The joint disturbances began to improve shortly after the thyroidectomy and within a month after the operation, the swelling of the joints of the hands commenced to subside, and within six months all the joint symptoms had completely disappeared. All that remained of the changes in the joints was a slight thickening about the proximal interphalangeal joints of the digits. Further reports from this patient show that she has completely recovered from all the joint symptoms of which she formerly complained.

Case II.—The patient was a woman fifty years of age who was admitted to the Cleveland Clinic on October 30, 1930. She complained of marked nervousness, tremor, palpitation, rapid heart, weakness, and exhaustion.

The patient was very emotional, and stated that the symptoms had been present for the preceding three years. Clinical investigation disclosed the presence of an adenoma of the thyroid gland with marked hyperthyroidism.

About seven months prior to her examination here, severe pain in the left shoulder developed which at the onset was spasmodic, but became more continuous, was persistent, and extended down the left upper extremity. The left shoulder became stiff, as did the dorsal and lumbar spine and the joints of the left hand. Later similar discomfort developed in the right shoulder.

Clinical examination disclosed distinct periarticular thickening about the metacarpophalangeal and interphalangeal joints of the left hand, with moderate flexion deformity in these joints and inability to extend or flex the digits fully, but no pathologic condition could be demonstrated in the elbow or wrist. There was demonstrable atrophy of the left deltoid muscle with marked limitation of abduction and of internal and external rotation in the left shoulder. Antero-

posterior movement was perfectly free. No pathologic condition could be demonstrated in the nose and throat. The basal metabolic rate was plus 30. Repeated urinalyses, blood counts, blood Wassermann test, and other forms of investigation revealed no departure from normal.

Despite the administration of all types of sedatives and all forms of treatment, the pain in the joints became progressively worse. The patient had difficulty in getting her arm back far enough to put on her coat, and had great difficulty in getting out of bed.

A thyroidectomy was performed on November 29th following a preliminary period of hospitalization during which the usual preoperative routine employed in cases of hyperthyroidism was carried out. A diffuse hyperplastic goiter was found on pathologic examination, and one small adenoma was present. Within twenty-four hours after the operation the joint symptoms began to abate. Within forty-eight hours the patient was very much improved, and since then she has improved until she is in a relatively comfortable condition.

When seen within two months after operation, she still had some restriction of movement in the small joints of the digits of the left hand, and also in the metacarpophalangeal joints. Only slight discomfort could be demonstrated on vigorous internal and external rotation of the left shoulder. The spine was completely free. No pathologic condition whatever could be demonstrated in the right shoulder.

Case III.—The patient was a man fifty-one years of age, who was admitted to the Cleveland Clinic Hospital, May 1, 1929, with a primary diagnosis of hyperthyroidism. His own principal complaint, however, was pain in the shoulders. Five months prior to admission he had become nervous and easily excited and was forced to give up his work. During the preceding February he had felt nervous and had perspired readily. He went to bed for sixteen days, during which time his shoulders became very sore and ached constantly. Later the fingers of both hands became stiff and painful. More recently he had noticed difficulty in closing his hands, he became increasingly weaker and nervous, his hands trembled and he perspired freely. He had lost 50 pounds in weight but under iodine medication he was improving.

The patient had been taking iodine for six weeks to the extent of 40 minims a day and had gained 4 pounds. There was no history of injury of either shoulder. There was no disability of the elbows

or wrists, and the lower extremities were free from pain but there was one painful point in the lower back, in the midline. He was constipated. He had lost all his teeth, had not had any sore throat and there was no history of venereal disease.

The patient complained bitterly of pain in both shoulders. The stiffness was particularly marked in the morning and was relieved slightly by motion. The tonsils were infected. The basal metabolic rate was plus 30 per cent. The patient manifested all the clinical symptoms of severe hyperthyroidism. There was atrophy of the soft tissues about both shoulders, particularly marked on the left side. There was perfectly free movement in the neck, and good anteroposterior movement in both shoulders without pain. Marked restriction of abduction, internal and external rotation was equally marked in both shoulders. No tender pressure points could be elicited. The movements of the elbows and wrists were perfectly free. Examination of the hands showed moderate periarticular thickening of the metacarpophalangeal and interphalangeal joints. There was no pain on passive flexion and extension. The laboratory examination revealed nothing of importance.

Despite every physical measure at our disposal, together with medication, the condition of the patient continued to become progressively worse. A thyroidectomy was performed twelve days after his admission to the hospital, and on pathologic examination of the specimen, a moderately diffuse hyperplasia of the thyroid gland was found to be present. Within ten days after the operation the pain in the shoulders was much less marked. The patient showed continued improvement and six weeks after the operation he was having no pain whatever, except when he began to move on rising in the morning. At this time there was some restriction of abduction and of internal and external rotation in both shoulders, without any pain. Within three months the patient was virtually well and within six months there was absolutely no evidence of any disability about the shoulders which presented a full range of movement. Recent examination shows that the patient has absolutely no joint disability. During this two-year period there has been no tendency toward recurrence of any of the symptoms which he presented on admission.

The type of periarticular change present in these cases constitutes a distinct entity and is one manifestation of the markedly disturbed metabolism of these individuals. Doubtless if such patients are permitted to go on without the direction of treatment toward the

basis of their disease, true joint changes will develop along with deformity and all the other manifestations of a chronic rheumatic state.

Patients with a preexistent rheumatoid arthritis show an exacerbation of symptoms during the course of the hyperthyroidism with relief following thyroidectomy. When they are treated adequately and early enough in the course of the disease, these patients recover from the periarthritic changes. The therapeutic effect of thyroidectomy is so dramatic that we do not question the direct etiologic relationship of hyperthyroidism to these joint changes.

Of our series of patients, approximately 65 per cent were women, an observation which is in accord with the experience of others. Sex incidence can readily be due to the unquestioned higher incidence of hyperthyroidism among women.

Over 60 per cent of these patients were between the ages of forty and sixty years and of this group at least two-thirds were between the ages of fifty and sixty years. Twenty-two per cent of these patients were in the sixth decade and 12 per cent of our patients were between the ages of thirty and forty and 28 per cent of the patients with this particular type of involvement were between the ages of twenty and thirty years. In these younger individuals the symptoms, although of considerable severity, were less persistent and not so likely to be accompanied by marked thickening of the soft tissues or atrophy. In the younger patients the hip joints were the principal site of disturbance. These observations appear to be significant particularly in view of the fact that the average age of patients with hyperthyroidism lies between twenty-five and forty-five years. The majority of the women who manifested joint symptoms had passed the menopause. Among the remaining patients, in only one instance is there a record of any disturbance of the menstrual function which in this case was manifested by menorrhagia. In none of these patients had the disturbance in the joints advanced to such a degree that gross evidence of intra-articular destruction was present. One patient who presented marked deformities had been suffering from joint disturbances for one and one-half years—flexion deformity of the knees, marked atrophy of the general musculature and marked periarticular thickening of the joints of the hands. Despite the severity of these changes, natural resolution of the process in all the joints occurred within a year. One may say with certainty that the changes are primarily periarticular. This is particularly evident in cases in which the shoulders show typical restriction of

movement and pain on abduction, internal and external rotation and relatively free flexion and extension. In many cases there occurs thickening of the soft parts about the metacarpal and the interphalangeal joints accompanied by marked restriction of movement and severe pain on attempted action and passive motion. Almost invariably there is freedom of motion of the wrists and elbows.

Even in the presence of these marked periarticular involvements we have been unable to demonstrate radiologically any gross bone or

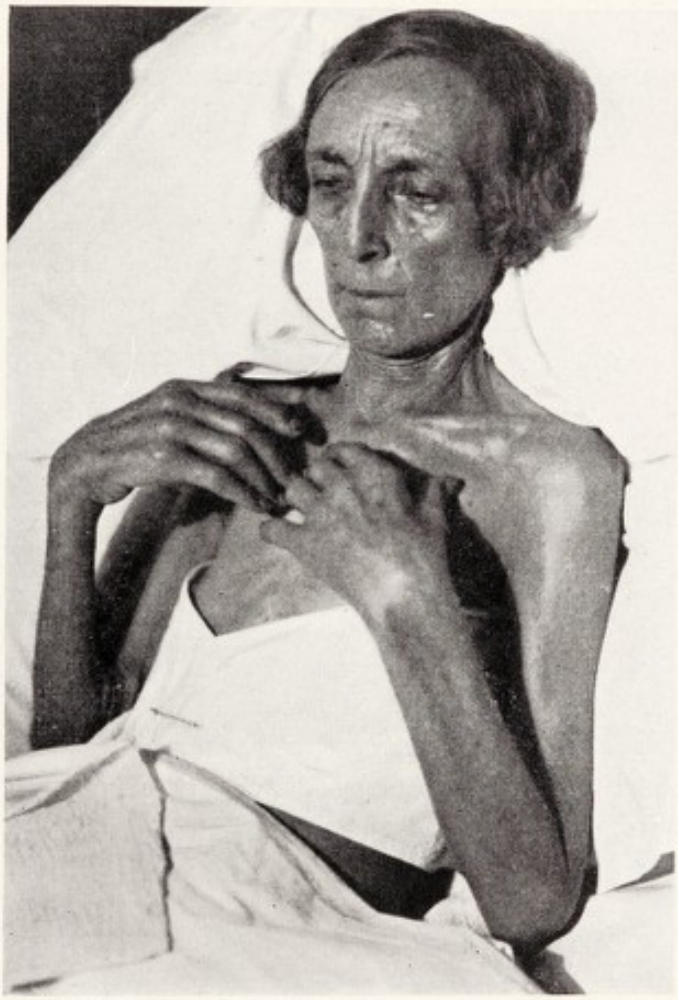

Fig. 62.—Photograph of patient in whom very severe generalized periarthritis was associated with marked hyperthyroidism.

joint changes apart from atrophy, except in some cases in which thickening of the subdeltoid mucosa has been apparent. Roentgenograms of the hands show swelling of the periarticular tissues. Subluxations and persistent joint deformities have not been observed in any case in this group.

Obviously the severity of the periarticular changes and the length of time that they have existed, as well as the general organic changes

due to the overactive thyroid gland, will determine the rapidity of recovery. An existing polyarthritis appears to be aggravated markedly during the course of severe hyperthyroidism and recedes markedly with the institution of radical treatment of the hyperactive thyroid gland.

The type of change found on pathologic examination of the gland appears to have no distinct bearing upon the joint affections although it is interesting to note that in about two-thirds of our series diffuse hyperplasia was present, adenomata being found in the remainder.

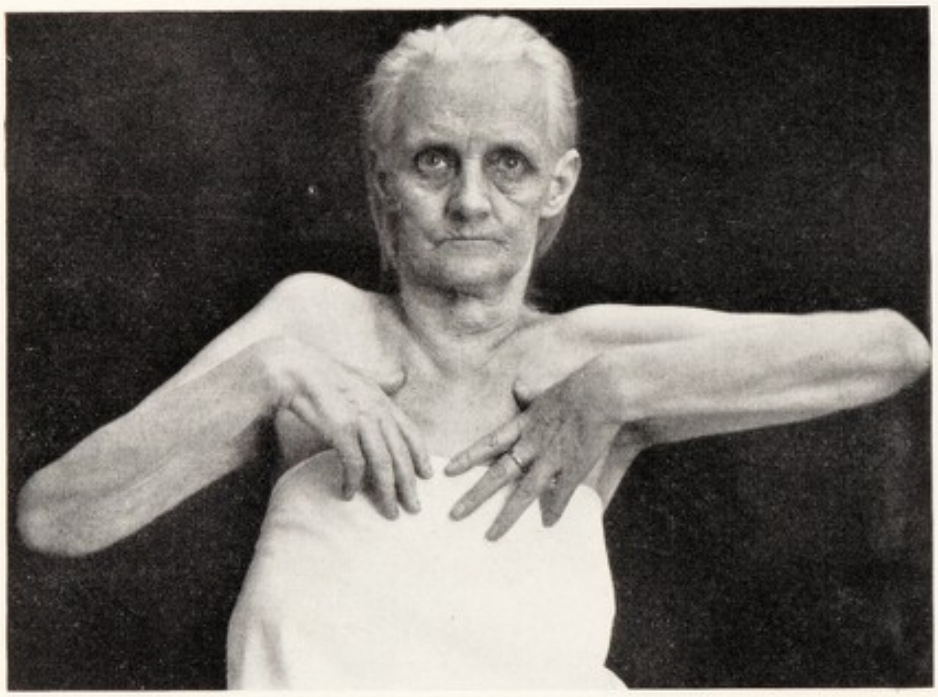

Fig. 63.—Periarthritis and hyperthyroidism. In this case, that of a patient sixty-seven years of age with an adenoma of the thyroid gland, the symptoms of hyperthyroidism developed gradually. There was marked calcific infiltration about the posterior portion of the capsule of the right shoulder joint. Following thyroidectomy this patient gained 68 pounds in weight and completely recovered from the arthritic disability.

Infected tonsils were present in 30 per cent of our cases and infected teeth in an equal number. Other individuals gave the history of marked intestinal stasis and among males chronic prostatitis was occasionally present. Obviously no attempt was made to remove the focus in the course of the acute disease. The onset of the joint condition frequently coincided with the greatest severity of the thyroid disease. In two instances, mild trauma appeared to be an inducing agent. However, experience shows that in the majority of these cases these joint symptoms developed in patients in bed

in a condition as close to absolute rest as was practical. The onset in all cases was quite similar as shown in the histories given above.

None of the routine laboratory procedures revealed anything of helpful significance.

None of these patients has been treated with *x*-rays. Each one has been subjected to thyroidectomy. In no case have glandular extracts been used. Treatment of the joint manifestations in the preoperative stage has given disappointing results. Despite complete rest in bed, local applications to the affected parts, heat in every

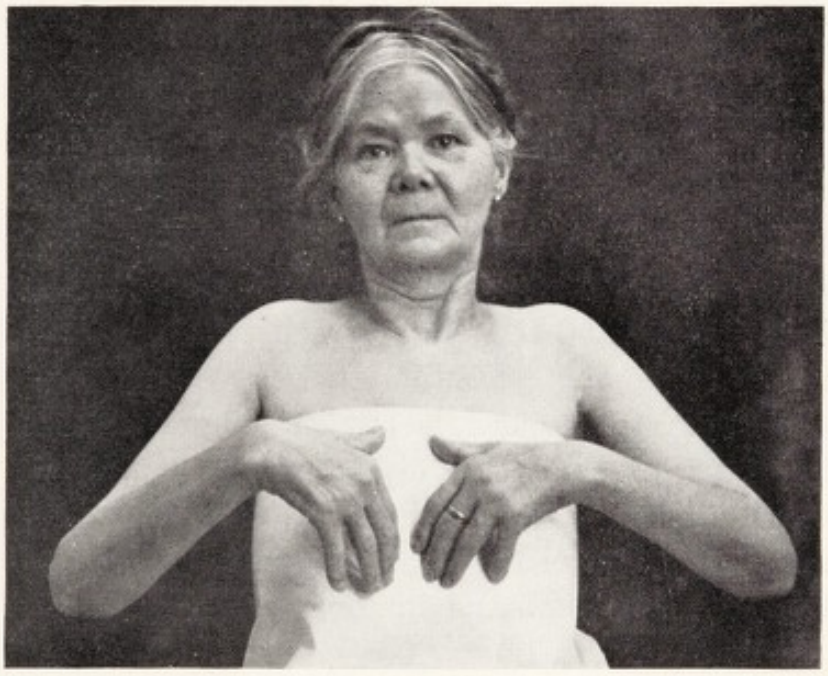

Fig 64.—Periarthritis and hyperthyroidism. In this case, that of a patient fifty-four years of age, some generalized symptoms in the joints especially in the shoulders had been present for several years and had increased with the onset of the hyperthyroidism which became very severe. The condition in all the joints showed immediate improvement after thyroidectomy with final complete recovery.

form including diathermia and infra-red irradiation, the use of salicylates, atropine and similar preparations, these patients have rarely manifested more than very slight improvement. Patients in the second decade, however, have responded fairly satisfactorily to the ordinary preoperative routine treatment for hyperthyroidism which has included complete rest in bed and the use of Lugol's solution. The application of diathermia to the affected joints has proved to be the most effective form of physical therapy.

On the other hand, there could be no more gratifying or dramatic response than that which follows thyroidectomy. Almost invariably

there is an extremely marked degree of improvement within from forty-eight to seventy-two hours after operation. It seems illogical to attribute this rapid improvement to the administration of sedatives in the first two or three days following operation, since the administration of the same sedatives, perhaps in slightly smaller quantities, prior to operation, has failed to be effective. From the time of the operation, there is a gradual progression toward complete recovery.

The most striking phenomenon is the rapid subsidence of the intense pain which is frequently referred from the shoulders to the hand.

Ligations, on the other hand, have rarely been followed by any improvement; in fact, the condition may become worse after this procedure. In the majority of instances a single lobectomy has been ineffectual.

The complete return to normal in these joints clinically, with the disappearance of the atrophy and other disturbances is in itself indicative that capsular and other soft tissue changes are present.

The length of the convalescent period is dependent upon the duration of these changes and their intensity prior to the thyroidectomy.

When the more acute manifestations have subsided gradual stretching of the structures and the application of heat in any form to the affected areas, preferably by diathermia, have been found to be helpful in restoring function. It is a fact that despite any form of local treatment once thyroidectomy has been performed these patients go on to complete functional and anatomic recovery.

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CHAPTER XIX

SYPHILIS AND HYPERTHYROIDISM

E. W. Netherton

It occasionally happens that either latent or late manifestations of syphilis are present in patients who consult a surgeon because of symptoms attributable to hyperthyroidism. In some cases it is apparent that the syphilitic infection is coincidental with the presence of hyperthyroidism; in others hyperthyroidism is associated with syphilitic involvement of the central nervous system; and in still another group symptom-complexes are presented which simulate very closely those of hyperthyroidism except that the basal metabolism is not increased.

At the Cleveland Clinic we have analyzed 62 cases in which syphilis was associated with some dysfunction of the thyroid gland. Of these 62 cases, 45 or 72.6 per cent had hyperthyroidism, 16 or 25.8 per cent had an adenoma without toxic symptoms and 1 or 1.6 per cent had a gumma of the thyroid. The duration of the syphilitic infection ranged from five to twenty-five years.

Of the patients with hyperthyroidism 15 or 33.3 per cent had syphilis of the central nervous system and 20 or 44.4 per cent had an adenoma with toxic manifestations. In 18 of these cases preoperative antisyphilitic treatment was given without noteworthy improvement in a single case. In one case in which paresis was associated with symptoms of hyperthyroidism, the patient improved without operation after receiving malarial treatment.

The antisyphilitic treatment consisted of injections of mercury, bismuth and neosalvarsan. Since there was no improvement and in a few instances the patient became worse the treatment was not intensified as the surgeons thought it advisable to resort to surgical treatment. The most difficult problems were those presented by cases in which parenchymatous neurosyphilis was associated with hyperthyroidism. It was found that the greater the mental deterioration the poorer the prognosis as the patients did not stand operative

interference well and the usual antisyphilitic therapy was of little benefit as a preoperative measure. Stokes[1] advocates preoperative treatment in these cases, especially if the basal rate is not high.

In one case severe hyperthyroidism developed during intensive antisyphilitic therapy while in one other case hyperthyroidism developed while the patient was under prolonged treatment with bismuth and mercury. In this case the patient was a woman, thirty-eight years of age, with a meningovascular type of syphilis of the central nervous system, who had been under treatment for syphilis for two years. During a course of treatment with neosalvarsan, bismuth and iodides, acute hyperthyroidism developed with a basal rate of plus 82. The hyperthyroidism cleared up after thyroidectomy. A pathologic study of the gland did not reveal the presence of an adenoma. This is the only case we have seen in which the possibility that iodide medication for syphilis might produce hyperthyroidism could be considered. It is doubtful if this was more than a coincidence in this case since iodides are used extensively in the treatment of syphilis while the incidence of hyperthyroidism in syphilitics is very low, according to our experience being only 0.7 per cent. However, the source of our material differs from that of Schulmann.

It is impossible to give a detailed account of all the cases of hyperthyroidism included in this study, but the inclusion of a few illustrative cases seems desirable.

Case I.—The patient was a man, thirty-six years of age. The family and early history gave no significant information aside from the fact that the patient had acquired gonorrhea nineteen years previously. The patient denied ever having had syphilis, or antisyphilitic treatment.

The chief complaint was "goiter" and pain in the knees and back. A year before he had been injured in a railroad accident and since then had been troubled with pain in the lower back and in the knees. One month after the accident he noticed a small lump in the neck. His eyes became prominent, he perspired a great deal, and was irritable. He had lost 40 pounds since his accident. He had not noticed any tachycardia and he had a good appetite.

Examination revealed marked exophthalmos, enlargement of both lobes of the thyroid, a bruit, tremor of the hands and tongue, hyperactive reflexes and tenderness in the lumbosacral region. The pulse rate was 130; basal rate, plus 43. Blood counts and blood sugar

examinations gave normal findings. The Wassermann test was 4 plus, and the Kahn test 4 plus on three occasions. There were no active signs of syphilis and the spinal fluid gave negative findings. A diagnosis of hyperthyroidism, toxic arthritis, and syphilis was made.

The patient was put to bed, and given three injections of bismocymol, and two of neosalvarsan and Lugol's solution. He did not improve clinically. The basal rate was slightly reduced to plus 33. A thyroidectomy was done. The patient made an uneventful recovery and in three months gained 28 pounds and was feeling well. The antisyphilitic treatment was continued after operation.

Pathologic examination revealed a hyperplastic thyroid gland containing multiple small adenomata. There was no change in the gland suggestive of syphilis.

Case II.—The patient was a man, thirty-one years of age. His family history gave no significant information. The personal history revealed the fact that thirteen years previously the patient had had a chancre which was cauterized. He had received no other antisyphilitic treatment. Eight months previously the patient began to lose weight and to become very nervous. He gradually became worse and noticed palpitation, dyspnea, tremor, and hyperhidrosis. He had lost 28 pounds.

Examination revealed a diffuse enlargement of both lobes of the thyroid gland with pulsatory vessels and bruit over the left lobe. There was no exophthalmos. The heart was slightly enlarged to the left and there was a systolic murmur at the apex, digital tremor and hyperhidrosis. The patient was nervous and excitable. The pulse rate was 104; basal rate plus 50. Laboratory findings were normal except for a 4 plus Wassermann. The examination of the spinal fluid gave negative findings. The patient was given twelve injections of mercury succinimide, $\frac{1}{6}$ grain, daily and three injections of neosalvarsan and Lugol's solution. He did not show noticeable improvement and a thyroidectomy was done from which he made a good recovery. Pathologic examination of the gland revealed a diffuse hyperplasia.

Case III.—The patient was a woman, twenty-seven years of age. At thirteen years of age she acquired a chancre of the eye from a cousin who had a chancre of the face. At that time she was treated

for six months with neosalvarsan. She had received no more treatment until three years before. For the previous three years she had taken almost continuous antisyphilitic treatment mostly intramuscularly. She had not taken iodides. Her last treatment was a month before she came to the clinic. Five months before, she had begun to have nervousness, increasing tachycardia, palpitation and irritability. Her appetite had been good, but she had lost ten pounds in weight. She perspired freely.

Physical examination revealed a fairly well-developed woman with a diffuse enlargement of the thyroid gland and marked digital tremor. All superficial lymph nodes were palpable. There were no abnormal eye signs. The pulse rate was 140 and the basal rate plus 62. No enlargement of the heart could be demonstrated. Wassermann test was 2 plus and the Kahn test 2 plus. She refused a spinal puncture. Blood sugar estimations and blood counts gave normal findings. Since she had recently received a great deal of antiluetic treatment it was thought advisable to perform a thyroidectomy without further preoperative antisyphilitic treatment. A thyroidectomy was performed from which she made a good recovery. Pathologic examination revealed a diffuse adenomatous goiter.

Case IV.—The patient was a man, forty-nine years of age. Past history disclosed the fact that the patient had had a chancre at twenty-four years of age. This was treated by local measures, no antisyphilitic treatment having been given until a year before. He was nervous and because the Wassermann test was positive, antisyphilitic treatment was advised by his physician. He was given twenty-four injections of neosalvarsan at weekly intervals but he did not improve. He did not take iodides, mercury or bismuth.

Three years before the patient came to the clinic, he had noticed palpitation on exertion. This gradually became worse and a year before he had become nervous, endurance became poor, and appetite increased. The hyperhidrosis and palpitation became worse. The pulse rate was 120; basal rate, plus 44. The right lobe of the thyroid gland was enlarged and slightly nodular. His palms were moist and he had a digital tremor and was very nervous. There were no abnormal neurological findings. The Wassermann test was 4 plus, Kahn test, 2 plus. Examination of the spinal fluid and other laboratory tests revealed nothing of significance.

A thyroidectomy was performed from which the patient made an uneventful recovery. Pathologic examination revealed a slightly hyperplastic goiter and multiple adenomata.

Cases I and II are examples of cases in which hyperthyroidism develops in individuals who had had asymptomatic syphilis for several years. These patients had not received antisyphilitic treatment and although the preoperative treatment was inadequate, not enough improvement was noticed to justify a delay of the operative treatment which eventually relieved the symptoms.

In Case III hyperthyroidism developed during a prolonged period of antisyphilitic therapy, while in Case IV intensive antisyphilitic treatment, which was instituted soon after the first symptoms were noticed, failed to influence the hyperthyroidism. In neither Case III nor Case IV were iodides used as a part of the treatment prior to the onset of the symptoms of hyperthyroidism. In none of the cases in which thyroidectomy was done did the pathologic appearance of the thyroid gland differ from that in similar cases in which there was no evidence of a syphilitic infection. In two cases attempts were made to demonstrate the presence of the Spirocheta pallida in sections of the gland but they were unsuccessful. We felt that our experience with this technic was too inadequate to allow final conclusions to be drawn, but there were no histologic changes in the gland that would suggest the presence of any organisms.

A careful differential diagnosis is of paramount importance in the consideration of the association of syphilis with hyperthyroidism, as the diagnosis in the recorded cases has been based upon the disappearance of the symptoms following antisyphilitic treatment. One must first definitely establish the diagnosis of hyperthyroidism. The following cases are cited as pertinent.

Case V.—The patient was a man, twenty-eight years of age, who eight months prior to our first observation acquired a chancre which was treated by cauterization and a salve. He does not recall having had secondary manifestations of syphilis. During the preceding three months he had become very nervous and troubled with insomnia. He had profuse perspiration, especially at night, and had noticed palpitation and tachycardia even when lying in bed. He had a headache a great deal of the time. He had lost 20 pounds in three months. His neck had recently become somewhat larger and he had been told by his physician that he had a goiter.

The only significant findings in the physical examination were slight diffuse enlargement of the thyroid gland, a coarse digital tremor and hyperactive reflexes. There were no abnormal eye signs. The pulse rate was 88; basal rate, plus 8. Spinal puncture was refused. The Wassermann test was 4 plus, Kahn test, 4 plus. Following the administration of four injections of mercury salicylate and two of potassium bismuth tartrate and potassium iodide by mouth the symptoms disappeared. The patient continued treatment elsewhere and later wrote that he was feeling very well.

Case VI.—The patient was a young woman, eighteen years of age, who came to the clinic because of a "goiter." For the preceding eighteen months she had had a persistent tachycardia, which was first detected by the school physician. She had recently become nervous. She had had no headaches. For the preceding two years the patient's neck had gradually enlarged. Lugol's solution had been administered but this irritated the patient's stomach so it was discontinued. Following this the swelling of the neck became more noticeable. The patient was uncomfortable in a warm room. During the preceding year she had gained 10 pounds.

Physical examination disclosed a diffuse non-nodulated enlargement of both lobes of the thyroid gland which was about three times its normal size. There was a digital tremor and a hyperhidrosis of the palms. The eyes were rather prominent. The pulse rate was 130; the basal rate, on two occasions, minus 7 and minus 1. After a rest in bed in the hospital the pulse rate dropped to 88. Repeated Wassermann and Kahn tests showed 4 plus each time. There were no abnormal neurological findings. There was no history of infection and there were no signs of congenital or acquired syphilis. Examination of the blood of the patient's mother and younger sister gave negative findings. Following active antisyphilitic treatment the thyroid decreased in size, the tachycardia disappeared and the general health returned to normal.

Case VII.—The patient was a woman, twenty-eight years of age, who complained of "goiter," tachycardia, nervousness and loss of weight. There was no history of any syphilitic infection but the patient's child had congenital syphilis. The patient's appetite was sometimes very good but recently had been poor, and during the past two years she had lost 20 pounds in weight. She had been nervous

and irritable for five years. Eight months before she had had a nervous breakdown and had been confined to bed for two months. She was troubled with constipation. She had frequent attacks of palpitation of the heart and had been troubled with persistent tachycardia. She perspired easily. She stated that she was unhappily married. Ten months before we saw her the patient had been told that her basal rate was plus 24 and seven months later that it was plus 39.

Physical examination revealed a well-developed but poorly nourished woman. The skin flushed easily and was moist. The eyes were prominent but no abnormal signs were noted. The thyroid gland showed a diffuse enlargement to about twice its normal size. The heart was normal except for a rapid rate. The pulse rate was 106; the basal rate, plus 9. The superficial reflexes were exaggerated. There were no digital tremors. There was a slight reaction to the adrenalin sensitization test. The Wassermann test was 4 plus, Kahn test, 3 plus. Tests of the spinal fluid gave negative findings. Following the administration of iodides, bismuth and neosalvarsan all symptoms disappeared, and the size of the thyroid gland decreased materially. This type of case is not especially rare.

Are these examples of syphilitic hyperthyroidism? They present all the symptoms that Levy-Franckel[2] and several other authors considered necessary to justify such a diagnosis, namely, tachycardia, nervousness, tremor and at times slight exophthalmos and enlargement of the thyroid gland. These symptoms were presented in individuals known to be syphilitic and they all disappeared or markedly improved under antisyphilitic therapy. In many of the reported cases there are no recorded studies of the basal metabolism and the clinical pictures as given are not sufficiently detailed, so that one feels reluctant to accept some of these cases as examples of true hyperthyroidism. An absence of an increased basal metabolic rate justifies the conclusion that we are probably not dealing with hyperthyroidism.

Most of the cases of syphilitic hyperthyroidism reported in the literature were observed before basal metabolism studies were extensively used and are no better examples of hyperthyroidism than the cases just cited. The case reports of Jensen[3] and of Henry[4] are the only ones I have reviewed that include a record of accelerated metabolism. It is our impression that the cases cited above are not cases of syphilitic hyperthyroidism but that the symptoms are produced by the effect of the Spirocheta pallida either on the central

or on the autonomic nervous system. In early syphilis one occasionally observes tachycardia and evidence of disturbances in the vegetative nervous system.

In Case V the patient presented clinical evidence of meningeal irritation and it is unfortunate that a spinal puncture was not permitted. The syphilis was of short duration. I am of the opinion that the nervousness, tachycardia, loss of weight, and tremor were manifestations of neurosyphilis, the enlarged thyroid being coincidental or due to parenchymatous syphilitic thyroiditis. Unfortunately we were able to observe the results of treatment for only a short period.

Cases VI and VII could more easily be accepted as cases of hyperthyroidism. However, in neither of these cases were such typical symptoms presented as emotional instability, state of apprehension and loss of weight associated with an excellent appetite which are usually seen in well-developed cases of Basedow's disease.

We feel that before one is justified in making a diagnosis of syphilitic hyperthyroidism a careful evaluation of the nervous and cardiovascular systems should be made to rule out the possibility of syphilitic involvement; there should be positive evidence of an accelerated metabolism and the symptoms should disappear with the return to a normal metabolism following the administration of mercury or salvarsan. Iodides in small amounts, together with rest in bed, will produce improvement in patients with hyperthyroidism. The administration of iodine in the form of Lugol's solution is a routine measure in the preoperative management of hyperthyroidism, consequently this drug should not be used as a therapeutic test.

REVIEW OF THE LITERATURE

That a syphilitic infection may cause hyperthyroidism or Basedow's disease has been suggested by several observers, whose conclusions have been based on the fact that in cases in which Basedow's disease has developed during the secondary late asymptomatic and late symptomatic stages of the infection, the condition responded to iodide, mercury, bismuth and salvarsan therapy. (We consider Basedow's disease and hyperthyroidism as synonymous terms.) That antisyphilitic therapy caused to disappear symptoms which simulate those produced by hypersecretion of the thyroid is not in all cases sufficient evidence to substantiate a diagnosis of syphilitic hyperthyroidism. Syphilis and hyperthyroidism are common diseases;

therefore it is relatively difficult to determine how frequently the occurrence of both in one individual is coincidental. Furthermore, it is our belief that syphilis may produce a symptom-complex which closely simulates that of hyperthyroidism. In such cases, however, that hypersecretion of the thyroid probably does not occur is evidenced by the absence of an increased metabolism. We do not deny that syphilitic hyperthyroidism does occur, nevertheless many of the reported cases are not convincing, especially in view of our own observations as indicated in the cases cited above.

If the mechanism of the pathogenesis of hyperthyroidism were understood we could more easily evaluate the importance of syphilis as a causative factor. It is not our intention to discuss the many theories in regard to the pathogenesis of hyperthyroidism. Suffice it to say that it is a syndrome in which there is an increase in metabolism and a disturbance in the vegetative nervous system, associated with a hypersecretion of the thyroid gland as well as disturbances in other endocrine organs; and that removal of a large portion of the thyroid will cause a disappearance of or marked relief from most of the major symptoms. It is not known whether the hypersecretion of the gland is primary or secondary in the course of the disease.

That a disturbance in the integrity of the endocrine system may have an influence on the mechanism of defense against a syphilitic infection has been shown by Pierce and Van Allen[5] in some experimental work in rabbits. They found that in animals in which complete thyroidectomy had been performed prior to inoculation with syphilis the disease was more severe than in the controls—markedly so in certain cases. When partial thyroidectomy was performed the disease was not so severe as in the controls. After complete thymectomy the effect was less pronounced than after either complete or partial thyroidectomy but in general resembled that in partially thyroidectomized animals.

In an article on the appearance of the basedowian syndrome in the course of syphilis, Levy-Franckel[2] cited eighteen observations most of which were made in the clinic of Professor Gaucher. Ten of these were cases of late syphilis, six of early and two of congenital syphilis. In 13 cases the thyroid gland was enlarged, in 11 tachycardia and tremor were present and in six there was some degree of exophthalmos. In six, clinical signs of syphilis of the nervous system were present. Two of the patients showed none of the signs of hyperthyroidism. In one

case the diagnosis apparently was based on the presence of tremor and flushing. In seven cases improvement followed antiluetic treatment.

In most of these cases Levy-Franckel based the diagnosis of Basedow's disease on the presence of tachycardia, an enlarged thyroid gland, and tremor, and he stated that the response to treatment is the most important means for the establishment of the diagnosis of syphilitic Basedow's disease. Many of Levy-Franckel's patients had ulcerative lesions in the oral cavity which he thought might have had a significant relation to the syndrome of hyperthyroidism. In seven of his cases the symptoms were influenced by treatment. In six there was no response to treatment and in the rest no record of the results of the treatment was made.

Gaucher and Levy-Franckel[6] reported the cases of two patients, both women, who had contracted syphilis five and two and one-half years respectively before the onset of symptoms of hyperthyroidism. Each patient had tachycardia, tremor, exophthalmos, irritability, and an enlarged thyroid gland. In each case all symptoms except the enlargement of the thyroid were relieved after injections of benzoate of mercury and neosalvarsan. Iodides were not given. In one case the exophthalmos disappeared.

Penzoldt (quoted by Gaucher and Levy-Franckel) has reported three cases of late syphilis in which the symptoms of Basedow's disease were relieved by iodine-mercurial treatment. In concluding his comments, Penzoldt states that the greater number of victims of Basedow's disease do not tolerate iodides well, but that by a small number of his own syphilitic patients, this substance was well tolerated. Because of this he concluded that in numerous cases of Basedow's disease syphilis plays a causative rôle.

Stümpke[7] observed the case of a woman, thirty-six years of age, in whom severe secondary syphilis was associated with malnutrition, depleted strength, nervousness, marked exophthalmos, a large, soft thyroid gland and pulse rate of 140. Prior to her infection this patient had been told that she suffered from mild Basedow's disease. Following the administration of neosalvarsan and inunctions of mercury the patient gained weight, the exophthalmos disappeared and the pulse rate was reduced to 100. The patient then disappeared so that the eventual outcome could not be recorded. Stümpke also cited a case reported by Ziegel, that of a woman, twenty-eight years of age, who had syphilis together with Basedow's disease and scleroderma. After two intramuscular injections of salvarsan she gained

30 pounds, the thyroid decreased in size, the nervousness and tachycardia disappeared and there was a corresponding improvement in the scleroderma.

Pfeiffer[8] observed three cases in which exophthalmic goiter of emotional origin developed in syphilitic individuals. In each case the emotional shock was produced by bombardment with heavy shells during the World War.

In one case the patient was a woman who had been terrorized by the projectiles. A week later the eyes began to protrude and the throat began to enlarge. Insomnia developed. The patient had tachycardia, a pulse rate of 120 to 130, tremor of the fingers, hands, and tongue, and enlargement of the thyroid gland. The Wassermann test gave positive findings and there was evidence of secondary syphilis. The second case was that of a soldier, in whom exophthalmos, tremor, and an enlarged thyroid gland developed soon after a bombardment with heavy shells. He had acquired syphilis twelve years before. The third case was that of a man who presented symptoms which Pfeiffer considered to be caused by exophthalmic goiter. Tests of the blood and of the spinal fluid indicated the presence of syphilis. Antisyphilitic treatment caused the tremor, tachycardia and exophthalmos in the first case to disappear. Pfeiffer was unable to follow the other two cases.

In numerous cases of shell shock seen during a period of eighteen months Pfeiffer observed only three cases in which the classical symptoms of exophthalmic goiter were present and in each of these cases the patient was also infected with syphilis. He concluded that emotion lights up a glandular trouble only when the gland is prepared for it, either by an infection of the gland itself or of the nervous centers commanding it. He believed that in these cases the syphilis had altered the cardiovascular sympathetic and glandular apparatus, thus making possible the fixation of symptoms produced by emotional shock.

Pfeiffer's report suggests the comment that, with the possible exception of the exophthalmos, the condition presented by these patients might have been neurocirculatory asthenia, or "soldier's heart," a condition which closely simulates hyperthyroidism, and is often mistaken for it.

In 1888, Barie (quoted by Gaucher and Levy-Franckel) expressed the opinion that sclerosis of the posterior column of the spinal cord prolonged as far as the medulla oblongata was the cause of the symp-

toms of Basedow's disease which are observed in certain cases during the course of tabes. Jaffray (also quoted by Gaucher and Levy-Franckel) believes that the simultaneous appearance of these two maladies is only a coincidence. Gaucher and Levy-Franckel, Ingelrons,[9] and Delearde[10] have noted that in the majority of cases, in which these conditions are associated, the symptoms of Basedow's disease precede the onset of the symptoms of tabes and that for this reason they could not be attributed to a lesion of the medulla.

Sainton[11] reported two cases of Basedow's disease in syphilitic patients. In one case, that of a woman with exophthalmos, a moderate enlargement of the left lobe of the thyroid gland, aortitis and tabes dorsalis, the symptoms failed to respond to antisyphilitic treatment or radiotherapy. In the other case, that of a soldier, thirty-two years of age, with aortitis of twenty-seven years' duration, severe albuminuria, and syphilis, there was a slight exophthalmos, positive Graefe's and Möbius's signs, and hypervagotonia. Following a series of injections of benzoate of mercury there was a rapid disappearance of all symptoms. Sainton believes that there are two varieties of syphilitic Basedow's disease, one presenting a precocious syndrome and the other a tardy syndrome. In cases which present a precocious syndrome, that is, one that occurs two or three years after the primary symptoms of syphilis, antisyphilitic treatment produces rapid results, while in cases which present a tardy syndrome appearing several years after the primary infection, treatment seems to be less efficacious.

Schulmann[12] has written a great deal about the rôle played by syphilis in the causation of exophthalmic goiter. He feels that in 15 to 20 per cent of the cases of exophthalmic goiter, syphilis is the determining factor. In his own statistics, based on 71 cases of exophthalmic goiter, syphilis was present in 50 per cent, but his material was taken from the Hospital St. Louis where syphilis is frequently seen. Among 36 patients, 8 males and 28 females, 10 had congenital and 26 acquired syphilis. Among 48 patients treated with iodides, mercury and arsenicals, 23 per cent were cured, 29 per cent were greatly improved, 25 per cent slightly improved and in the remaining 23 per cent, the treatment failed to produce any curative results. The patients with congenital syphilis responded more slowly than those in whom the infection was acquired. Schulmann maintained that the effect of antisyphilitic treatment is one of the best proofs which we possess of the rôle syphilis may play in the cause of ex-

ophthalmic goiter. However, in his thesis in the International Clinics he reported three additional cases as examples of syphilitic exophthalmic goiter, one in which slight improvement followed treatment with neosalvarsan while in the other two cases the diagnosis was based solely on the history of infection and the presence of positive serological findings in patients who presented symptoms of hyperthyroidism.

Schulmann stated that in 1888 Jaffray presented seven cases of tabes with tachycardia before the Society of Medicine at the Hospital of Paris and showed that in six of these cases there was more or less protrusion of the eyes while in two cases hypertrophy of the thyroid gland and tremor were present. He thought that in four of these seven cases Basedow's disease was present and he concluded that locomotor ataxia might give rise to tachycardia and perhaps to a slight degree of hyperthyroidism, either on account of some central lesion, a change in the peripheral nerves, or some simple functional disturbance.

Reinhold (quoted by Schulmann), after comparing Basedow's disease with paroxysmal tachycardia in cases of leptomeningitis of the base, thought that in syphilitics the origin of the former disease is bulboprotuberential. He reported the case of a syphilitic patient with paroxysmal tachycardia in which basal leptomeningitis was especially marked over the protuberance, found at autopsy.

Schulmann observed a family of eleven children of whom seven had syphilis. In three of these children, the tabes was associated with symptoms of mild hyperthyroidism, in four, definite exophthalmic goiter was present. Schulmann collected from the literature 20 cases in which the syndrome of exophthalmic goiter was present in which the syndrome disappeared after treatment with mercury and iodides, and in one case with neosalvarsan.

Jensen[3] reported the case of a young woman, thirty-three years of age, who had symptoms of hyperthyroidism—falling out of the hair, tachycardia, tremor, loss of weight, and a basal rate of plus 34; and the Wassermann test gave positive findings. The symptoms were relieved by antiluetic treatment. Jensen did not make a spinal puncture and his report did not rule out the presence of syphilis of the central nervous system. He found in the literature 20 cases in which syphilitic infection was associated with a toxic goiter syndrome.

Henry[4] observed a woman, forty-six years of age, who was nervous and irritable, had a palpable thyroid and a basal rate of plus 52 and

plus 44. The Wassermann test gave positive findings. This patient responded promptly to active antisyphilitic therapy.

Clark[13] reported the case of a woman, twenty-four years of age, with an enlarged thyroid, tachycardia and violent attacks of nervousness. She finally became comatose, had a pulse rate of 200 and vomited continuously. A Wassermann test of the blood of the patient and of her mother each gave positive findings. At the age of twelve this patient had had convulsions. The author did not cite any signs of involvement of the central nervous system. The symptoms disappeared after treatment with iodides and later with inunctions of mercury and arsenicals. The author felt that this was a case of exophthalmic goiter due to syphilis. His conclusion, however, can not be accepted as the symptoms could have been due to syphilis of the central nervous system.

Smit[14] reported the cases of two women, thirty-four and fifty-two years of age respectively, who suffered from insomnia, and had a pulse rate of 140 and sluggish pupils. These symptoms disappeared rapidly under antisyphilitic treatment. He considered these to be cases of hyperthyroidism.

Koopman[15] reviewed cases reported by Ziegelroth, Bernhardt, Alquier, Fritz and Schulmann as examples of conjugal Basedow's disease. He stated that syphilis was present only in those reported by Bernhardt and by Schulmann; his conclusions that the evidence that the infection was the cause of the Basedow's disease are very unconvincing. Conjugal hyperthyroidism is very rare and the possibility that syphilis may be an etiologic factor is of interest.

Koopman reported the following observation: A school girl, unmarried, consulted him because of Basedow's disease. The first sign had been tachycardia. Suddenly the disease became worse. The Wassermann test gave strongly positive findings. The patient acknowledged that she was in love with an infantry officer. This man had no exophthalmos, but had a pulse rate of 140 to 180 on account of which a diagnosis of neurasthenia had been made. The thyroid gland was enlarged and the patient had lost weight. The Wassermann test gave positive findings. Four weeks after the first conjugation the patient had acquired a chancre and a year later Basedow's disease developed. In this case treatment was denied.

Koopman believed that in these two cases the cause of the Basedow's disease was syphilis. There is nothing in the report to warrant such a conclusion although the development of Basedow's disease in a

woman who had contracted syphilis from a man who had symptoms suggestive of Basedow's disease is of interest. It is unfortunate that observations as to the response to treatment in these cases were not available.

Rowstron[16] presented a short report of the case of a girl four and one-half months of age with congenital syphilis, an enlarged thyroid, nervousness, and showing a positive Graefe's sign. He offered no report as to the treatment or progress of the patient.

Simonton[17] observed five cases in which he thought that syphilis was the cause of disease of the thyroid gland. Two of these appeared to be cases of hyperthyroidism. His third case was probably one of gumma of the thyroid. In one of these cases, that of a man, twenty-nine years of age, the patient had protrusion of the eyeballs, enlargement of both lobes of the thyroid, had lost 50 pounds in three weeks, had diarrhea and tremor and was troubled with insomnia and restlessness. The Wassermann test was 2 plus. Under treatment with salvarsan all the symptoms disappeared.

In the second case, that of a woman, twenty years of age, the patient had an enlargement of the thyroid gland. It was the size of a small orange and of the consistency of putty. There was marked loss of weight, a fine tremor, protrusion of the eyeballs, pulse rate of 130 and the Wassermann test was 4 plus. The patient had been pregnant for two months and was very nervous. Under salvarsan treatment she showed marked improvement and gave birth to a healthy child. One year later the pulse rate was 86, the gland much smaller and the eye signs were hardly noticeable.

Hazen[18] observed a case of what he considered to be a vagotonic hyperthyroidism in a woman suffering from cerebrospinal syphilis. Her symptoms cleared up following antiluetic treatment.

Howard[19] has stated that there still is not sufficient proof that syphilis plays more than a minor rôle in the etiology of exophthalmic goiter. He quoted Castex as saying: "The most common cause of disturbances in thyroid function in Argentinians is syphilis, both acquired and inherited."

From the study of the literature and from our own observations, I have formed the opinion that syphilis is of little importance as an etiologic factor in the production of hyperthyroidism. All authors agree that syphilitic hyperthyroidism does not differ clinically from that seen in nonsyphilitics, and justify the diagnosis on the disappearance of symptoms following specific therapy. There could be no

objection to this if the diagnosis of hyperthyroidism in these cases could have been definitely established before treatment was instituted. This has been done in a few of the cases reported while in others the accuracy of diagnosis is doubtful. It is my opinion that through the effect of syphilis on the vegetative nervous system the symptoms of a syphilitic infection may simulate those of hyperthyroidism, and in some cases, the usual neurological examination and tests of the spinal fluid may give negative findings.

In one third of the cases of hyperthyroidism included in the series of cases reported above, there was clinical or serologic evidence of neurosyphilis. This high percentage is of interest because of the frequency with which this association has been noted in the literature. This association led some of the earlier observers to the opinion that some central involvement of the nervous system was the cause of Basedow's disease in the cases reported by them—a theory which has not been accepted by many students of the disease.

Of more practical importance is the question as to what influence syphilis has on the management of hyperthyroidism. My experience has been that patients in whom syphilis is associated with hyperthyroidism respond to surgery as well as do the nonsyphilitic patients. Convalescence is not prolonged and when subsequent antisyphilitic treatment is instituted desirable results usually are obtained. Although my series of treated cases is small I have not observed any marked benefit from preoperative treatment and in some instances the patient has become worse. The delay necessary for the application of antisyphilitic treatment as a therapeutic test is great enough to cause serious myocardial damage in a case of active hyperthyroidism and antisyphilitic treatment is contraindicated unless the syphilis is in the early stages.

In cases complicated by neurosyphilis the surgeons are reluctant to operate when there is a mental deterioration, as the results are usually poor. In one of our cases with syphilis of the central nervous system, the patient died soon after preoperative treatment was started, in another active paresis developed after operation but the patient was benefited by malarial treatment, and in a third case the patient became maniacal and died several weeks after operation. Patients with tabes dorsalis did well following operation, but in most instances preoperative treatment with bismuth or mercury seemed to be beneficial.

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CHAPTER XX

ROENTGENOLOGICAL OBSERVATIONS IN THYROID DISEASE

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ROENTGENOLOGY has taken its place in the diagnosis and treatment of the pathologic thyroid gland as in other fields of medicine. However, in this chapter we shall limit our discussion to diagnosis of the substernal thyroid, and to some phases of the metastases which follow primary malignant disease of this organ.

INTRATHORACIC GOITER

By substernal or intrathoracic goiter we indicate that type of enlarged thyroid which lies wholly or partially within the thoracic cavity. Those cases in which one or more lobes of the hypertrophied gland extend only a short distance into the thorax beneath the clavicle, we choose to term cases of *struma profunda*, after the teaching of Kocher. This latter type of substernal tumor is usually lifted out of the thorax when the head is hyperextended, as is the case in the usual operative position. Therefore, the presence of a *struma profunda* is usually entirely unobserved at the time of operation. There is also a group of true substernal thyroids in which the substernal portion is a projection from a lobe or the isthmus of the thyroid which extends into the thoracic cage, to various extents and in different positions.

There is also the possibility that a true intrathoracic goiter may develop from an aberrant thyroid located in the mediastinum. It is believed, however, by some observers, especially by Pemberton, that such aberrant glands may result from protrusions of the thyroid through the fascia at the point of entrance or exit of the thyroid vessels, this protruded portion becoming pedunculated and later entirely cut off from the original gland.

It is the province of the roentgenologist to detect intrathoracic enlargements of the thyroid gland and to identify them and to differ-

entiate them from other lesions which may occur in the upper mediastinum.

A consideration of the mode of development of an intrathoracic goiter may be of considerable aid in making the diagnosis. Intrathoracic goiter may develop from either lobe of the thyroid or from the isthmus. In determining the origin of a mediastinal mass in

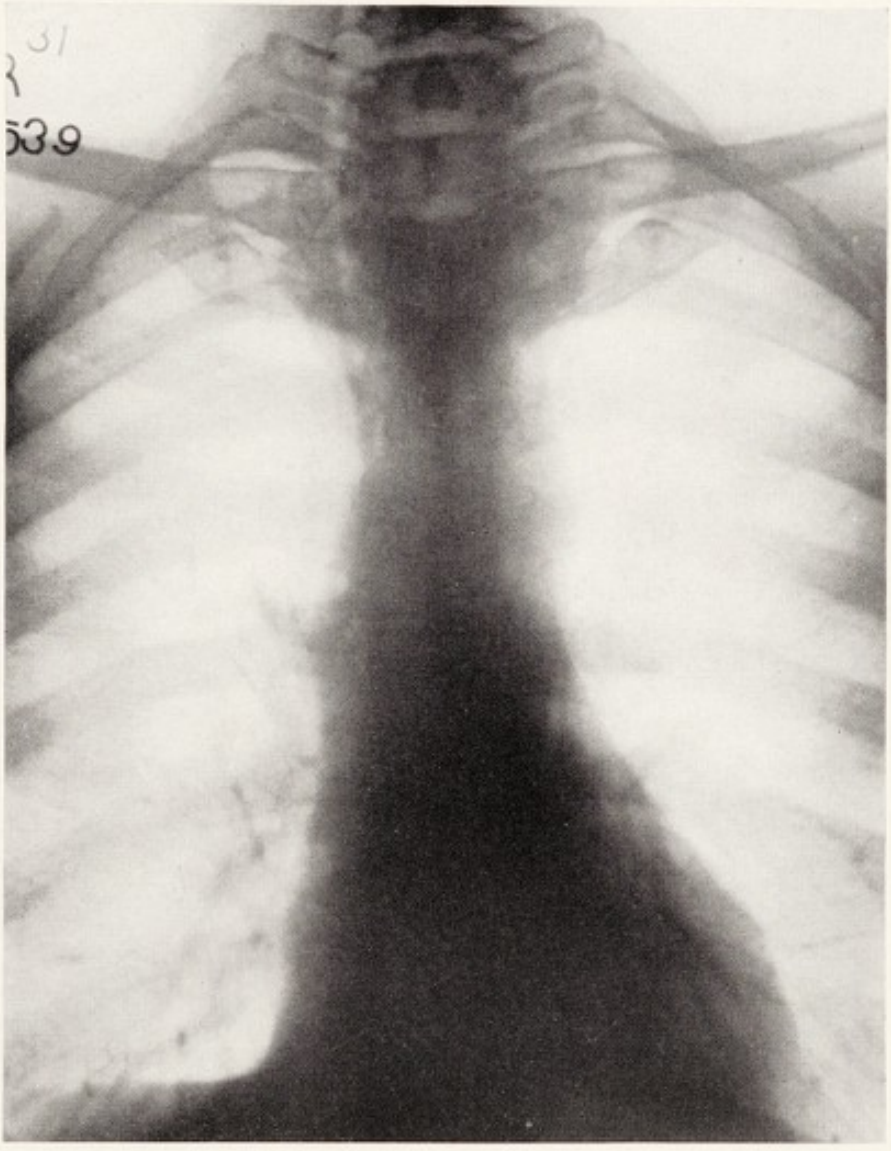

Fig. 65.—Cystic adenoma of the thyroid with substernal extension, compression, and displacement of the trachea to the right.

any given case, we may be able to detect on the roentgenogram a continuation of the right or left lobe of the thyroid gland, as such a prolongation will produce a homogeneous shadow extending into the thorax. Perhaps of even greater importance in determining the origin of a mediastinal mass, however, is the position and character of the tracheal shadow.

The trachea being an air-filled organ with a cartilaginous wall may be readily displaced and compressed, such displacement or compression being readily discernible on an *x*-ray film. The appearance of this air-filled organ may be a most valuable aid in cases in which the goiter itself cannot be seen. An extension of the left lobe of the thyroid alone will usually displace the trachea to the right of

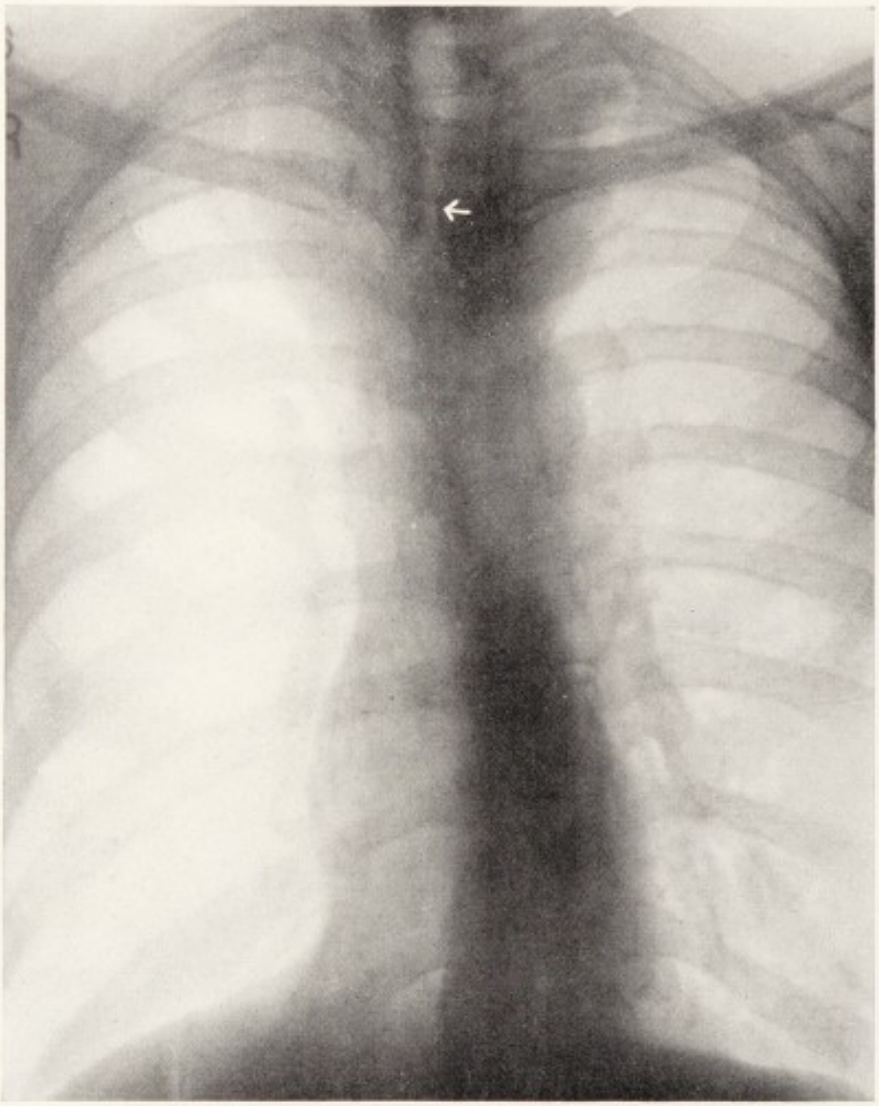

Fig. 66.—Substernal goiter extending down from both lobes with compression of the trachea from both sides producing a typical saber-sheath trachea.

the median line with a concavity on the right side (Fig. 65); while if the course of the extension should be from the left lobe the exact opposite of this picture would be shown. These extensions, also, may displace the trachea anteriorly or posteriorly against the spine.

If there is extension from both lobes, the trachea will be compressed by the opposing forces which will narrow its lumen and

produce the so-called "saber-sheath trachea" (Fig. 66). If the extension is from the isthmus the goiter will usually lie posterior to the trachea (Figs. 67, 68) and will either directly compress the trachea

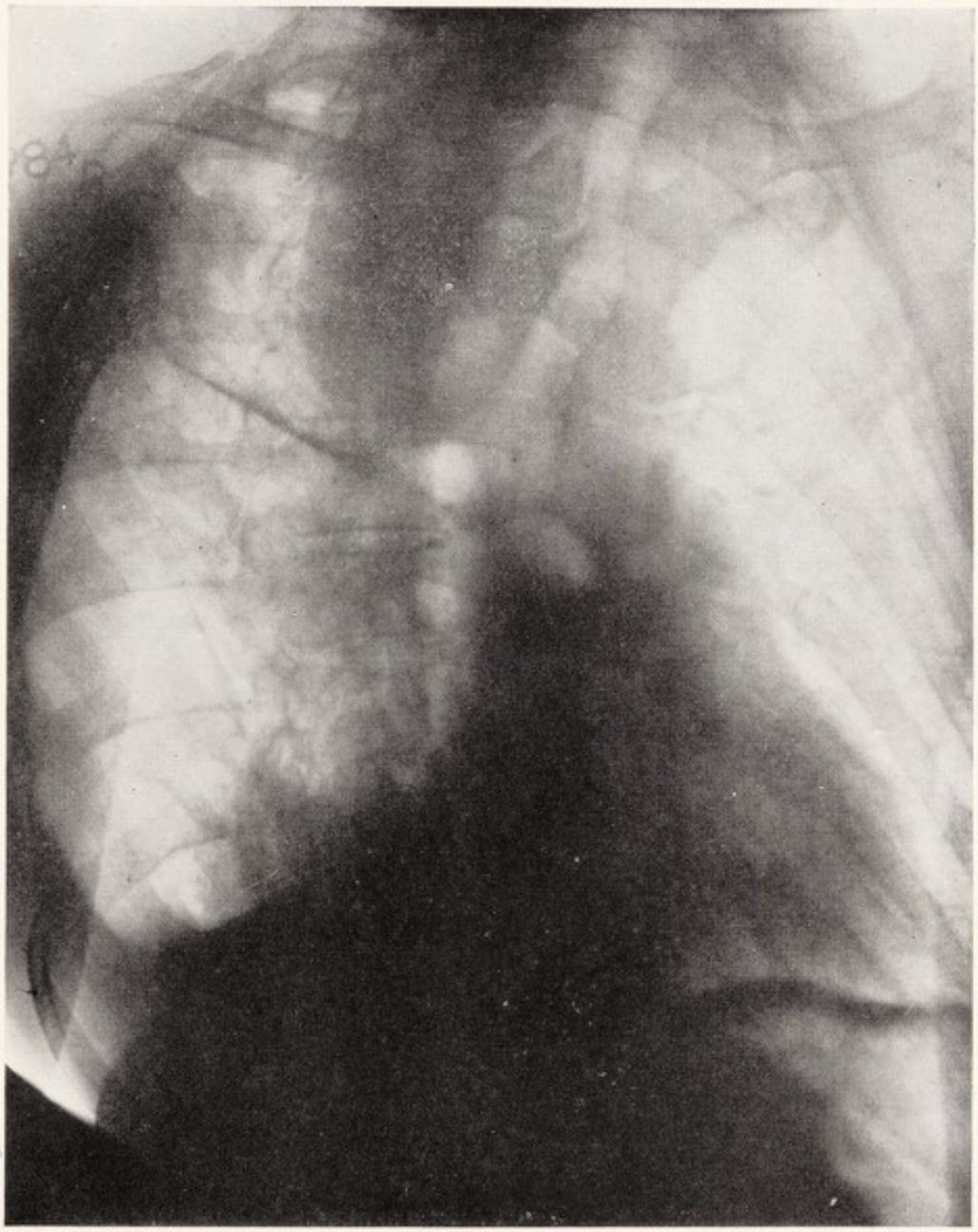

Fig. 67.—A cystic adenoma of the thyroid with extension well down into the chest to the aortic arch with displacement of the trachea anteriorly. In this case the lumen of the innominate artery was markedly constricted as the result of thrombosis. There was also pressure on the superior vena cava.

from behind forward leaving it in the midline as a broadened and collapsed tube but such an extension may displace the trachea either to the right or left particularly if the goiter is asymmetrical.

This compression of the trachea can usually be best determined by examination of a lateral view. In any questionable case the injection of lipiodol into the trachea will outline its wall very nicely (Figs. 69, 70).

To determine the presence of an intrathoracic goiter by the *x*-ray both the radiographic and fluoroscopic methods should be used, as

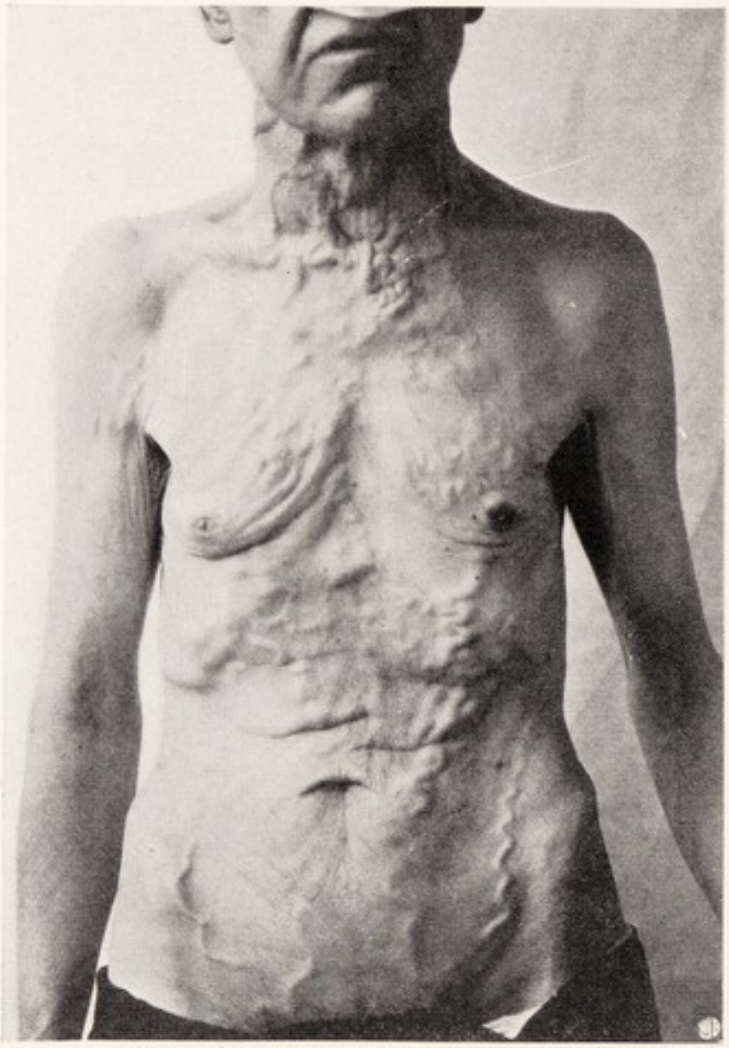

Fig. 68A.—Venous thrombosis from obstruction due to intrathoracic goiter. Photograph of patient whose roentgenogram is shown in Fig. 67, a man sixty-two years of age, showing distention of jugular veins and of veins over chest and anterolateral portions of the abdomen.

each may contribute important findings which will aid in establishing the diagnosis. It is our procedure to make anterior-posterior stereoscopic radiographs, the plate being placed across the anterior chest wall with the patient either in the standing or reclining position. In addition, plates should be made with the patient in both the right and left oblique positions with the right or left nipple centering on

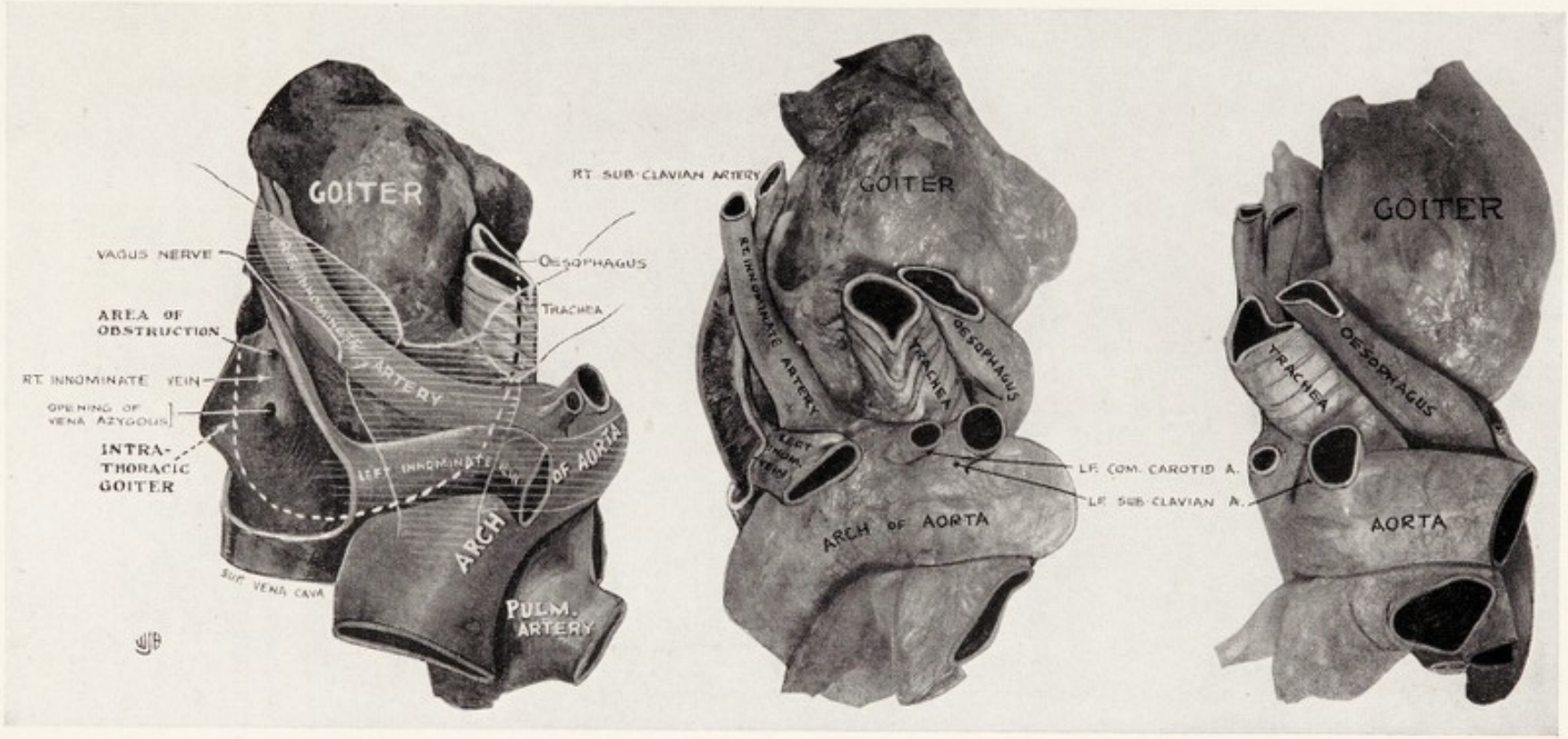

Fig. 68B.—Autopsy specimen showing marked hyperplasia of both lobes of the thyroid gland and of the isthmus with an intrathoracic extension from lower pole of the right lobe. The right innominate vein was almost completely obliterated by fibrosis which doubtless resulted from the organization of a thrombus.

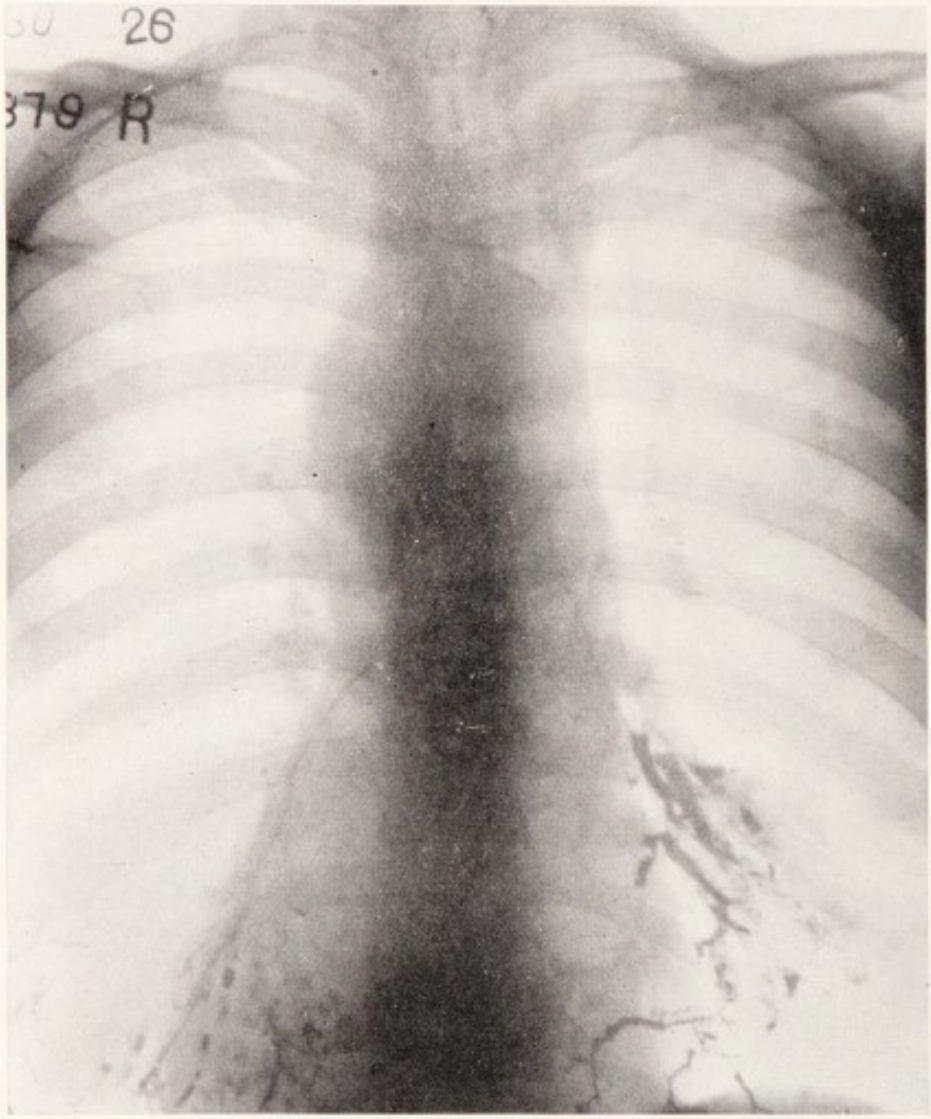

Fig. 69.—Aneurysm of the aortic arch taken after the injection of lipiodol into the trachea. Note the compression of the trachea and its displacement by the aneurysm.

the film and the central line of radiation extending from the inner border of the opposite scapula directly through the nipple. A true lateral radiograph of the neck and upper mediastinum should be made also. The fluoroscopic examination is made best with the patient in the upright position.

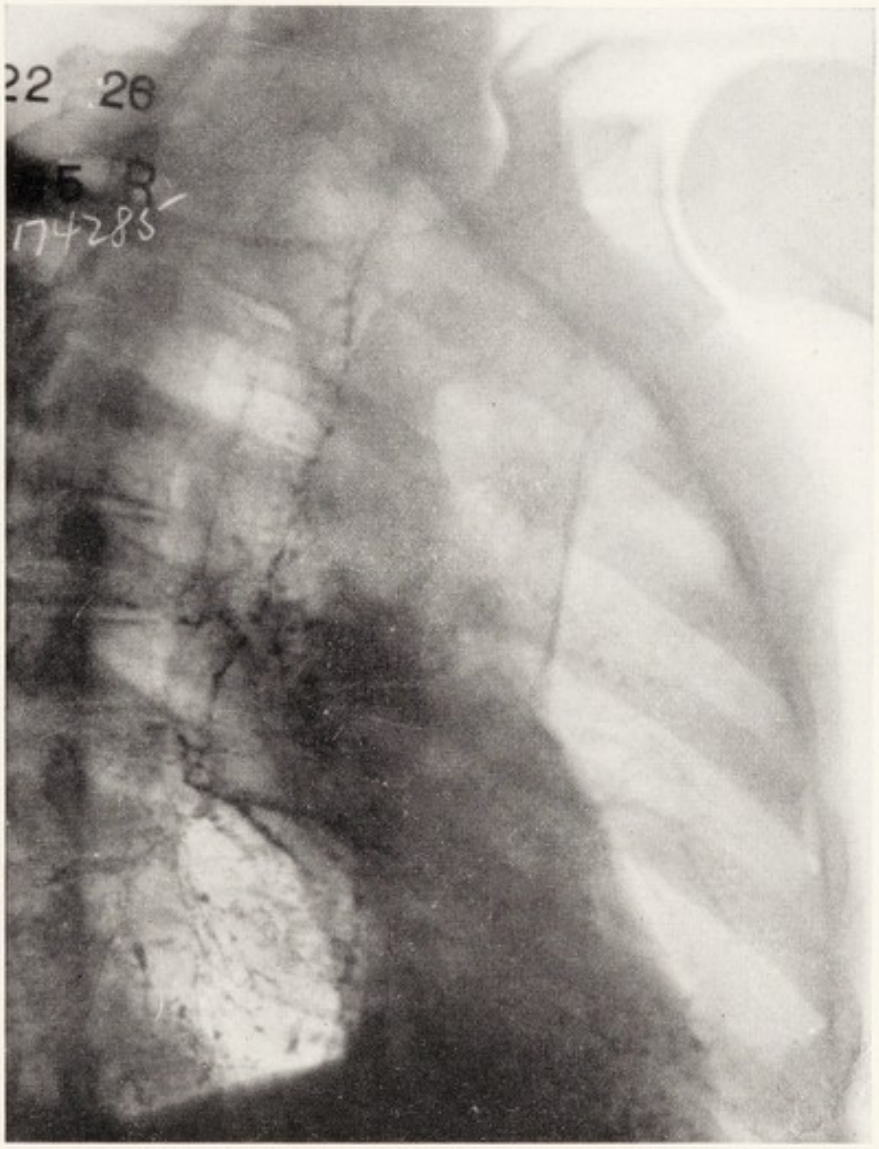

Fig. 70.—A lateral view of the trachea shown in Fig. 69 showing the clear delineation of its border after the introduction of lipiodol.

The important points in the radiographs are the sharpness and regularity of the outline of the shadow as well as the outline and condition of the trachea. They also form a permanent record and guide the surgeon at the time of operation since they determine the location and extension of the tumor.

DIFFERENTIAL DIAGNOSIS OF INTRATHORACIC GOITER

The shadow of an *intrathoracic goiter* usually lies high in the mediastinum and appears as a continuation of the supraclavicular shadow of the thyroid (Figs. 71–76). The outline is regular in cases in which the goiter is not nodular or malignant in character

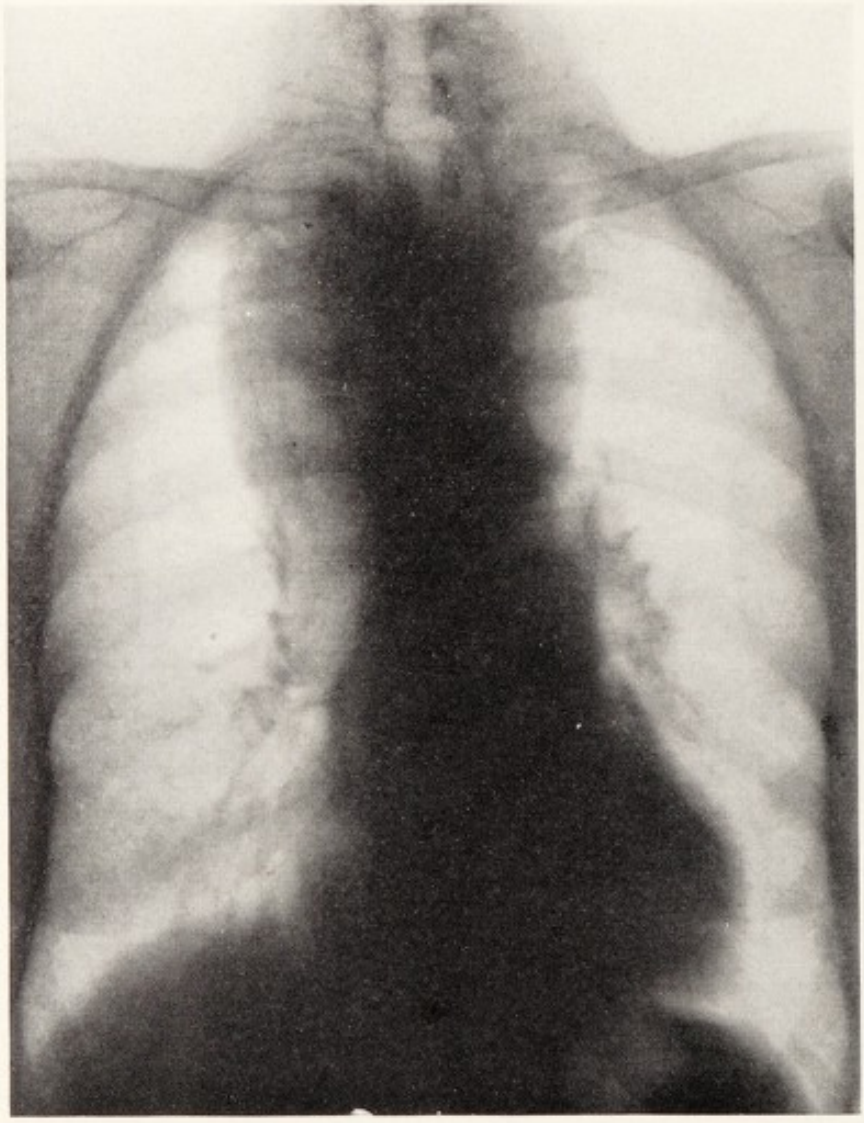

Fig. 71.—Colloid adenoma of the thyroid extending substernally to a point below the aortic arch. This struma is continuous with the thyroid and overshadows the aortic arch with compression of the trachea from both sides.

and it is usually silhouetted over the pneumonic cavity on one or both sides of the mediastinum. In the fluoroscopic examination of an intrathoracic goiter the goiter usually makes a dense shadow in the upper mediastinum.

In the case of an extension from a supraclavicular goiter the shadow broadens out above to join the tumor in the neck. The outline

is regular and moves up and down during deglutition and on deep inspiration and expiration. If the goiter comes in contact with the mediastinal vessels it may appear to pulsate. This appearance, however, is due to a transmitted impulse and is not expansile in character.

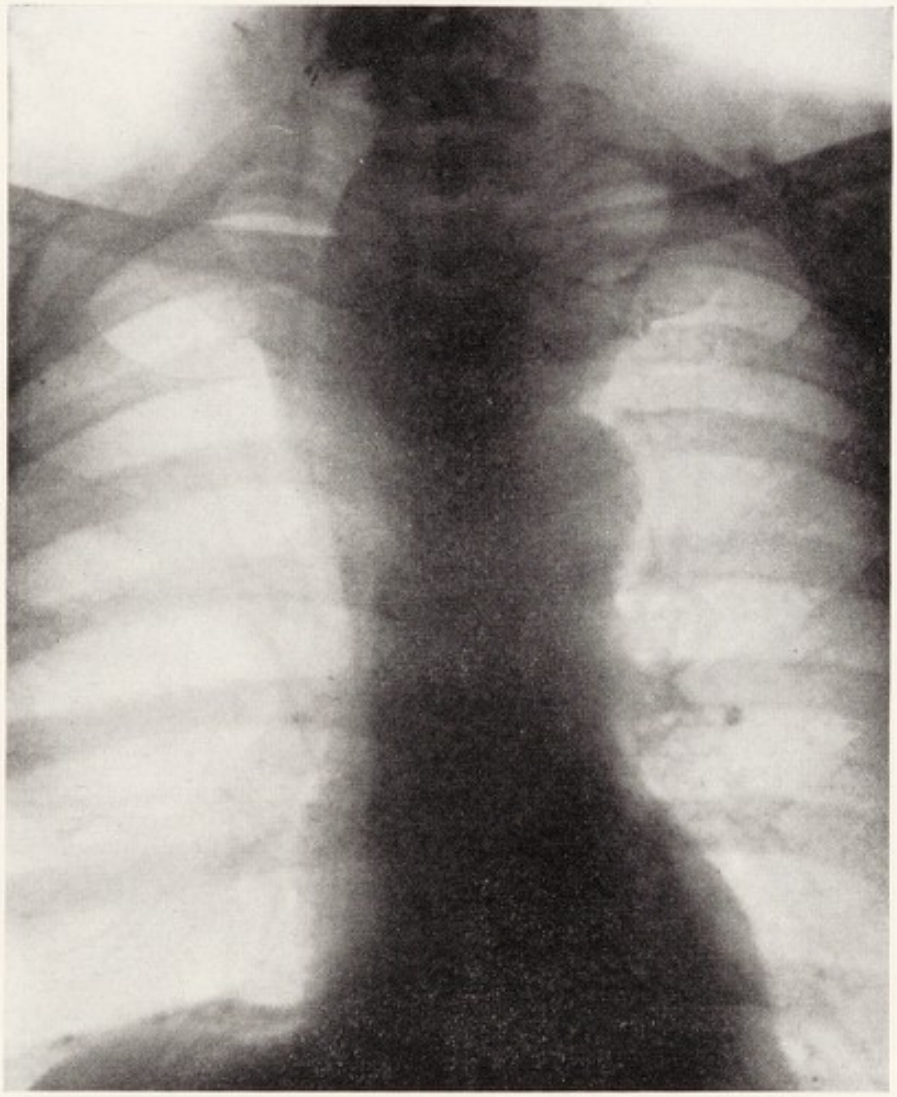

Fig. 72.—Adenoma of the thyroid with a large substernal extension. Trachea compressed and displaced to the right. This patient also had marked hyperthyroidism.

From stereoscopic films of the chest made with the patient in the anterior-posterior position we may study the outline of the tumor to better advantage and also determine the effect of the goiter on the air-containing trachea, which as described above may be compressed or displaced or both. A goiter does not usually cast as dense a shadow as the heart and great vessels, and therefore very frequently the vascu-

lar shadow and heart shadow may be distinctly seen through that of the thyroid extension.

The nodular carcinomatous type of intrathoracic goiter offers the greatest difficulty in diagnosis, to establish which it may be necessary to consider the clinical symptoms as well as the history and the findings in the physical examination, in addition to the roentgenographic findings.

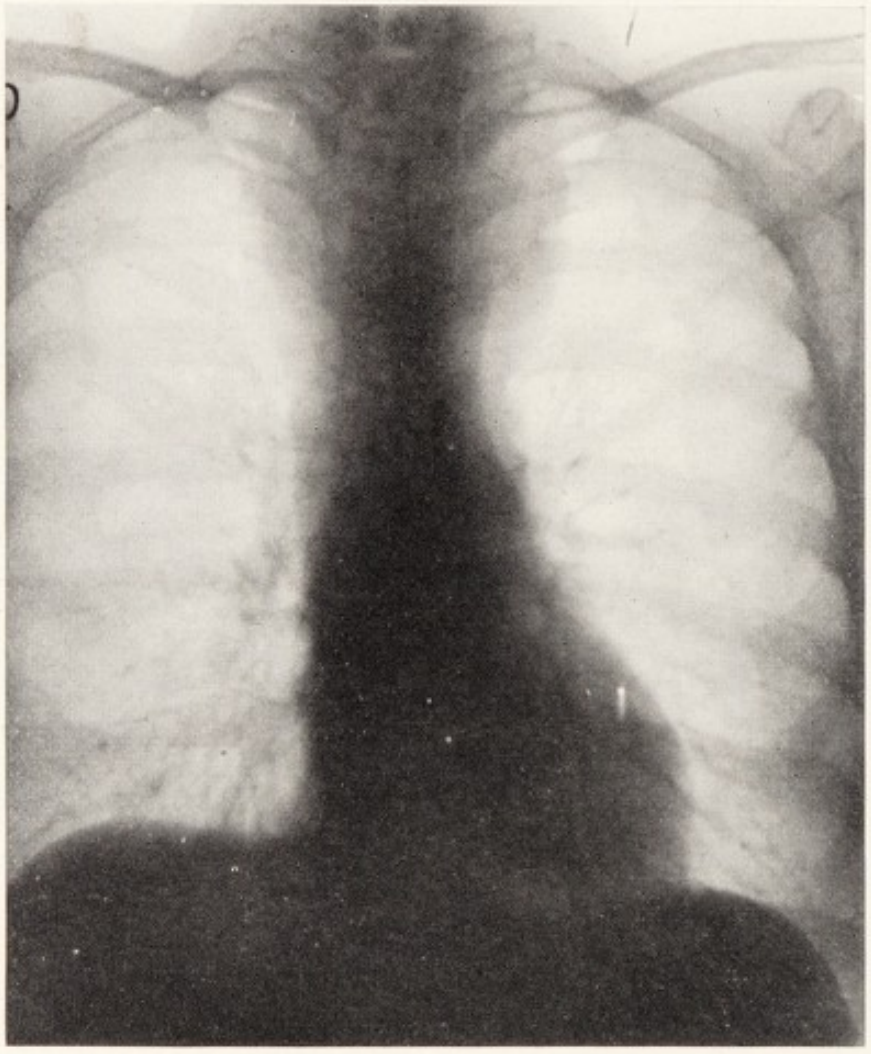

Fig. 73.—Adenoma of the thyroid with substernal extension to a point below the aortic arch. The angle between the aorta and the thyroid shadow was seen to separate on deglutition. This patient had a marked hyperthyroidism.

Roentgenograms of the mediastinum give the best results if there has been a rapid exposure. We are at the present time experimenting with a technic in which a current of 1000 milliamperes is used through a rapidly rotating circular Bucky grid at a distance of 6 feet with a time exposure of one-thirtieth of one second. Every roentgenologist is familiar with the excursion of the mediastinal shadow during

pulsation of the heart and adjacent vessels, which moves the bronchi and supporting tissue to varying extents depending upon the activity of these organs. This movement of the mediastinum may be quite sufficient to render indistinct the outline of a mediastinal mass, a difficulty which can be obviated only by a very rapid technic.

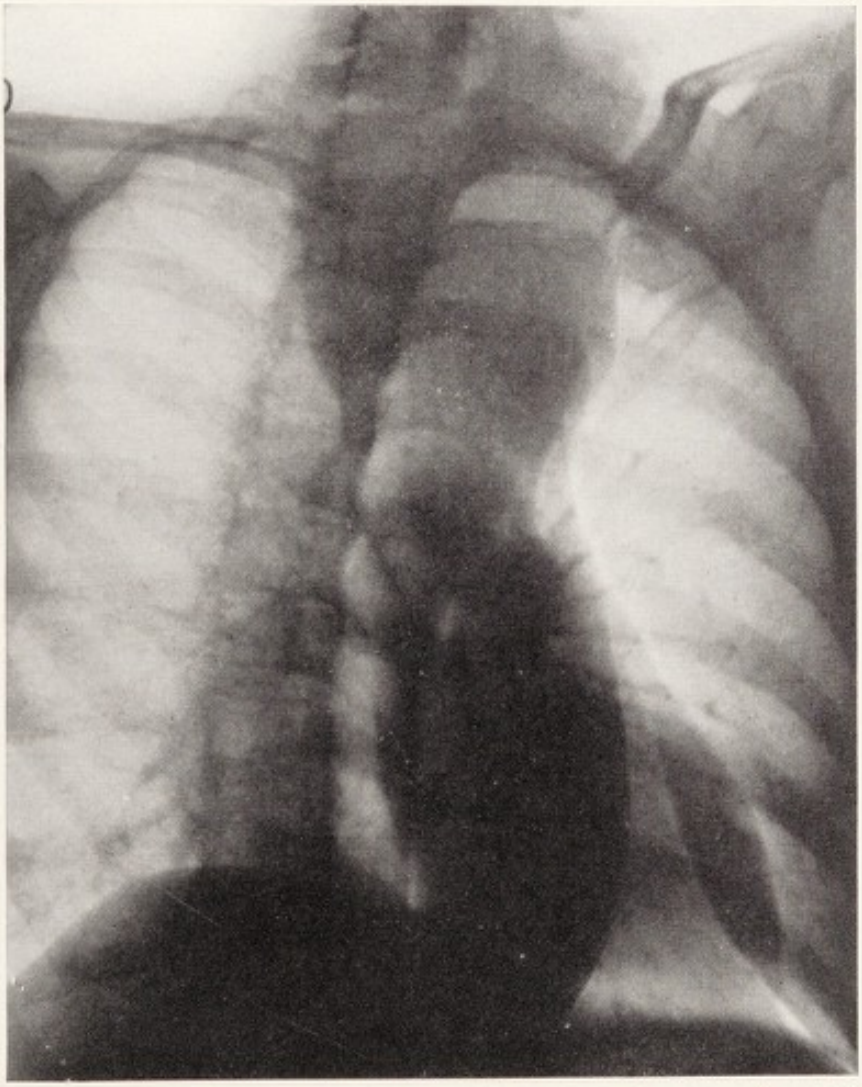

Fig. 74.—A lateral view of case shown in Fig. 73 showing the extension of the struma and displacement of the trachea.

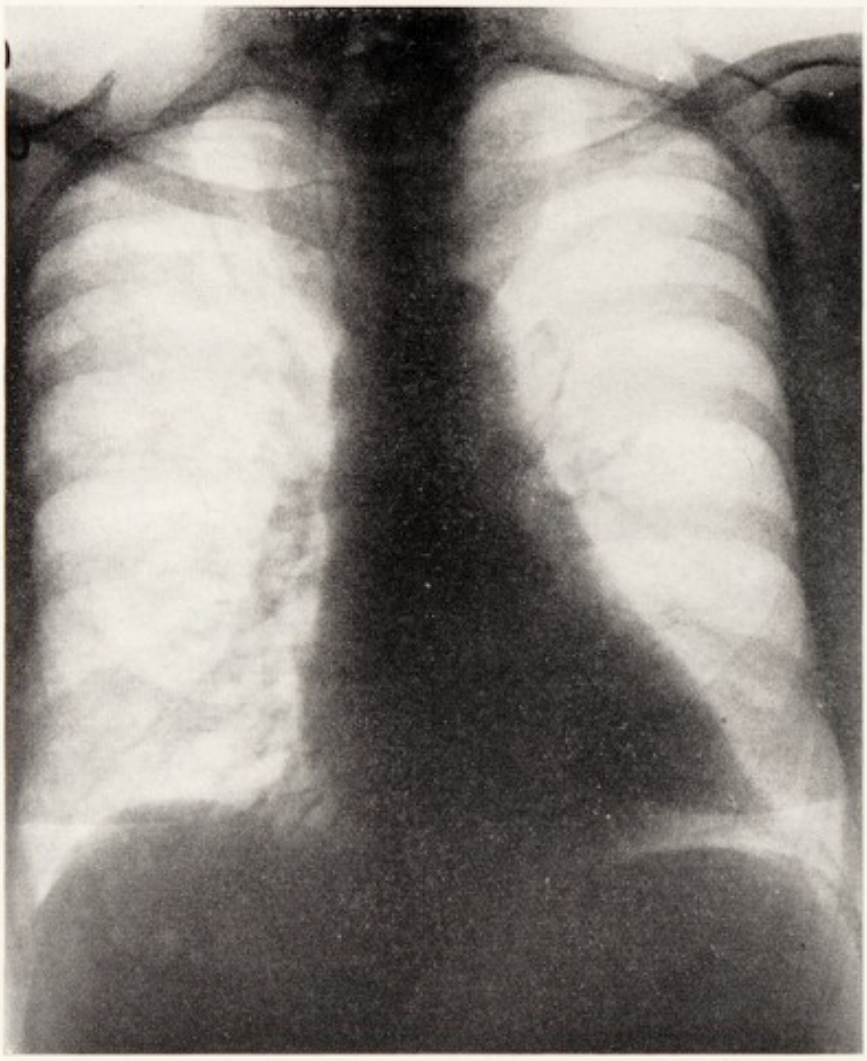

Fig. 75.—Adenoma of the thyroid extending into the chest substernally to a point below the aortic arch. The aorta can easily be distinguished from the shadow of the struma.

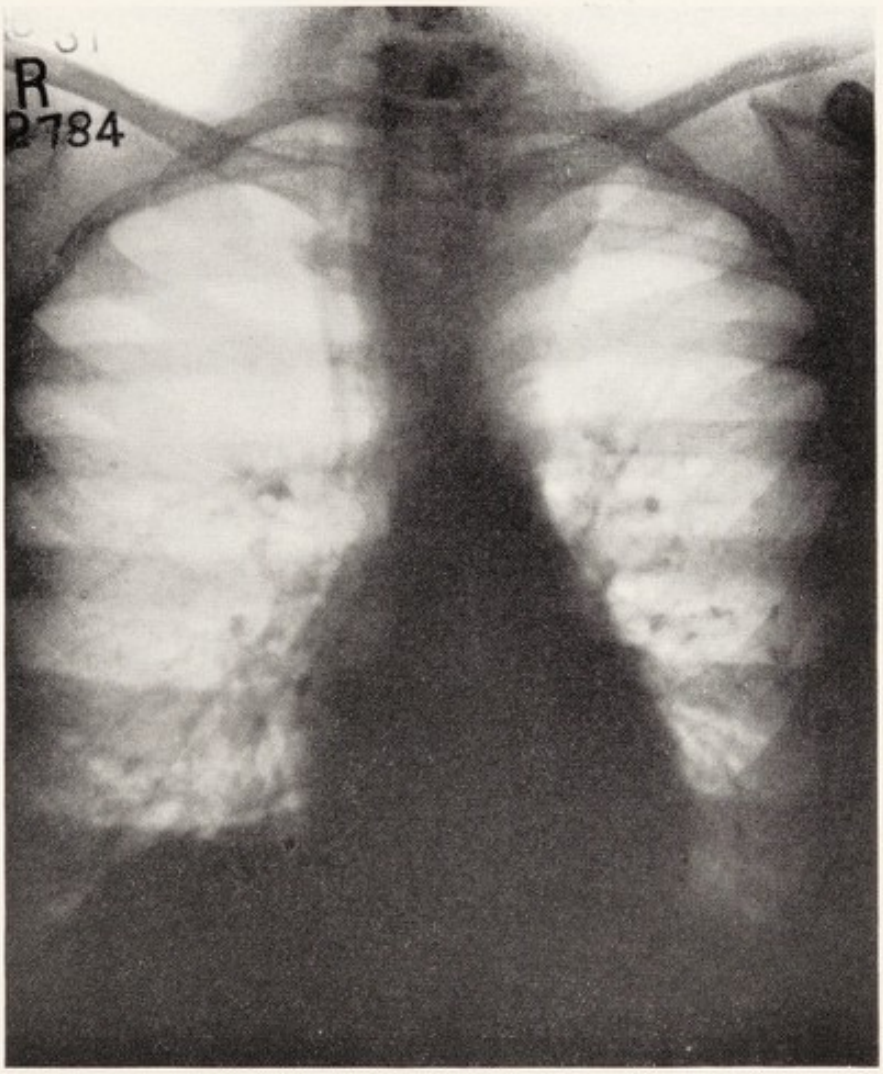

Fig. 76.—Adenoma of the thyroid extending substernally into the chest from the left lobe with compression and displacement of the trachea to the right.

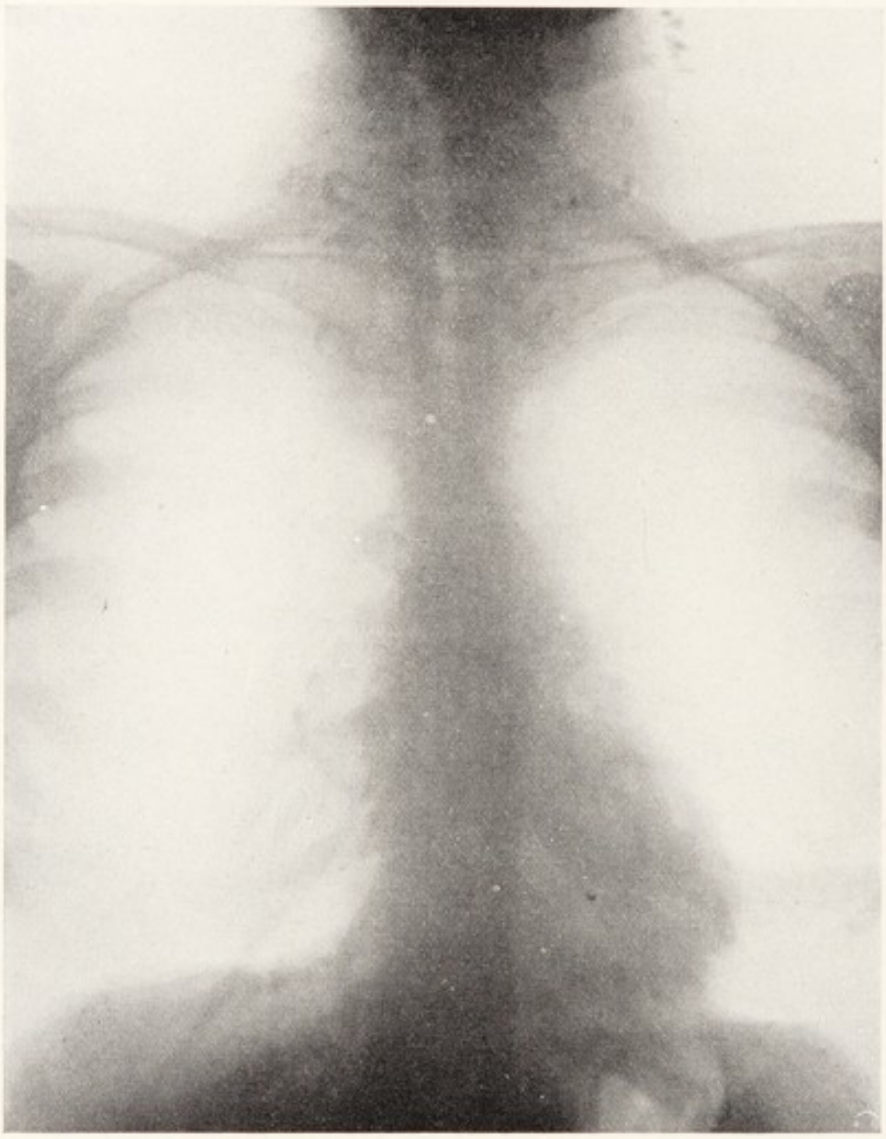

Fig. 77.—Large adenoma of the thyroid with extension only a short distance substernally. The struma is characterized by extensive calcific deposits which may represent small hemorrhages into the gland followed by calcification.

The shadows made by supraclavicular and infraclavicular calcifications in the mass may be of distinct help in determining that the larger shadow is cast by a thyroid tumor as such calcification may represent old hemorrhagic areas (Fig. 77), and the circumscribed calcified areas represent a cystic adenoma with calcium in the cyst walls (Figs. 78–80).

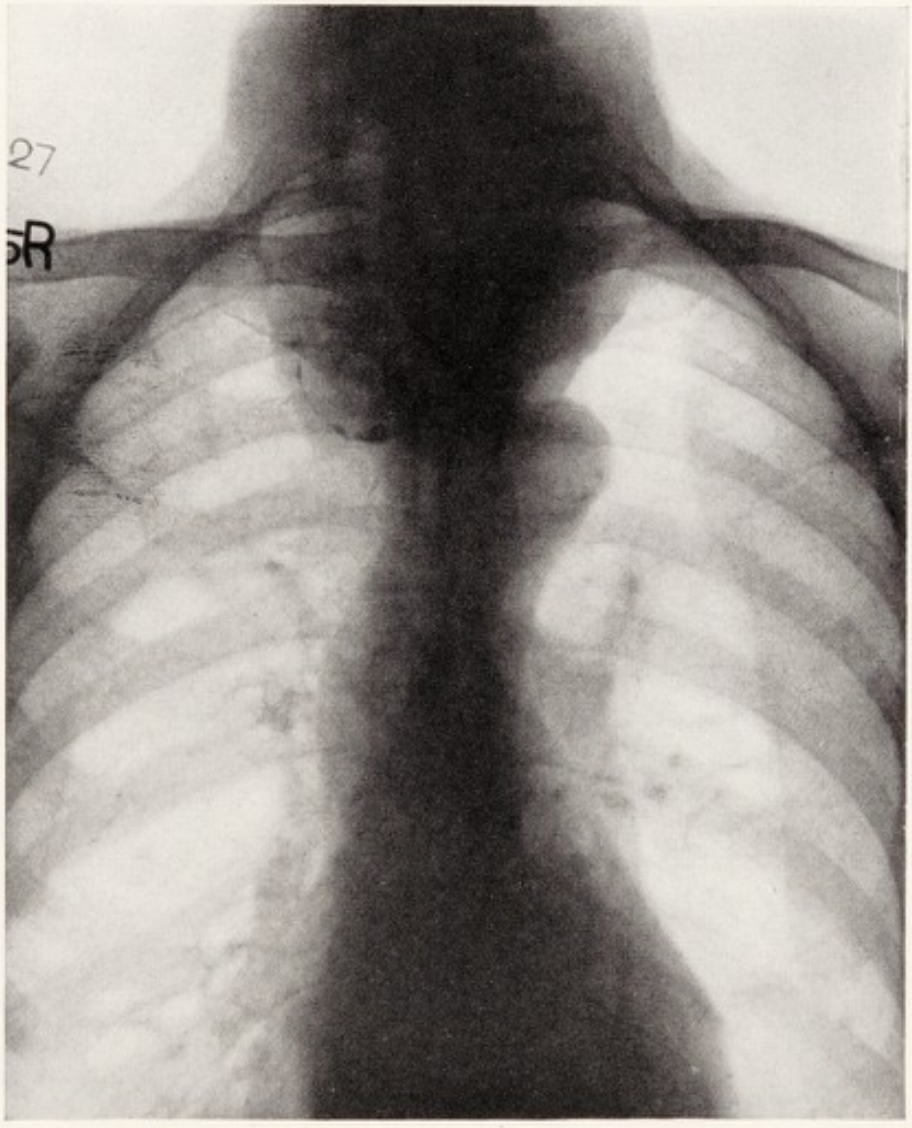

Fig. 78.—Cystic adenoma of the thyroid extending substernally into the chest. The shadow is continuous with the thyroid and the widening of the notch between the struma and the aortic arch is seen on deglutition. There are many calcified areas showing the cystic form which is characteristic of cystic adenoma.

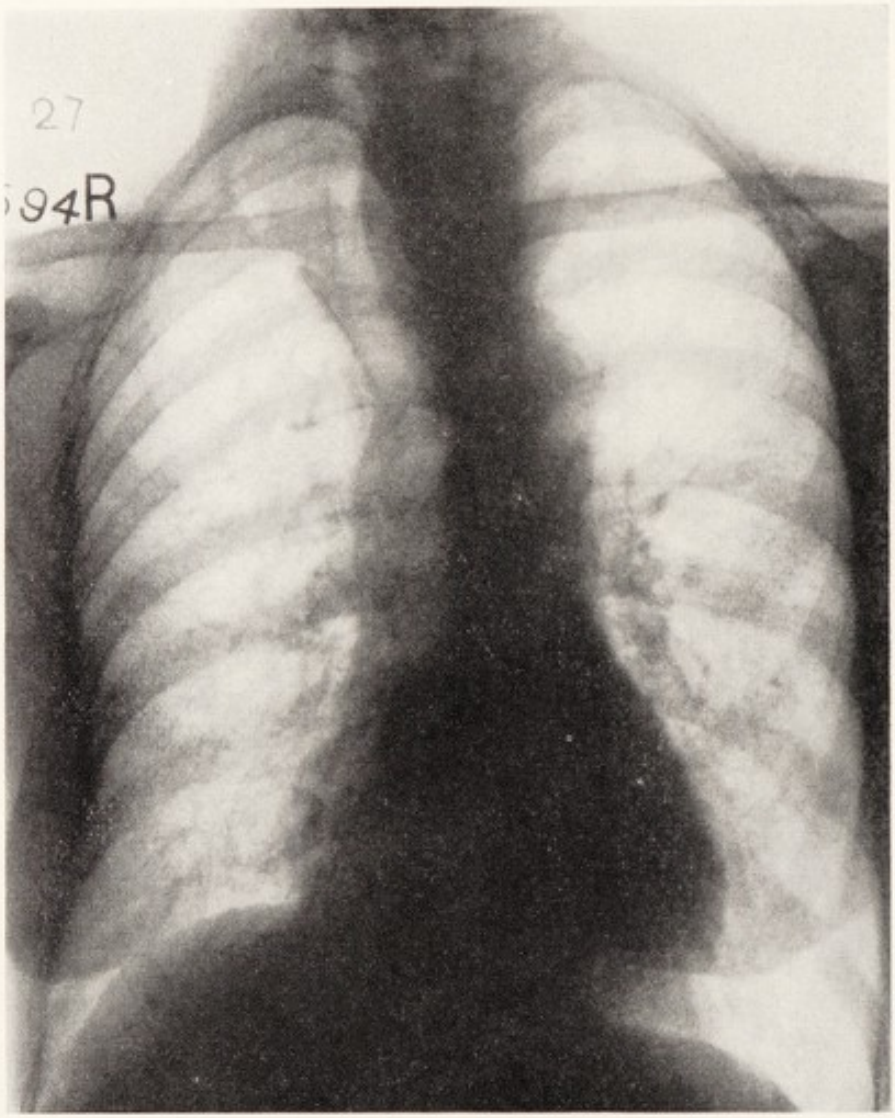

Fig. 79.—Adenoma of the thyroid with hyperthyroidism, the mass extending from the left lobe with displacement of the trachea to the right.

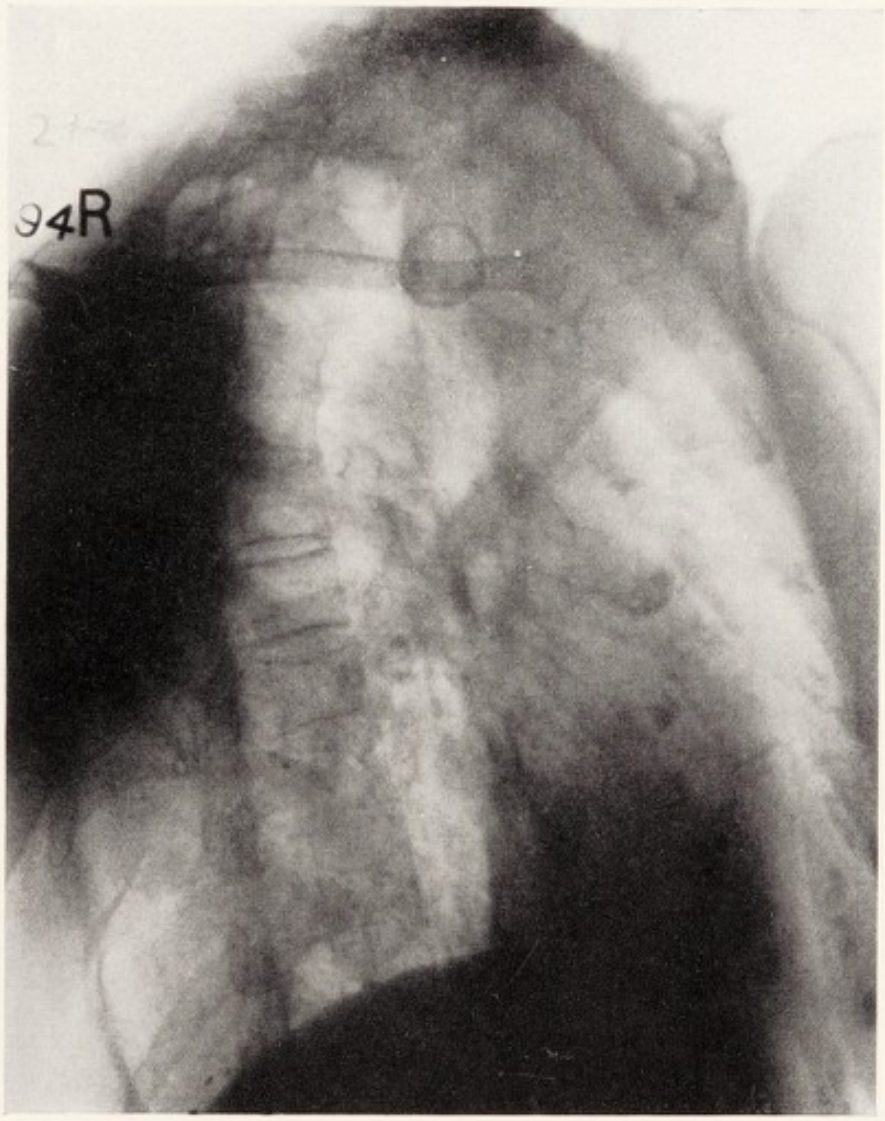

Fig. 80.—An oblique view of case shown in Fig. 79 more clearly outlining the cystic area in the thyroid.

Thoracic aneurysm is perhaps one of the most important pathologic conditions to be found in the upper thorax. It gives a picture which it may be difficult to differentiate from that of an intrathoracic goiter (Figs. 81–85). An aneurysm appears on the radiograph as a clean-cut shadow, regular in outline, and may appear as a distinct bulging or an expansion of the aorta or great vessels of the thorax.

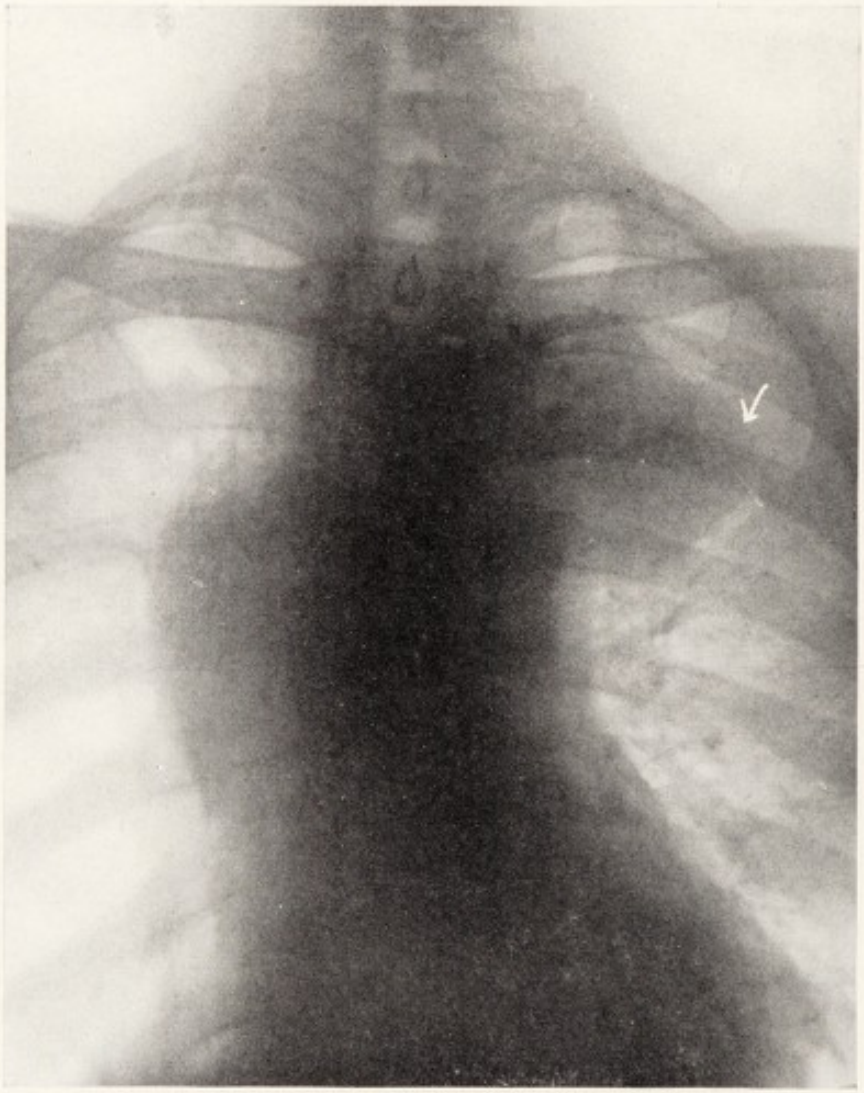

Fig. 81.—Large aortic aneurysm. The mass is continuous with the aorta and is not continuous with the thyroid shadow above the clavicle.

An aneurysm may also produce displacement and compression of the trachea and mediastinum and may even cause erosion of the vertebrae.

Although the diagnosis of an intrathoracic aneurysm may be difficult, films made with the patient in the oblique position, so that the aorta and great vessels are silhouetted in the posterior auricular

space, will usually show the shadow of the lesion to be a continuation of that cast by the aortic or great vessels. The fluoroscopic examination may aid in the diagnosis. We should not rely upon the presence of a definite expansile pulsation, however, as many aneurysms have markedly thickened walls in which there is no typical expansile

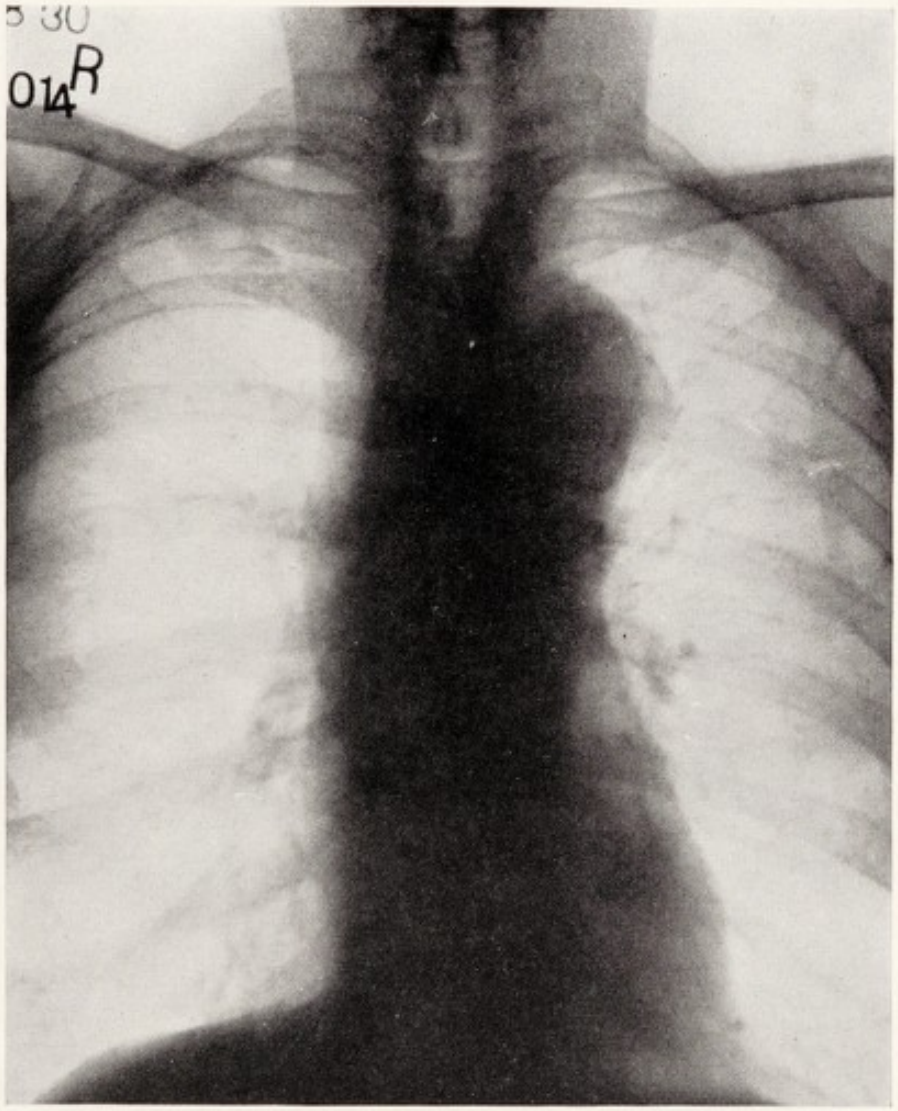

Fig. 82.—Aortic aneurysm showing a distinct expansile pulsation. The mass is continuous with the cardiac shadow.

movement, but rather a movement similar to that produced in other masses by transmitted pulsation.

In the presence of an intrathoracic goiter, the identification of a coexistent aneurysm may be especially difficult. In the fluoroscopic examination, however, if the patient is asked to take a deep breath we may see an increase in the aneurysm between the shadow of the substernal goiter and the aortic shadow due to the rising of the intra-

thoracic goiter in such a muscular effort. This is a very important diagnostic finding.

If careful radiographic and fluoroscopic examinations and a Wassermann test of the blood are made, little difficulty should be encountered in determining the presence of a thoracic aneurysm.

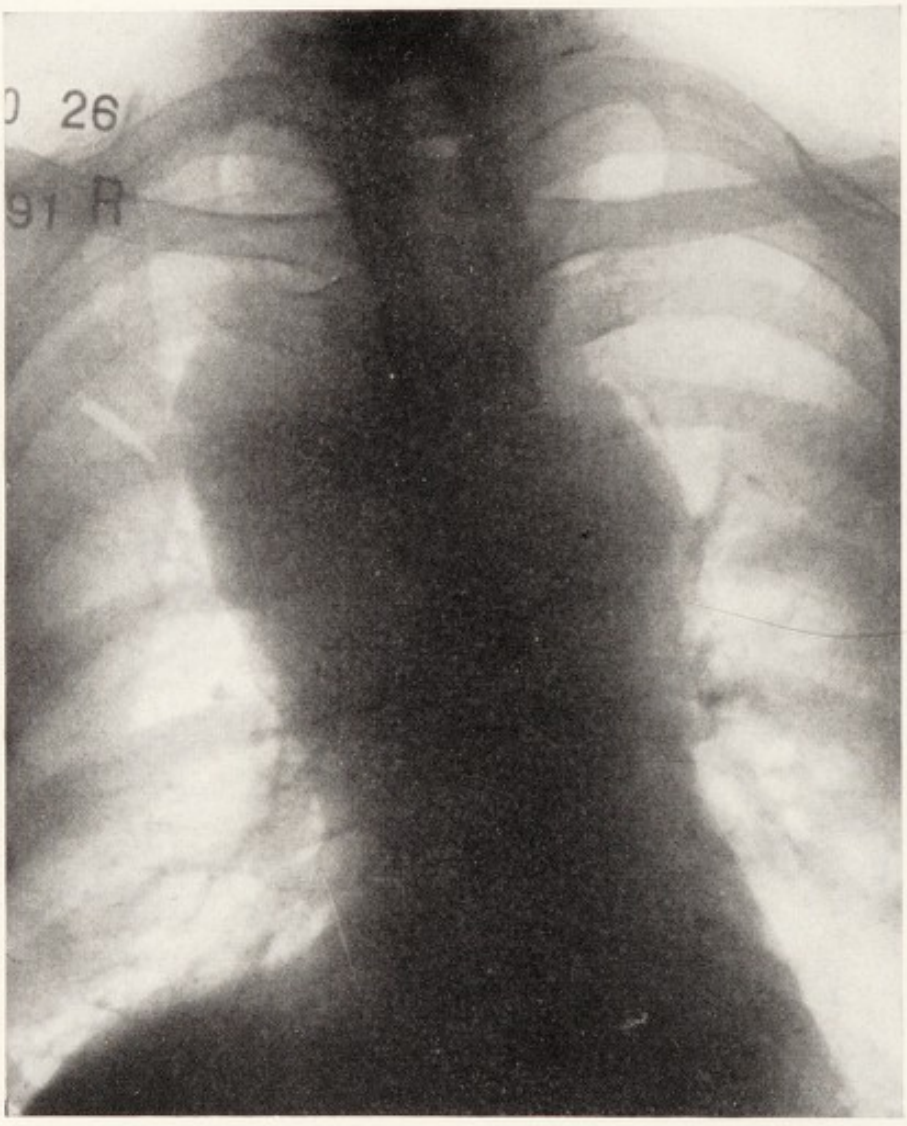

Fig. 83.—Large aortic aneurysm not connected with the thyroid but continuous with the aorta and with a distinct expansile pulsation.

A **dilated** or **elongated aorta** frequently makes a confusing shadow when we are trying to determine the presence or absence of a substernal goiter. The transverse position of the heart which is frequently enlarged and shows a continuous shadow with that of the upper mediastinum, together with an elongated, dilated aorta is often sufficient to establish the diagnosis. Also, the left oblique

position of the patient, by which the aorta and vessels in the retrocardiac space are shown, will usually definitely determine the termination of the aorta.

The **thymus gland** usually lies lower in the chest than does an intrathoracic goiter and it overshadows the heart. The shadow of a

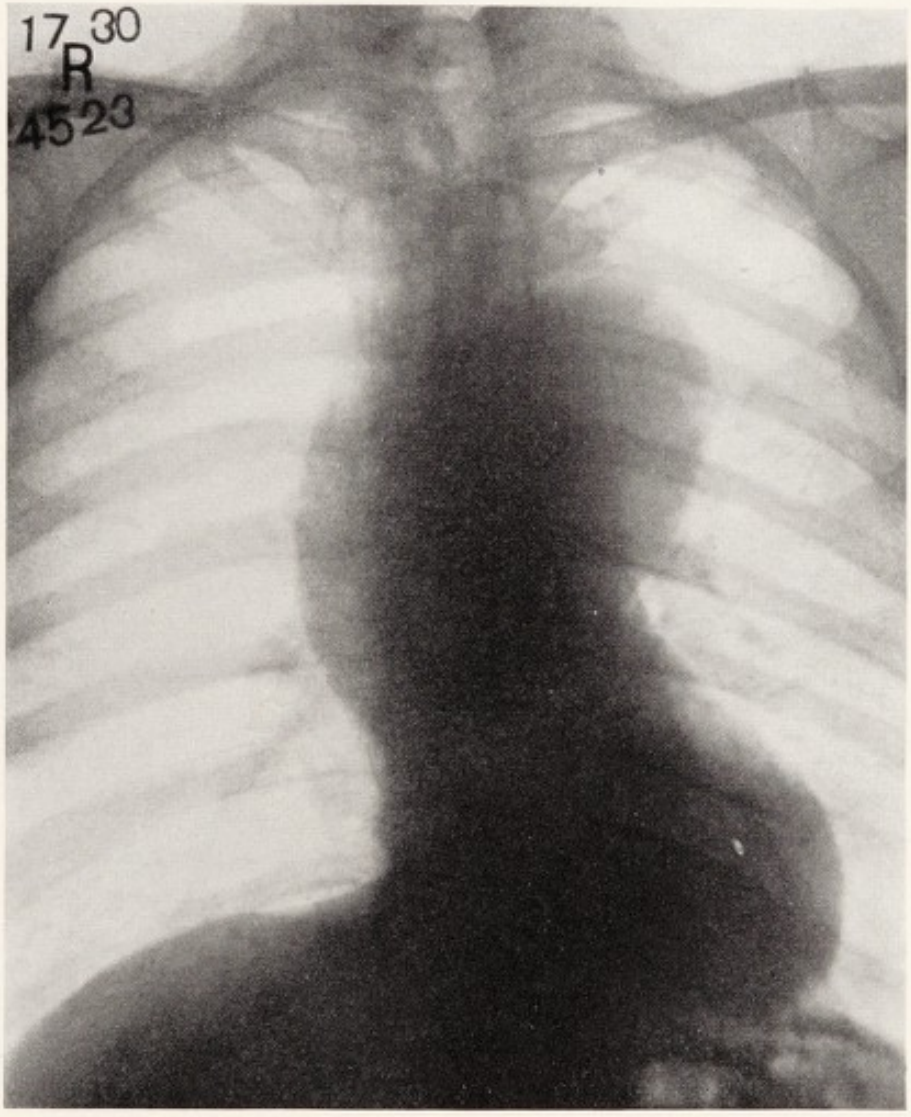

Fig. 84.—Aortic aneurysm continuous with the heart shadow extending well out on both the right and left sides. A characteristic expansile pulsation could be noted in this case.

thymus is triangular in shape and an oblique fluoroscopic observation shows it to lie anteriorly in the chest. The majority of thymus tumors occur in children but occasionally a persistent thymus is encountered, which offers a grave complication in goiter cases. For this condition deep radiotherapy is indicated, by means of which very striking results in the reduction of the gland may be secured.

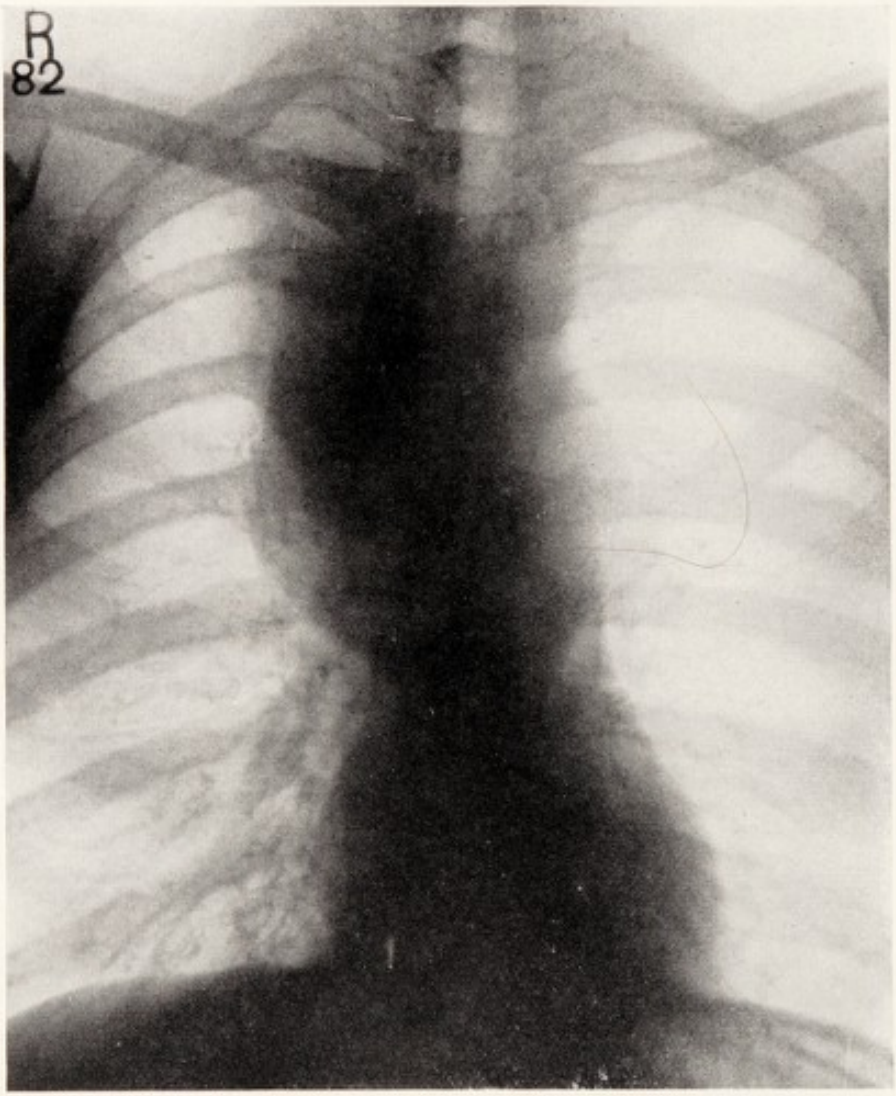

Fig. 85.—Aortic aneurysm of moderate size the shadow of which is continuous with that of the arch of the aorta on the left side. There is also a substernal goiter extending from the right lobe, the shadow of which is distinctly separate from the aneurysmal shadow. These two masses separated distinctly during deglutition.

A true thymoma may be present which offers a similar confusion in the diagnosis of substernal goiter (Figs. 86, 87).

A **large Pott's abscess of the dorsal spine** may produce a shadow in the mediastinum somewhat simulating that cast by a substernal

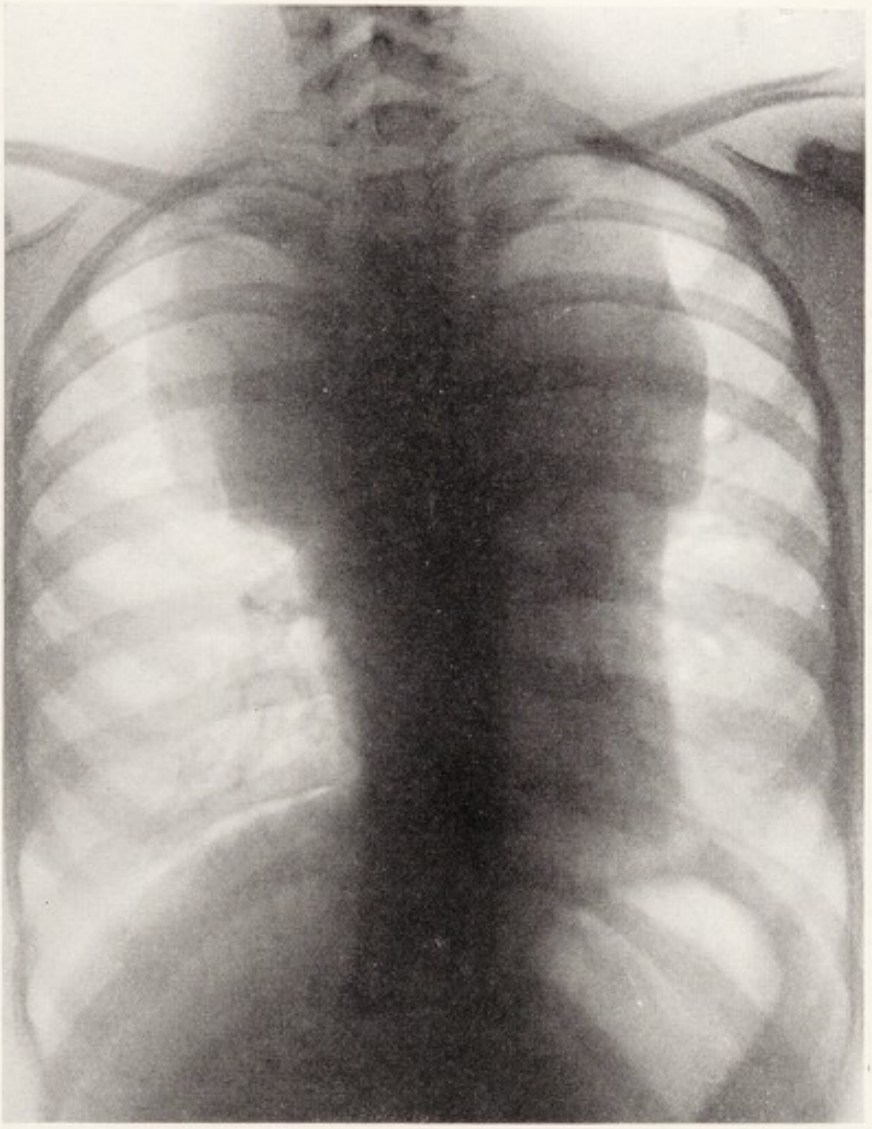

Fig. 86.—Thymoma. This large tumor mass in the mediastinum was not connected with the thyroid gland and simulates Hodgkin's disease or lymphosarcoma.

goiter. However, a carefully taken radiograph of the dorsal spine which will show the destruction of the vertebrae with the accompanying kyphosis will usually establish the diagnosis beyond any doubt.

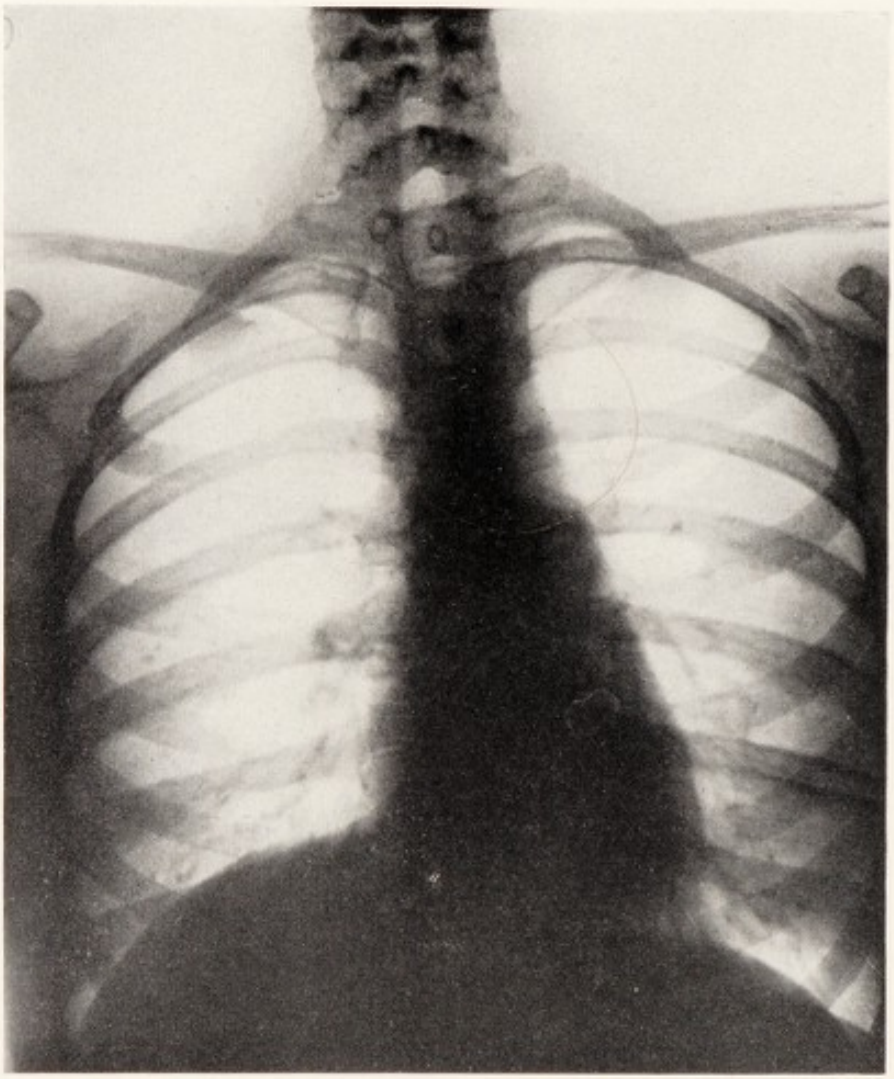

Fig 87.—Radiograph in the same case as in Fig. 86 taken four months after the application of radiation therapy. The tumor completely disappeared following a therapeutic test. The rapidity of its disappearance was the basis for the diagnosis of a thymic tumor.

The large heterogenous group of **lymphomas** found in the chest, which include lymphosarcoma and Hodgkin's disease, quite frequently confuse the differential diagnosis (Figs. 88, 89). Some of these, particularly those present in Hodgkin's disease, frequently show multiple enlarged indistinct nodules which readily establish their

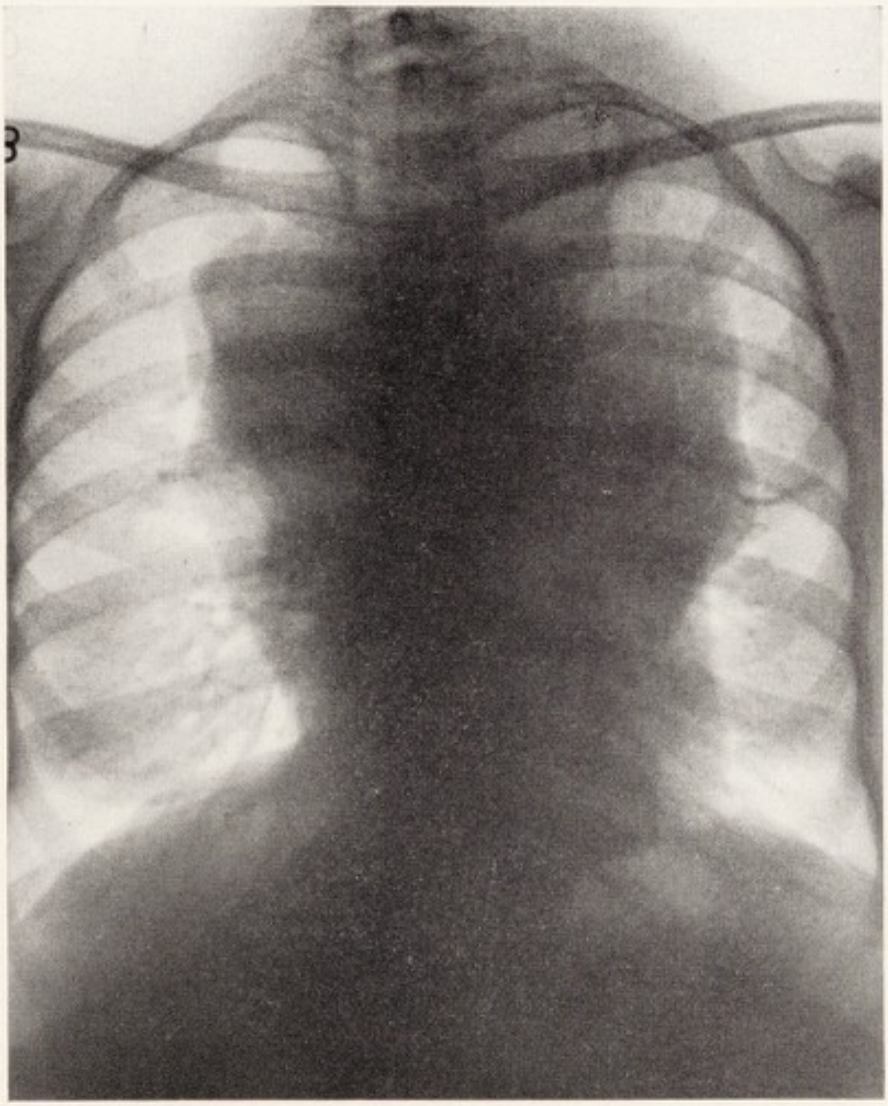

Fig. 88.—Hodgkin's disease. The fact that this large mediastinal mass was not connected with the thyroid and rather nodular in outline ruled out the diagnosis of a substernal goiter.

identity. True lymphosarcomata, however, may show a somewhat regular border and simulate a substernal goiter. In the presence of these lesions, the elevation of the thyroid mass during deglutition in the course of the fluoroscopic examination is of extreme importance in establishing the differential diagnosis. The presence of enlarged glands in other portions of the body or the pathologic findings after

biopsy of a small gland may be an important aid in identifying these lesions.

Occasionally a **dermoid cyst** of the mediastinum may be encountered (Fig. 90). In such a case, unless tell-tale remnants of the fetus are present, identification of such a tumor is quite impossible,

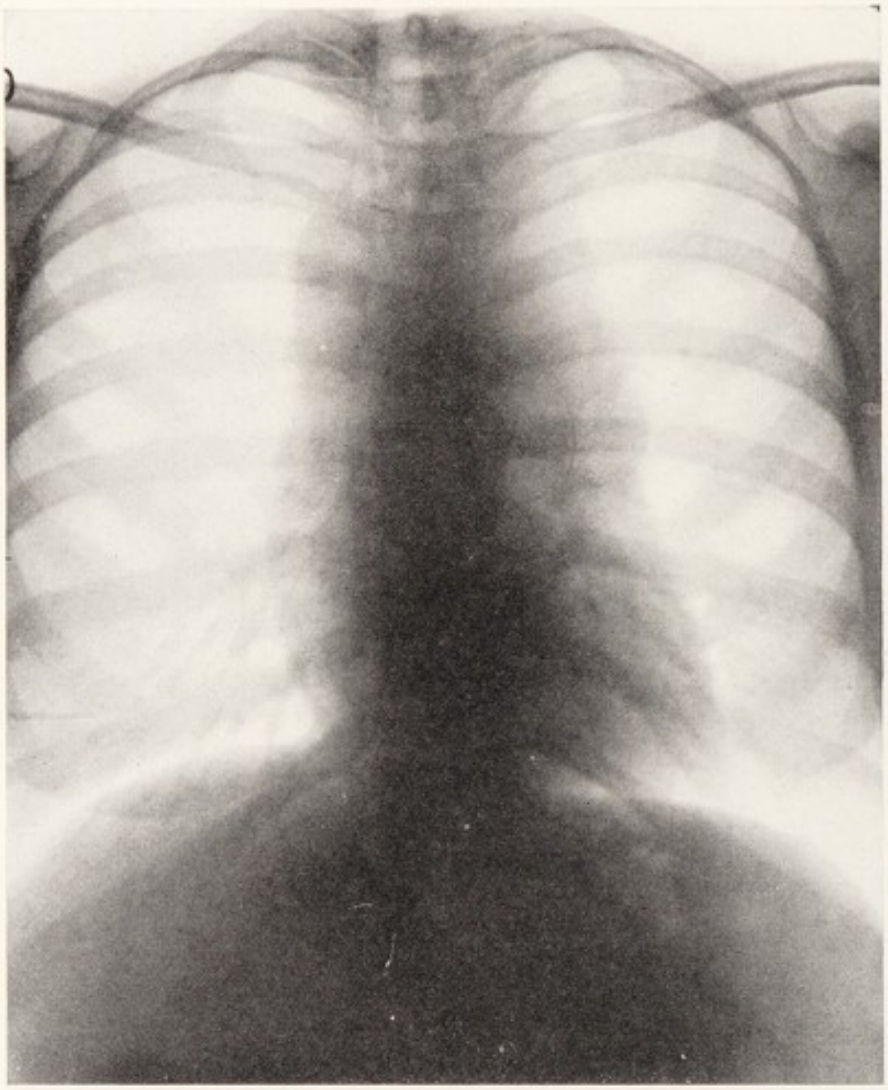

Fig. 89.—Roentgenogram of the chest shown in Fig. 88 made twelve weeks after *x*-ray therapy was started shows a marked reduction in the size of the mediastinal mass. This therapeutic test justified the diagnosis of Hodgkin's disease which was confirmed by biopsy.

but still the differentiation from a thyroid tumor can be readily established.

The possible presence of a primary **malignant tumor of the lung,** particularly sarcoma, may sometimes have to be considered. Such tumors may rise in the mediastinum or from the parenchyma of the lung. In their development the mediastinal shadow is frequently

displaced to the opposite side and an effusion from the lung may be present. A primary carcinoma of the lung shows a shadow with an irregular indistinct outline and should never be confused with a

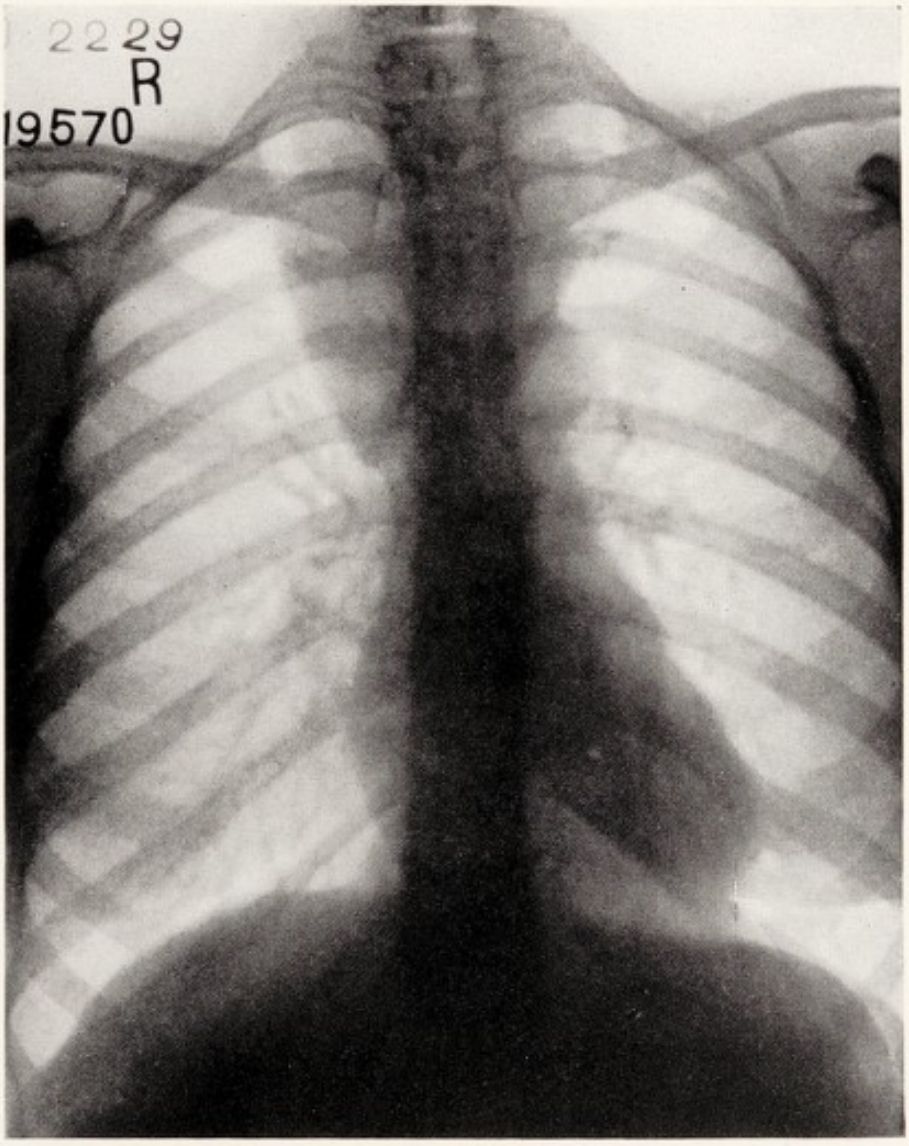

Fig. 90.—Dermoid cyst. This shadow simulates perfectly that of a substernal goiter and the diagnosis was not made until after operation.

substernal goiter (Fig. 91). Occasionally a rarely encountered tumor of the lung such as a neurofibroma may confuse the diagnosis (Fig. 92).

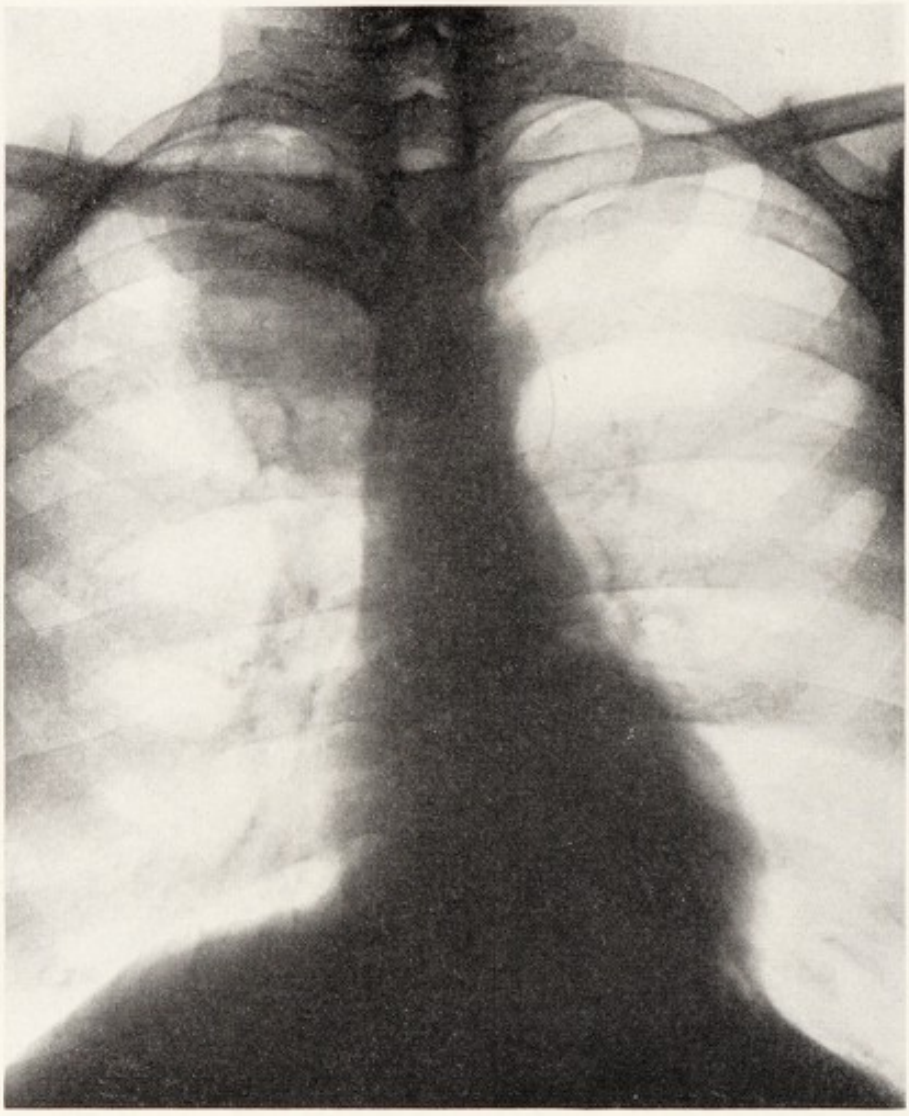

Fig. 91.—Carcinoma of the upper right lung. This mass is separate and distinct from the aorta and not continuous with the thyroid gland. It is irregular in outline. No response to therapeutic radiation.

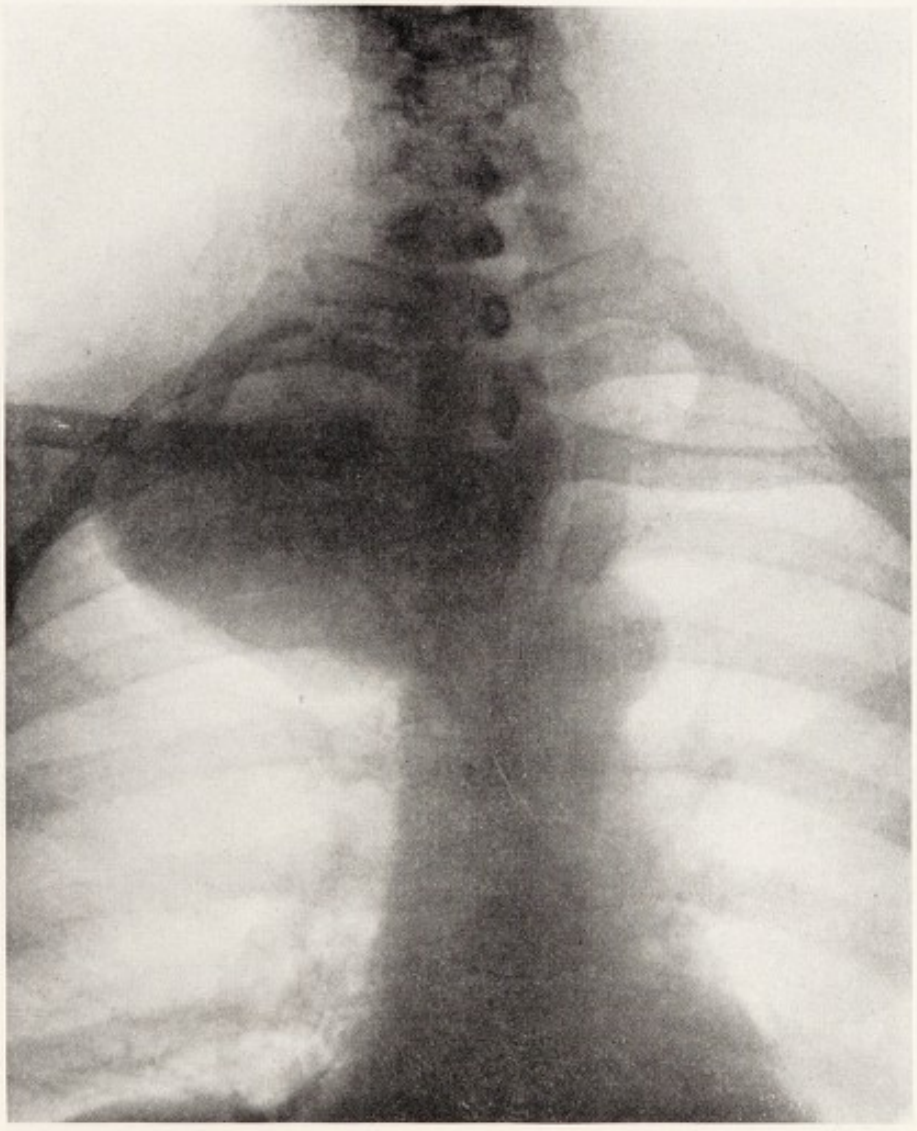

Fig. 92.—Neurofibroma of the upper right mediastinum with compression and marked displacement of the trachea to the left. The mass is distinctly separated from the thyroid. Biopsy report showed the growth to be a neurofibroma.

MALIGNANT DISEASE OF THE THYROID

Malignant disease of the thyroid itself presents an important diagnostic problem to the roentgenologist. In many instances a diagnosis can be definitely made (Figs. 93, 94). In cases of thyroid enlargement in which the *x*-ray film shows an irregular nodular outline, the presence of malignant disease should be suspected, but to

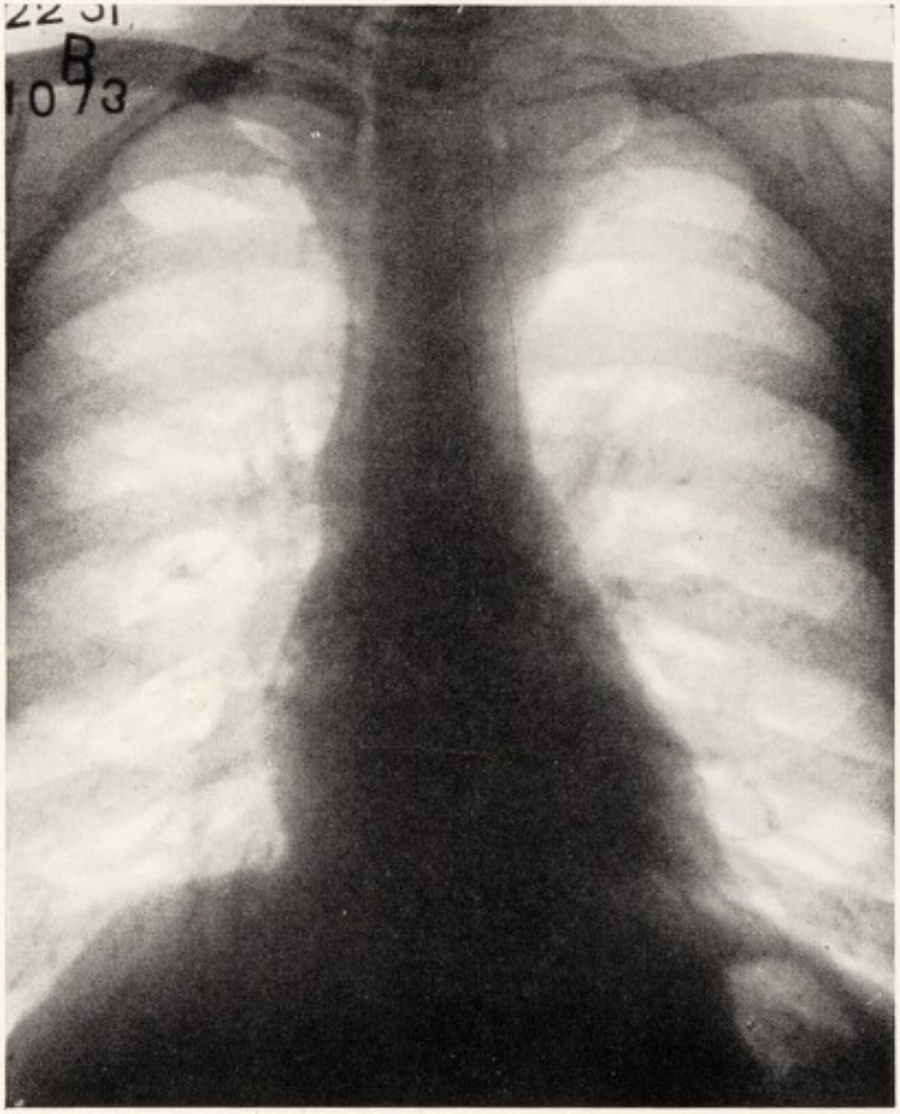

Fig. 93.—Spindle-cell sarcoma of the thyroid. Small regular thyroid enlargement with a moderate extension substernally on the left side with compression and displacement of the trachea to the right. Pathologic report: Spindle-cell sarcoma.

the information secured from radiographs of the thyroid itself should be added the findings in radiographs of the areas of the body where metastases may occur (Figs. 95–97). If metastatic nodules are found, the diagnosis of malignant disease will usually be confirmed at operation.

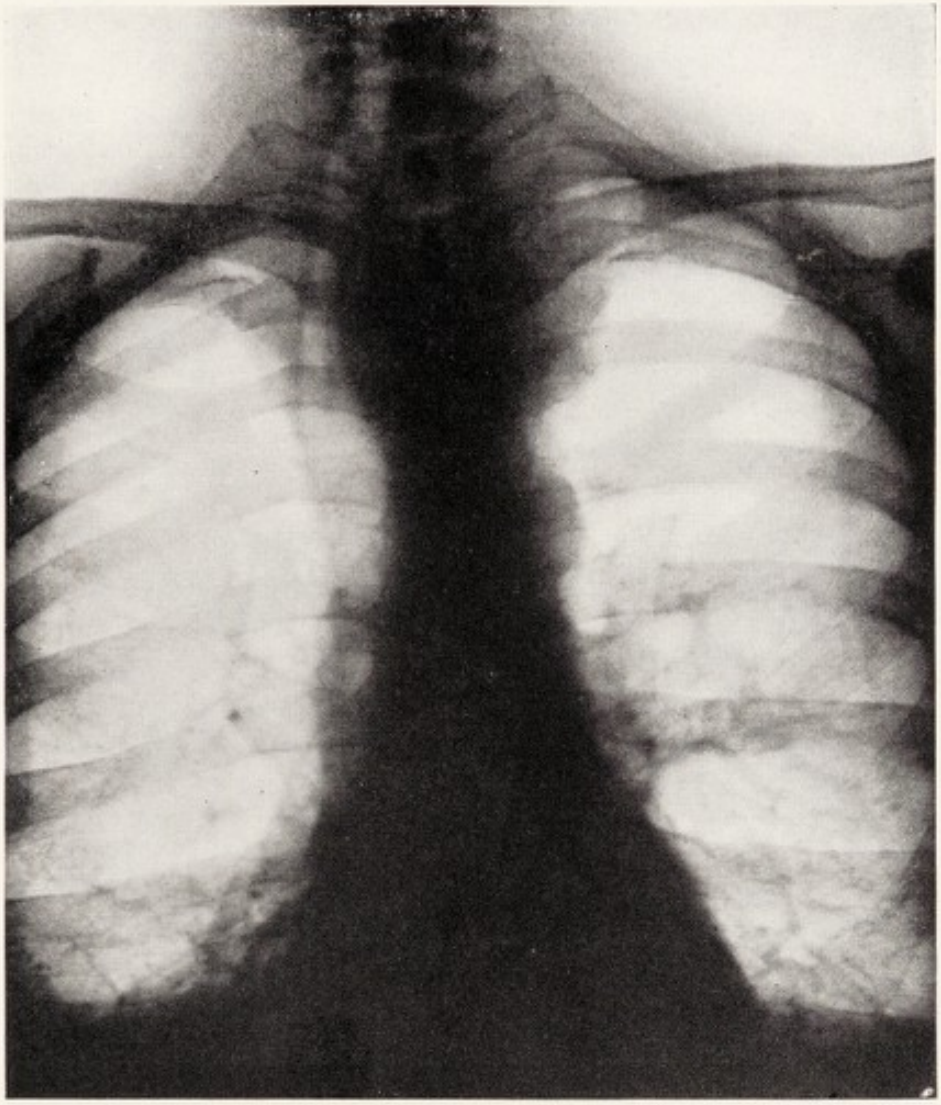

Fig. 94.—Lymphosarcoma of the thyroid. The irregular mass extends substernally from the left lobe of the thyroid with compression and displacement of the trachea to the right. Pathologic report: Spindle-cell sarcoma.

A survey of 268 cases of malignant disease of the thyroid, showed that in 55 cases definite metastases were found, in 34 of which roentgenologic demonstration was possible. The locations of the metastases in these 34 cases were as follows:

	Cases.
Chest	22
Pelvis	4
Sternum	2
Clavicle	2
Skull	1
Spine	1
Ribs	1
Knee	1

This survey indicates the importance of a roentgenologic study of the chest in cases of suspected malignant disease of the thyroid as the chest is the most probable site of metastases. We have found these metastatic lesions to be of two types, rather firm miliary well-disseminated lesions or large circumscribed, rather well-rounded lesions

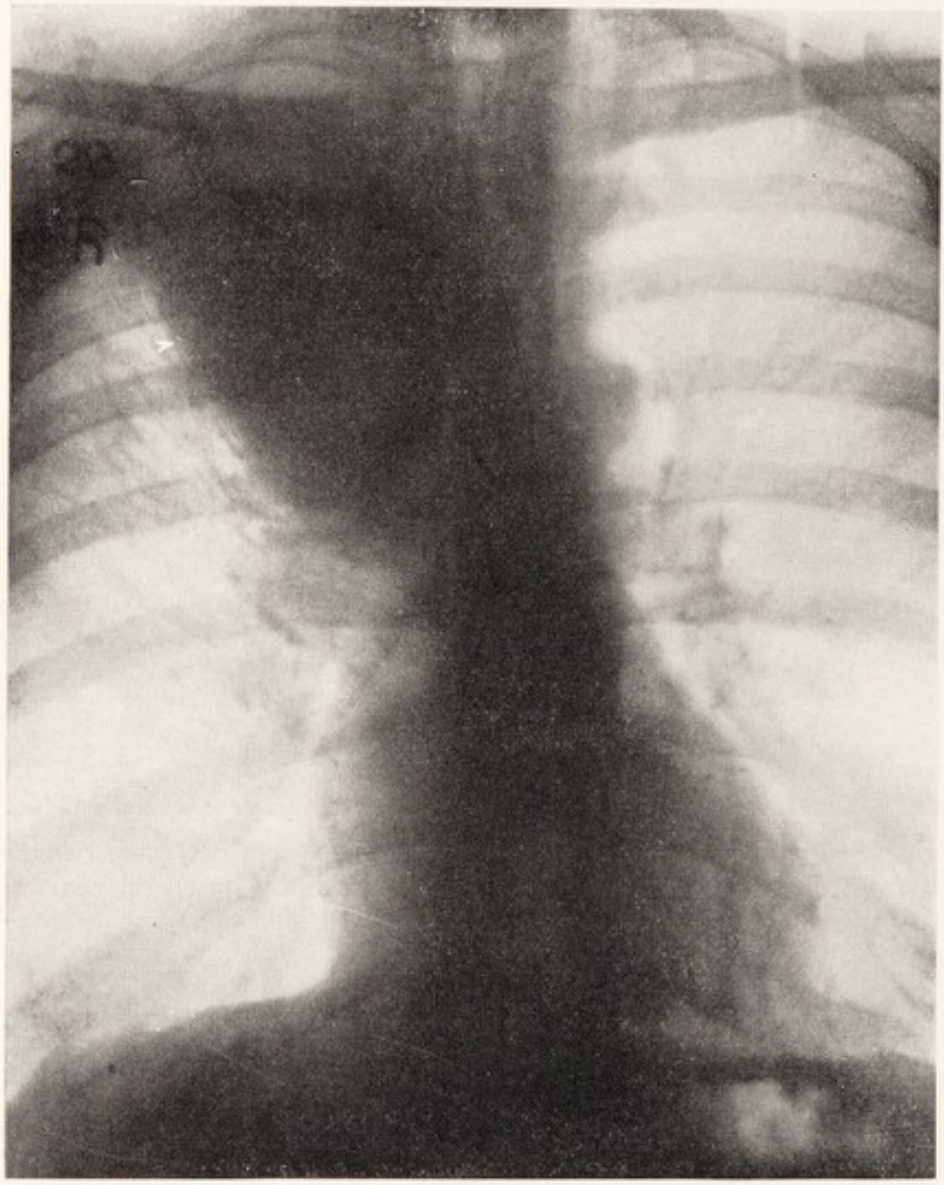

Fig. 95.—Large carcinoma of the upper right lobe of the lung apparently not connected with the thyroid or the aorta. No response to therapeutic radiation.

similar to metastases from a hypernephroma of the kidney. When such lesions are found in the chest, the thyroid or kidney should immediately be suspected as the primary focus.

In our series the next most frequent location for metastases from malignant disease of the thyroid was the pelvis. We therefore feel

that at least the chest and pelvis should be examined by *x*-ray in every case in which the presence of a malignant disease of the thyroid

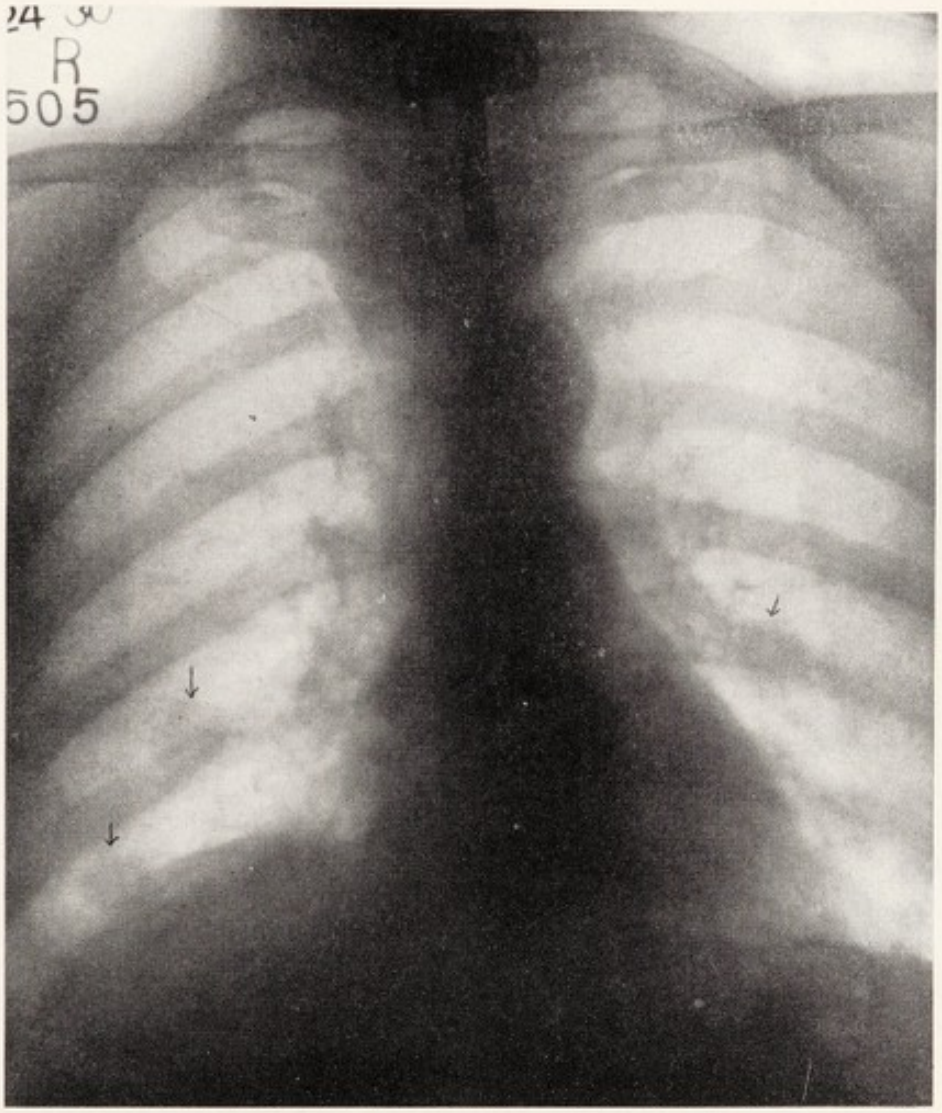

Fig. 96.—Metastases in both lungs from carcinoma of the thyroid. Characteristic nodular type. The thyroid gland had been removed and a tracheotomy tube was in place.

gland is suspected whether the enlargement of the gland is substernal or supraclavicular.

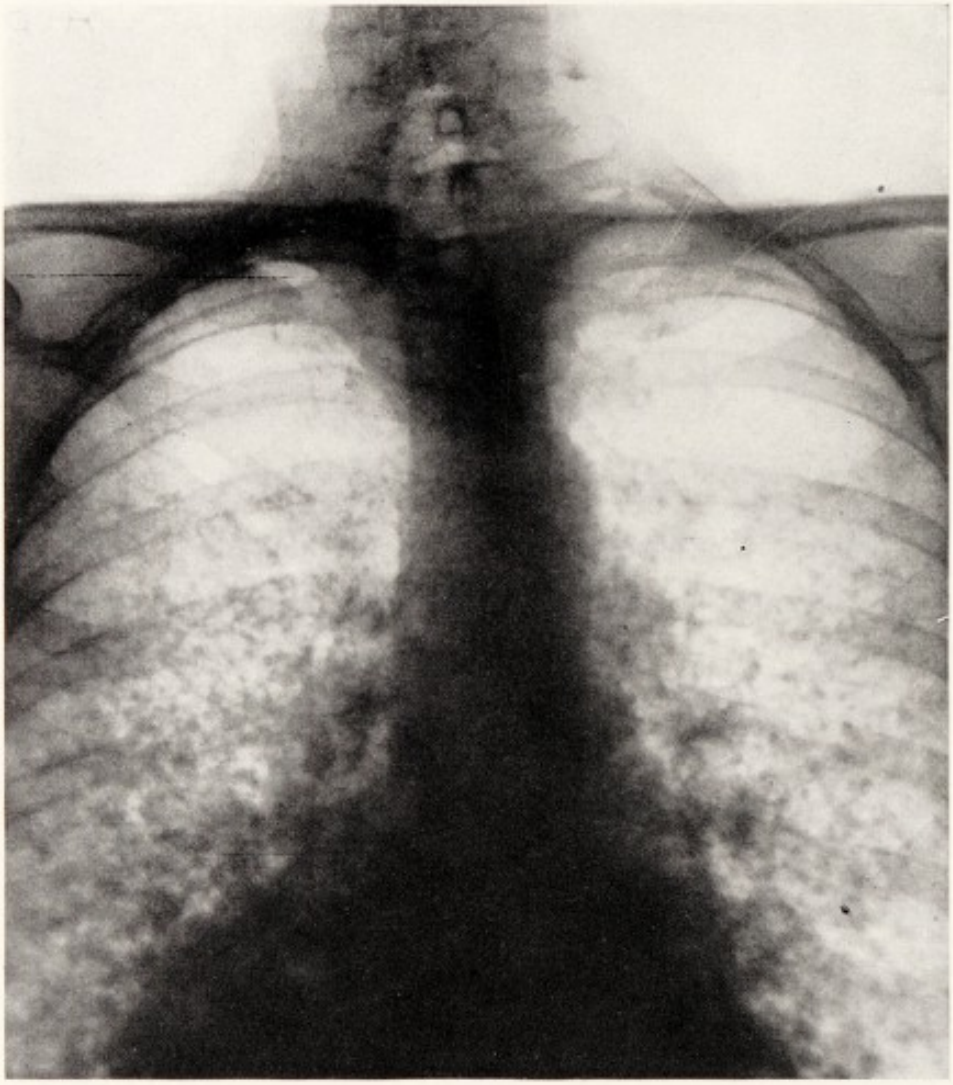

Fig. 97.—Metastatic carcinoma of the lungs from carcinoma of the thyroid; three years after operation. Miliary type.

CHAPTER XXI

MALIGNANT TUMORS OF THE THYROID GLAND

GEORGE CRILE AND U. V. PORTMANN

THE classification of the different types of malignant tumors of the thyroid gland is still in confusion although such simple classifications as that of Graham (p. 324) are coming into general use. The difficulty has been that pathologists have grouped their cases on the basis of morphology alone. The morphological picture in itself, however, is often an insufficient criterion whereby to differentiate types of malignant growths of this gland nor does it accurately indicate the clinical course of the disease.

Graham[1] has pointed out the following reasons for this confusion in the classification of these growths:

1. In no other organ do malignant tumors of epithelial origin generate so directly in a preexisting benign tumor (adenoma).

2. Malignant epithelial tumors of no other organ (except hypernephromata and chorio-epitheliomata) exhibit such a high incidence of metastases through the blood stream.

3. In no other organ does the histologic appearance of the cells and tissues of a malignant growth so closely resemble the benign parent tissue in such a significant percentage of cases.

In the thyroid, as in any other organ, a malignant condition may develop in any of the cellular structures of which it is composed. Parenchyma or stroma cells may become neoplastic, and the resultant tumor will have the same type of cells as does the structure from which it arises. The neoplasm may involve the entire gland or one or more localized areas. Localized, discrete and encapsulated hyperplastic areas are known as adenomata and are classified according to the predominant type of acini which are found. The development of the thyroid and the structure of its tissues and of the benign and malignant neoplasms which are found in it leads to the conclusion that a very high percentage (approaching 90 per cent) of malignant tumors of the thyroid originate in preexisting adenomata.

Malignant Adenoma.—In about 90 per cent of the cases, carcinomata of the thyroid can be proved to have originated in a preexisting adenoma (Fig. 98). According to Graham,[2] the term malignant adenoma is used to designate those carcinomata which originate in

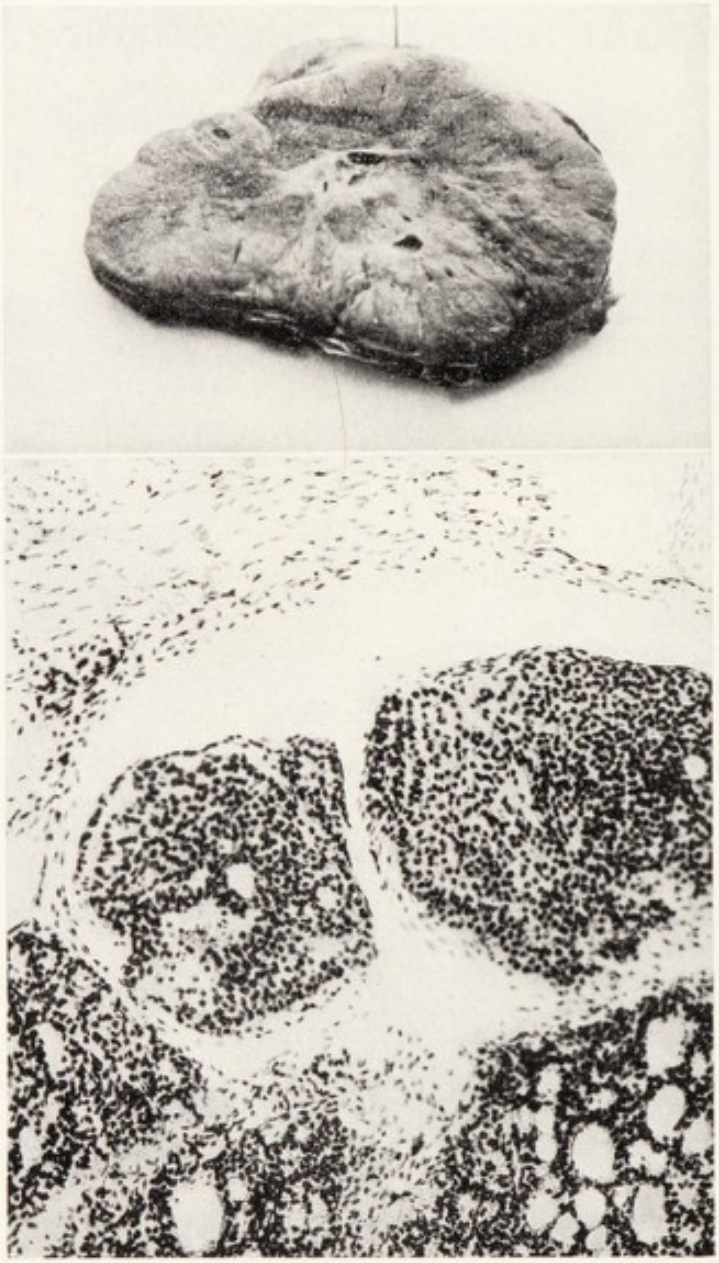

Fig. 98.—Gross and histologic picture presented by malignant adenoma of the thyroid gland.

preexisting adenomata, exclusive of the papillary cystadenomata. This type of malignant tumor of the thyroid gland presents many combinations of morphological transitions and degeneration of fetal, intermediate or mixed colloid adenomata, any one, two or all of which may be found in a single tumor of this type either as a localized area

or throughout the gland. Rarely the tumor is composed of one type of neoplastic cell. There are usually areas in which the morphological characteristics of fetal adenoma are mixed with others which show the characteristic structure of adenocarcinoma, medullary, scirrhous or papilliferous carcinoma, or of a carcinoma which resembles sarcoma, or there may be any combination of these forms. This explains why it is difficult, if not impossible, to make a diagnosis or to classify the malignant tumors of the thyroid on the basis of the morphological appearance alone. It is necessary, therefore, to consider not only the cellular changes and their structure but also the type of the preexisting adenoma, the duration of the tumor and its rate of growth, the character and reaction of the stroma and capsule, and especially the evidences of involvement of the blood vessels or capsule of the adenoma. Occasionally it is impossible to prove conclusively that the malignant change has originated in a preexisting adenoma but this does not disprove the fact that it may have done so. The malignant tumors which originate in benign adenomata are primarily encapsulated but may break through by direct extension, and in almost every instance there is invasion of the blood vessels which will be found to be filled with neoplastic cells. Malignant adenomata extend by way of the blood stream because of the local invasion of the blood vessels, although the neoplasm may not have broken through its capsule. If the tumor remains within its own capsule it does not disseminate through the lymphatics. The fact that there is a meager lymphatic communication between the adenoma and the neighboring tissue is a favorable factor in the prognosis.

Scirrhous Carcinoma.—Scirrhous carcinoma of the thyroid gland is similar to scirrhous carcinoma of any other organ as it has the same gross and histologic characteristics which are easily identified (Fig. 99). In this type of neoplasm the fibrous tissue predominates and the epithelial cells occur in masses of strands. There is seldom, if ever, any invasion of the blood vessels and since it is not encapsulated the growth envelops and invades the neighboring structures, which are destroyed by direct extension, and the tumor is therefore adherent to the surrounding tissues. Clinically these tumors are extremely hard and, because of the invasive nature of their growth, they are usually fixed and the lymph nodes are involved quite early. They grow slowly and progressively and are of a comparatively low grade of malignancy, if considered from the standpoint of rapidity of growth, but are attended by a mortality of almost 100 per cent.

Papillary Carcinoma.—Papillary carcinoma of the thyroid is associated with cystic degeneration just as are similar types of papillary neoplasms which occur for example in the ovary and breast (Fig. 100). They are composed of multiple finger-like processes from the walls of the acini which are lined with columnar epithelium and they

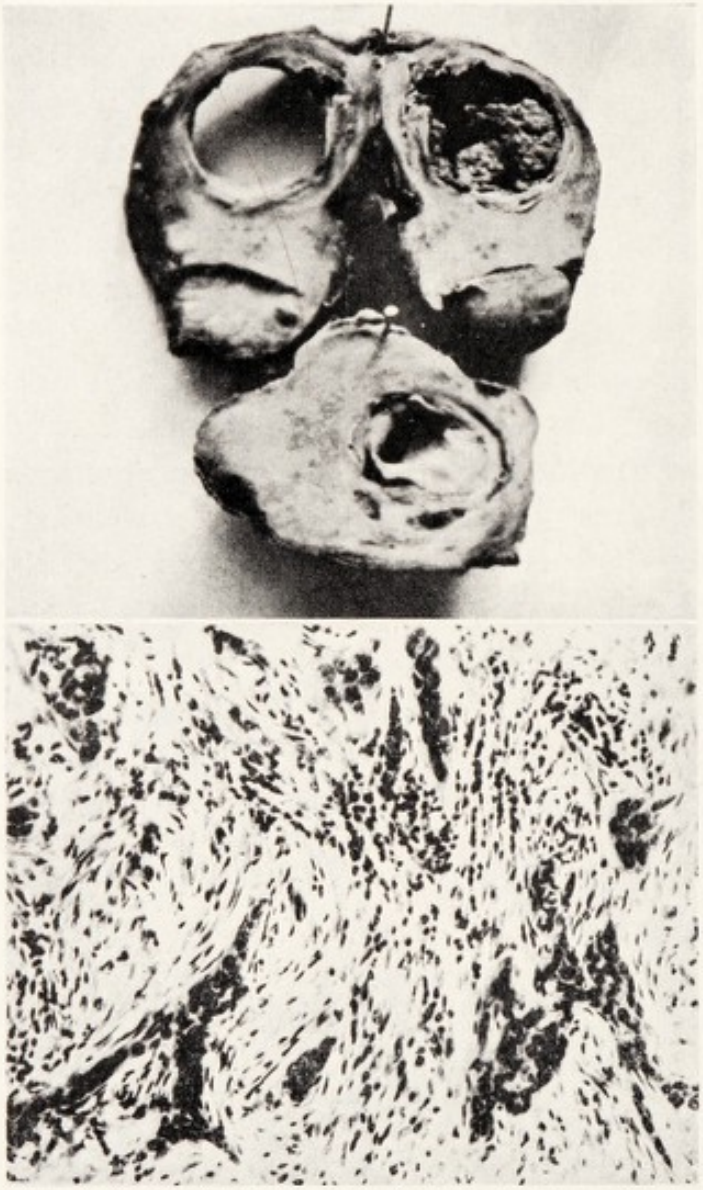

Fig. 99.—Gross and histologic picture presented by scirrhous carcinoma of the thyroid gland.

break through the stroma at their base to invade adjacent acini. They also metastasize and extend through the lymphatics and are of a very low grade of malignancy. These true papillary carcinomata should not be confused with a form of papilliferous growth which occasionally occurs in localized areas in preexisting adenomata. In these, although

the growth is of papilliferous formation, it is a malignant adenoma and should be included under that classification. In contrast to the true papillary carcinomata the papilliferous malignant adenomata are very much more malignant as they invade the blood vessels, break through their capsules and extend to and invade adjacent structures and lymph nodes.

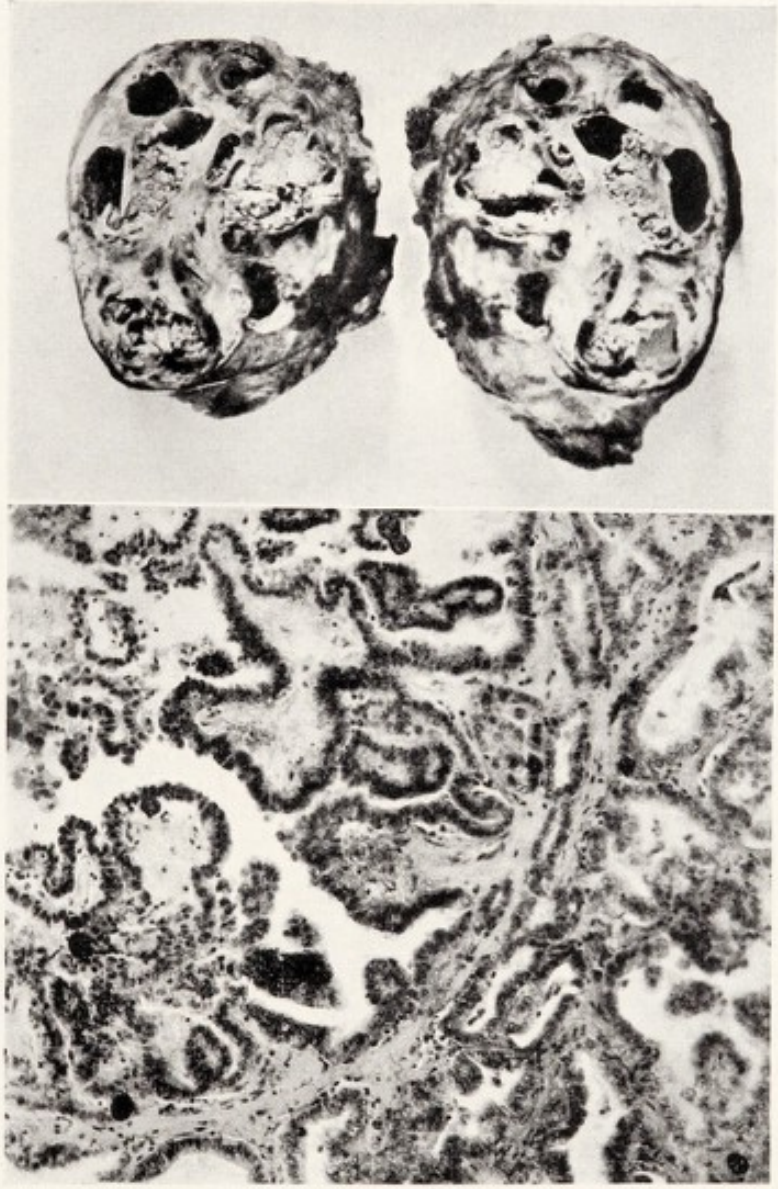

Fig. 100.—Gross and histologic picture presented by papillary carcinoma of the thyroid gland.

Carcinoma-Sarcoma.—Carcinoma-sarcoma is a rare tumor of mixed type which shows both carcinomatous and sarcomatous elements. This tumor has an abundance of stroma which presents the appearance of fibrosarcoma. It shows numerous mitoses and atypical

arrangements. The epithelial elements show the malignant changes which are characteristic of carcinoma. This tumor is usually considered to be a carcinoma though occasionally it is classified as a fibrosarcoma. It is very malignant and is fatal in 100 per cent of the cases.

Sarcoma.—Although the literature contains many reports of sarcoma of the thyroid, true sarcoma occurs but rarely in this gland. If we consider the great preponderance of the epithelial elements in the thyroid over the mesoblastic elements we must realize that, according to the laws of probability, a true mesoblastic tumor can occur comparatively infrequently. Sarcomata have usually been confused with some form of malignant adenoma. It is often difficult to distinguish between sarcomata and certain malignant adenomata on the basis of morphology because of the cellular character of each. Sarcomata are purely mesoblastic in character and originate in the stroma, and, therefore, the type of cell is dependent upon the stroma cell in the thyroid. Lymphosarcoma, which is the most common, originates in the lymphatic structures and has the characteristics of lymphosarcomata of other regions (Fig. 101). The sarcomata are highly malignant but may be controlled for a time by radiation therapy. Cures by operation are rare.

Fibrosarcomata also are seen occasionally.

According to the above classification the malignant diseases of the thyroid gland will occur in about the following percentages: malignant adenomata, 72 per cent; papillary carcinomata, 10 per cent; scirrhous carcinomata, 3 per cent; carcinoma-sarcomata, 4 per cent; sarcomata, 10 per cent.

Clinical Diagnosis and Symptoms.—The incidence of malignant disease of the thyroid is difficult to determine. It is probable that in large hospital centers and clinics the incidence will be higher than in general practice. In our series of 16,908 thyroidectomies, malignant disease has occurred in approximately 2 per cent.

The clinical diagnosis of malignancy of the thyroid is difficult and can be made in only about 50 per cent of the cases. The patients are usually between forty-five and sixty years of age and give a history of rather sudden rapid growth of a goiter which has existed for years. There may be occasional periods of quiescence or even of regression which apparently have no relationship to physiologic function, but as a rule the gland enlarges slowly but steadily in size and often changes in consistency, becoming harder or nodular. Coincident with

the changes in size and consistency, the symptoms of tracheal pressure or laryngeal involvement may take place in more advanced cases. Increasing difficulty in breathing indicating mediastinal or pulmonary involvement and hoarseness caused by extension into the larynx or trachea are late evidences. Symptoms and signs of hyperthyroidism are often present, but usually one or two of the diagnostic evidences of this syndrome are absent. Some of the symptoms of hyperthy-

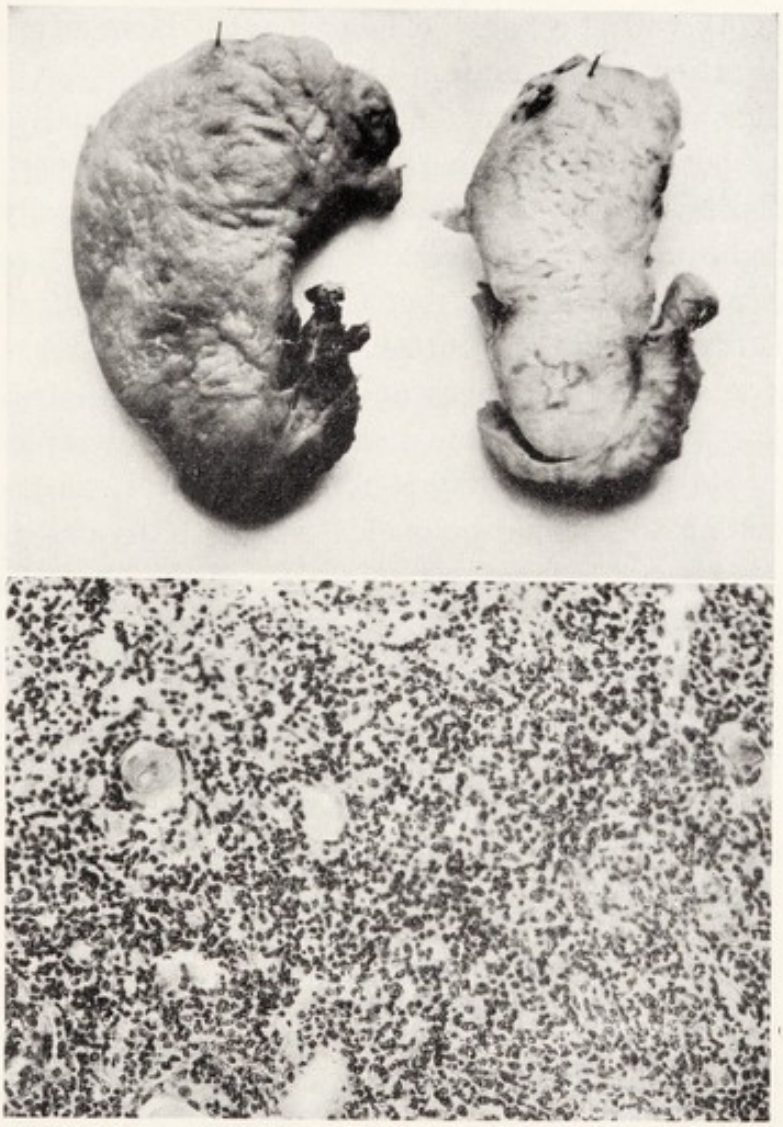

Fig. 101.—Gross and histologic picture presented by lymphosarcoma of the thyroid gland.

roidism occur in almost half of the patients with malignant tumors of the thyroid, especially in older patients who have had preexisting adenomata. Pain is a late symptom, though choking or a sensation of constriction is sometimes complained of in early stages. Actual pain indicates involvement of the sensory nerves and that the process

is in a late stage having broken through the thyroid capsule. Local pain and tenderness may indicate the occurrence of a hemorrhage within the gland.

Cough and hoarseness are caused by pressure upon the recurrent laryngeal nerve or direct extension into the larynx, though these symptoms occasionally indicate metastases or extension into the mediastinum or lungs. Difficulty in swallowing is an uncommon and a late symptom and is due to pressure upon or involvement of the esophagus with probable displacement. Hemoptysis is a late sign of infiltration and ulceration into the trachea.

A malignant enlargement of the thyroid is usually unilateral, irregularly nodular, firm or hard in consistency. When the tumor is fixed, the diagnosis is evident and the fixation is usually the determining diagnostic sign. However, fixation is present in less than half of the cases and indicates that the disease has infiltrated through the capsule of the gland and into surrounding structures. Superficial venous engorgement of the neck and chest is associated with mediastinal obstruction and is a late manifestation of a rapidly growing neoplasm. No patient with goiter, whether it is suspected to be benign or malignant, should be operated upon or treated by radiation before making a radiographic examination of the chest for evidence of pulmonary metastasis.

An important group of cases in which recurrence of a malignant goiter occurs must not be overlooked. Some patients are operated upon for a supposedly benign goiter and the presence of malignant disease is not suspected or discovered either at operation or upon subsequent microscopical examination but the growth recurs within a few weeks after operation. The recurrence of a thyroid enlargement always suggests the possibility of neoplastic changes.

Since it is possible to make a clinical diagnosis of malignant goiter in only about one-half of the cases the other 50 per cent are discovered at operation or by the pathologist who carefully searches the tissues to determine whether a neoplasm is present. The best results which are obtained by thyroidectomy alone are obtained in those cases in which the diagnosis of malignancy was not made clinically, the growth being in so early a stage or so small as to be discovered only on subsequent microscopical examination. It is a safe general rule for surgeons to consider as inoperable from the standpoint of curability those cases in which there are clinical evidences that the growth has extended through the capsule of the thyroid, this invasion

being manifested by fixation of the gland, by involvement of the lymph nodes or by metastases.

Treatment.—The treatment of malignant disease of the thyroid gland, like the treatment of simple goiter, is mainly a problem of prevention. The significant fact has been noted that in about 90 per cent of the cases of carcinoma of the thyroid the neoplasm was due to the degeneration of a fetal adenoma and inversely that about 8 or 10 per cent of all fetal adenomata seen at operation are cancerous. For these reasons it would appear that a fetal adenoma should always be removed. The important question arises: Is it possible to identify a fetal adenoma in advance of operation? In general it is possible since the patient is born with it; it is a discrete well-rounded tumor, is separated from the rest of the gland, is usually unilateral and is freely movable. As for the treatment of any malignant tumor of the gland it should be removed if possible; if it cannot be removed it should be treated by radiation.

A patient with an inoperable carcinoma of the thyroid gland will live without radiation for about one year. As for the length of life after radiation there is no basis upon which to found a final judgment. Sometimes the mass disappears; in other cases radiation does not seem to be of any avail. In cases in which the patient is suffering from obstruction and resultant partial asphyxiation a decompression operation will serve to give temporary relief. The operation should be followed by radiation. In such cases an acute myxedema may develop which is readily cared for by the administration of thyroid extract.

The treatment and prognosis in the presence of the different types of malignant disease of the thyroid gland is discussed in Chapter XXII.

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CHAPTER XXII

THE OUTLOOK FOR THE PATIENT WITH MALIGNANT GOITER

ROBERT S. DINSMORE

IN the determination of the outlook for the patient, in whom the presence of a malignant goiter is suspected, it is necessary to consider first, the extent of the tumor, and second, the type of the lesion.

There are several points in the history of these patients which are significant; namely (1) age—most of these tumors occur in patients over forty-five years of age; (2) the history and characteristics of any previous thyroid enlargement; and (3) the rapidity of the growth. In our experience, in practically 90 per cent of the whole group of cases, the tumor has arisen in a preexisting adenoma. In a patient, beyond middle life, who has had a preexisting goiter for many years, the history of a sudden, rapid enlargement of the thyroid is suggestive, although, of course, the possibility of a hemorrhage into one of these glands is always to be considered. There may be occasional periods of quiescence or even regression, but as a rule the gland enlarges steadily.

The patient may describe some change in the consistency of the growth as it may become harder and nodular. It is necessary also, to know whether any other discrete nodules or swellings in the neck have been noticed as these suggest the presence of metastatic lesions in the cervical glands.

A certain number of these patients will give a history of having had hyperthyroidism during the growth of the tumor and this must be carefully analyzed, as in approximately one-third of the cases, patients will have some symptoms of overactivity of the gland.

Hoarseness is a very significant symptom, as it usually means that the tumor has broken through the capsule and that the recurrent nerve is either actually invaded or is affected by pressure. Likewise, pain in the neck may mean that a nerve trunk has been involved either by actual extension of the growth or by pressure on the nerve.

Pain is a late symptom but choking or a sensation of constriction may be complained of in the early stages.

Pulmonary symptoms such as cough, hemoptysis or pain in the chest are late symptoms and usually indicate metastasis as does pain in the long bones or in the spine.

Another important point in the history is whether or not these patients have had a previous operation on the thyroid gland, inasmuch as in a certain number of cases, a malignant tumor of the thyroid is not recognized until the tumor recurs.

Physical examination alone often does not give sufficient information on which to make a prognosis. The important point after determining the character of the lesion is to determine whether or not it is confined to the neck, and whether or not the tumor is fixed, the presence of palpable cervical glands suggesting that it is not.

Chest signs and localized tenderness over the long bones are occasionally present. Laryngeal examination may reveal paralysis of one or both vocal cords and in addition to this, in many instances, examination will show that an extension into the pharynx has taken place. It is important to remember that in cases of nonmalignant swellings of the neck, involvement of the recurrent laryngeal nerves is extremely rare, unless it is in an occasional case of thyroiditis, or of intrathoracic goiter.

An *x*-ray examination of the chest must be made. In a review of a series of 55 cases in which metastases from malignant tumors of the thyroid gland were suspected, Nichols found metastases in 35 which were distributed as follows: in the abdomen, 1; in the bones, 12 (skull, 1; spine, 1; sternum, 2; ribs, 1; clavicle, 2; pelvis, 4; knee, 1); and in the chest, 22. Of course, localized tenderness over any of the long bones or the spine is significant and these points must be gone over carefully. Additional information may be obtained from roentgenograms of the neck.

In my own experience I have most frequently been confused by the presence of a tense or very hard cyst with a calcified wall. The roentgenogram will often show, in addition, calcified nodules in the tumor. Generally speaking, the presence of calcifications in a thyroid tumor is evidence that it is not malignant.

Since the prognosis depends not only upon the local manifestations and other factors already described, but upon its type it is necessary to classify these tumors. We use Graham's classification which is as follows[1]:

1. Sarcomata:
   (*a*) Lymphosarcoma.
   (*b*) Spindle-cell sarcoma.
2. Mixed tumors.
   (*a*) Carcinoma sarcoma.
3. Carcinomata:
   (*a*) Scirrhous carcinoma } not in adenomata
   (*b*) Adenocarcinoma }
   (*c*) Papillary carcinoma } in adenomata
   (*d*) Malignant adenoma }

The **lymphosarcomata** probably arise from the lymphoid tissue of the thyroid. These are hard, rapidly growing tumors which terminate fatally within a short time (Figs. 102, 103). Although the rapid growth is characteristic, the last patient with a sarcoma whom I

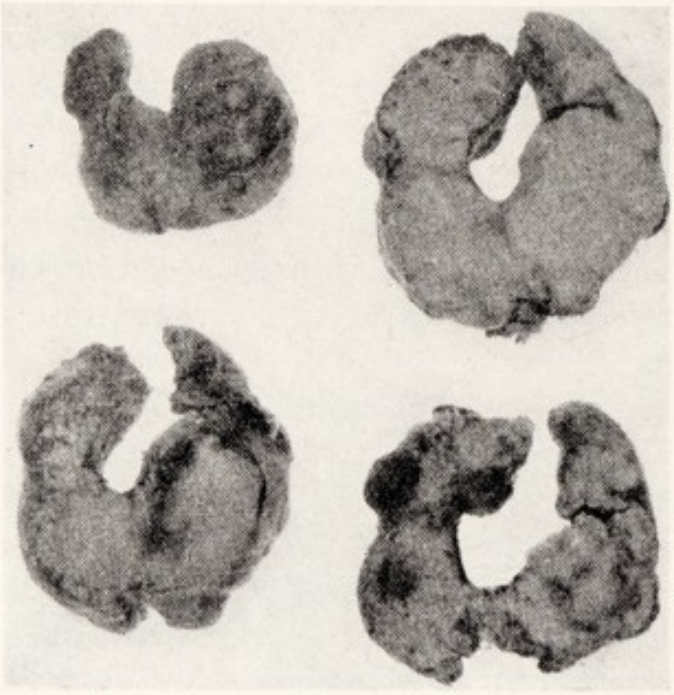

Fig. 102.—Lymphosarcoma which had completely encircled the trachea. This growth occurred in a patient sixty-four years of age who had first noted a small nodule in the midline of the neck about two years before the growth was removed. The growth gradually increased in size, and dyspnea and coughing occurred. There had been rapid growth during the preceding two weeks.

saw, a woman sixty-four years of age, stated that she had first noted a small nodule in the midline of the neck two years previously, and that during the first year, it had slowly increased in size, but did not become a hard, generalized enlargement of both lobes of the thyroid until during the second year. Bilateral palpable cervical glands were also present in this case. At operation, a hard, diffuse enlargement

of the whole gland was found, the tumor completely encircling the trachea. The tumor was a firm, yellowish-white mass, and proved to be a lymphosarcoma.

The **spindle-celled sarcomata** are less frequently seen and resemble the fibrosarcomata and spindle-celled sarcomata seen elsewhere in the body. These tumors also grow rapidly and terminate fatally. In one of these cases, the tumor apparently arose in a preexisting goiter in a woman sixty-seven years of age, who, for forty-three years, had had a unilateral enlargement of the thyroid (Fig. 104).

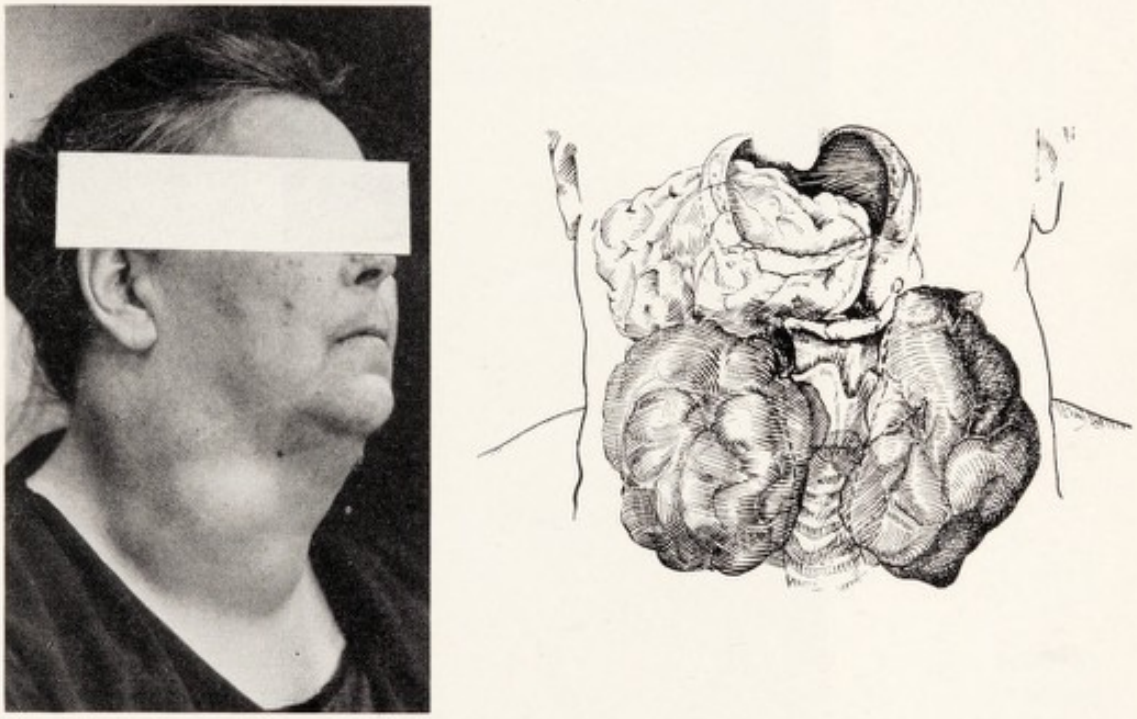

Fig. 103.—Lymphosarcoma of the thyroid gland. A patient, sixty years of age, who had had a goiter for thirty-eight years. Recently rapid growth had taken place at the right upper pole. Laryngeal examination showed that the tumor extended into the pharynx.

I have seen twenty patients with these tumors among whom none has survived for three years; only two patients are living but less than that period has elapsed since they were first seen. The tumors are characterized by their rapid disappearance under *x*-ray therapy and their equally rapid reappearance within a few months, when they are unaffected by *x*-ray.

There is a **mixed cell type of tumor** in which Graham has found both mesoblastic and epithelial elements and has classified them as **sarcoma-carcinomata**. These tumors are rare, and are highly malignant. In a small group of these cases all have terminated fatally

within a short period of time. The mesoblastic elements apparently predominate, sections in fairly large areas resembling fibrosarcoma.

The **scirrhous carcinomata** of the thyroid gland are easily identified. They resemble the scirrhous tumors seen elsewhere in the body, presenting the same gross and histologic picture. This tumor is comparatively rare and is universally fatal. Clinically, the tumor is extremely hard and on account of its invasive characteristics may

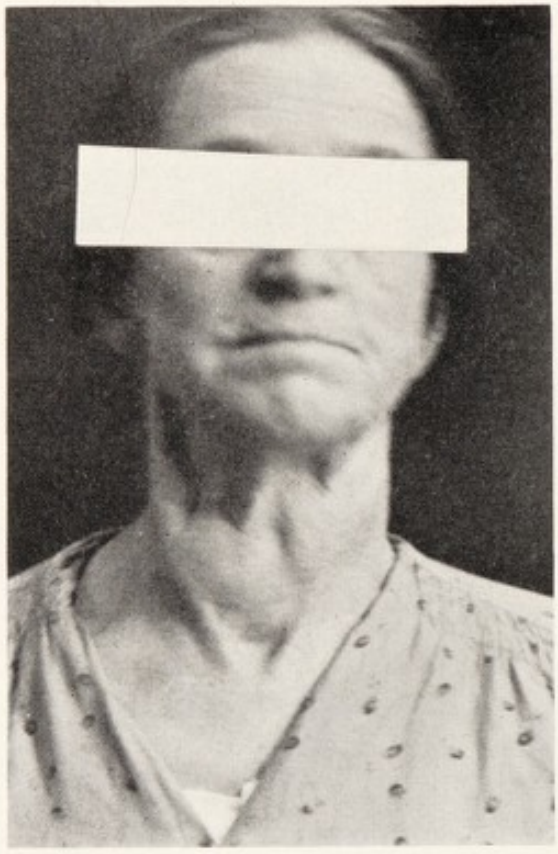

Fig. 104.—Fibrosarcoma of the thyroid gland. The patient, sixty-seven years of age, had had a goiter since girlhood. One year before this picture was taken the goiter began to grow and to become harder. On palpation a hard nodular mass was found. Pathologic report: Fibrosarcoma.

be adherent to the surrounding structures. It has been pointed out that its rate of growth is slow as compared with other epithelial tumors in the thyroid, in which very little stroma is present. Scirrhous carcinomata do not arise in previously existing adenomata.

There is another small group of tumors described by Graham as **adenocarcinomata** which like scirrhous carcinomata do not arise in adenomata. These tumors are small, firm and nonencapsulated and seem to have their origin in nontumorous portions of the gland

(Fig. 105). They are not diagnosed clinically but are always found by the pathologist. In gross appearance, they resemble adenocarcinoma of the breast. In our series of 16 cases, all the patients are living.

By far the most important group of malignant tumors of the thyroid gland are those which arise in adenomata and include papillary carcinomata and malignant adenomata.

Papillary carcinoma arises in a **cystic adenoma**. At first it is encapsulated and does not metastasize as long as it remains within its capsule. When it does metastasize it does so through the lymph

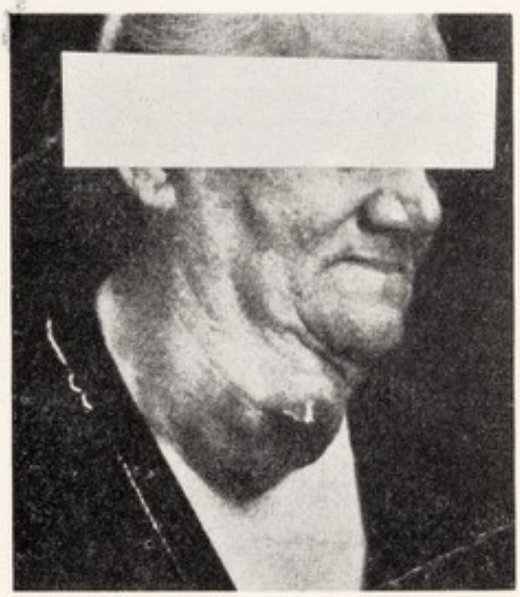

Fig. 105.—Papillary adenocarcinoma of the thyroid gland. Patient, seventy-one years of age, who had first noted a small nodule on the right side of the neck five years before this picture was taken. The growth had steadily increased in size during the preceding four years; and had grown rapidly during the preceding year. On removal the growth was found to be a large broken-down tumor mass with bluish discoloration over the surface.

channels and not through the blood stream. A papillary carcinoma is composed of multiple finger-like processes from the walls of the acini and at the base of these projections it invades the stroma and extends into the neighboring acini. These tumors often grow rather slowly and often reach a rather large size. The last case I saw was in a woman seventy-one years of age, who had noted a slow gradual growth of her thyroid during the preceding five years. Although the tumor had broken down, it was removed and *x*-ray therapy was given. This patient has lived for over two years, although there is now a recurrent nodule which she refuses to have removed.

When these patients are treated by surgery and *x*-ray, three-year cures result in 50 per cent of the cases.

Malignant adenoma is the most important and most frequently encountered type of malignant goiter (Figs. 106, 107). In a total series of 288 cases of malignant tumors of the thyroid gland malignant adenomata had been present in about 85 per cent. These tumors have given rise to a great deal of confusion and Graham has pointed out that blood vessel invasion is the most important criterion on which to base a diagnosis. They metastasize through the blood vessels

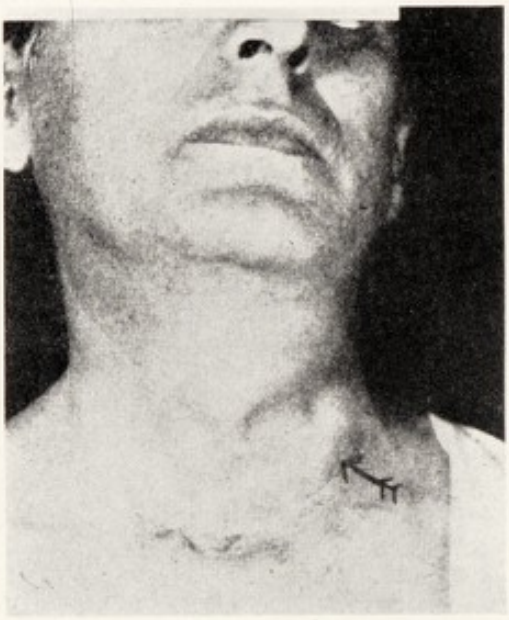

Fig. 106.—Malignant adenoma. Patient, forty-six years of age, who had had a tumor removed from the thyroid sixteen years before this picture was taken. There had been six recurrences in these sixteen years and seven courses of *x*-ray therapy had been administered; the general condition of the patient was satisfactory. (Arrow indicates recurrent nodule.)

and in every case thus classified in which recurrence and metastasis had occurred, invasion of the blood vessels could be demonstrated.

The tumor presents a great variety of morphological transitions and only rarely is the tumor composed of but one type of neoplastic cell. This is the reason why it is so difficult to classify these tumors on the basis of their morphological aspect alone. Their proper classification demands an investigation to discover whether or not the blood vesels and capsules are involved.

These tumors originate in adenomata which are primarily encapsulated but in almost every instance some of the blood vessels will become filled with neoplastic tissue as the result of direct extension.

It must be borne in mind, however, that metastases from a totally encapsulated tumor may be carried through the blood stream.

The typical history is that of a patient beyond middle life who has had a goiter for a long time which suddenly begins to grow. The tumor is usually hard and the patient will often note a change in its consistency. In some cases the rate of growth may have been relatively slow and sometimes apparent regression may occur. I have seen one case in a woman, forty-four years of age, in which there was a perfectly smooth tumor of the size of a small grapefruit

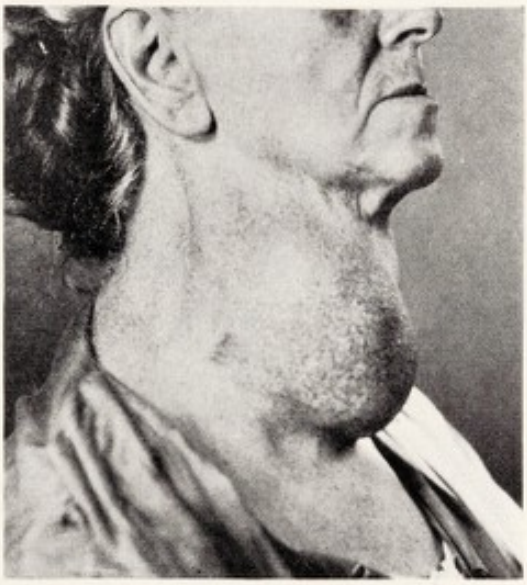

Fig. 107.—Malignant adenoma. Patient, fifty-nine years of age, who had had a goiter for thirty-five years which had gradually increased in size until three years before this picture was taken the growth had become rapid. Recurrent laryngeal paralysis was present. The tumor was inoperable.

on the right side of the neck (Fig. 108). The patient stated that the whole mass had appeared within a period of twelve weeks. I felt quite sure that there had been a hemorrhage into an old cyst, but at operation the tumor was found to be a very tense encapsulated malignant adenoma. A recurrence appeared three months after operation and the patient died eighteen months later from general metastases.

x-Ray therapy has been a valuable adjunct to surgery in the treatment of these cases. The best results are obtained in those cases in which the diagnosis is made by the pathologist; that is, in cases in which the whole tumor has been removed and the operator has no evidence that a malignant tumor is present.

In the treatment of this type of tumor combined surgery and *x*-ray has given cures in 25.8 per cent of the cases.

There is a group of patients with malignant tumors of the thyroid gland for whom little can be done, inasmuch as they present a perfectly hopeless situation (Fig. 109). A palliative operation, consisting of a decompression is occasionally done. In this procedure, the preglandular muscles are divided transversely and the vessels in the cut ends ligated, the skin being closed over the tumor which projects up between the muscles. In many instances this gives the patient a

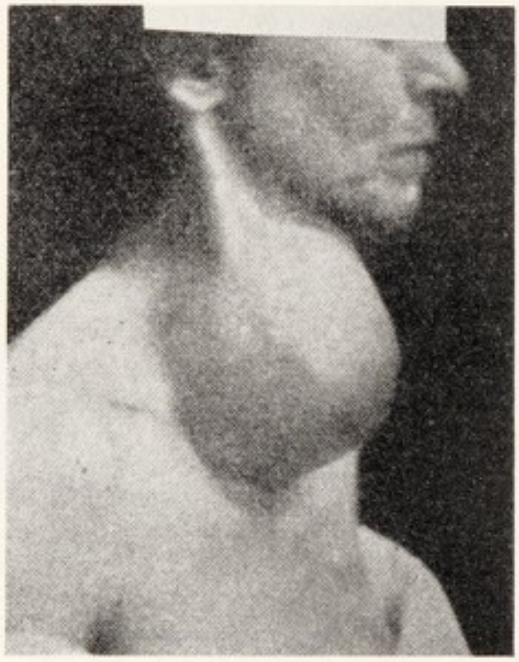

Fig. 108.—Malignant adenoma. Patient, forty-four years of age, who had always had a full neck but the enlargement shown had only been present for three months This was a movable, smooth, apparently cystic growth which was found to be an encysted tumor completely filled with neoplastic tissue.

great deal of comfort and it is also an advantage in the administration of the *x*-ray therapy.

Another palliative measure is tracheotomy and this also may be necessary to admit the administration of *x*-ray therapy. A marked stridor and cyanosis develop in many of these cases and the operation can be performed only with great technical difficulty, inasmuch as the tumor may be firmly fixed in the neck and it may be very difficult to find the trachea, and having found it, it is often difficult to recognize it, as it is sometimes a cordlike structure. It is, of course, also very difficult to secure a bloodless field.

It is important to remember that in some of these so-called "inoperable cases" which formerly were definitely classified as hopeless, the patients have lived for a long time after *x*-ray therapy has been administered. As Pemberton[2] and Coller[3] have pointed out, it should

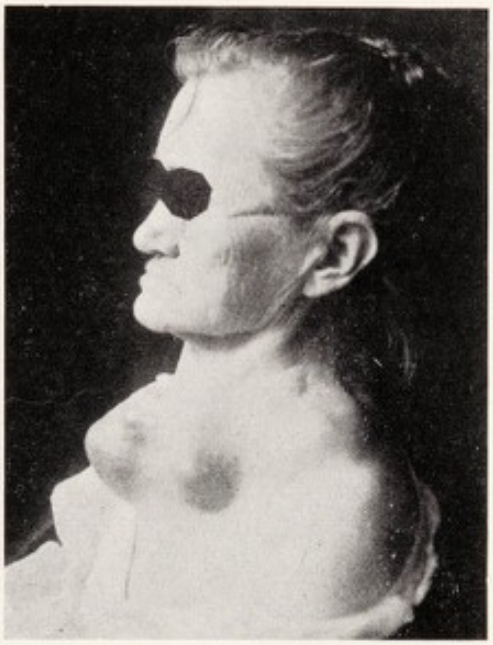

Fig. 109.—Malignant tumor of thyroid gland presenting hopeless prognosis Patient sixty-four years of age who stated that she had "always had a goiter." The tumor began to grow rapidly fifteen months before this picture was taken. She died a few weeks after admission to the hospital.

be borne in mind that the prognosis in a case of any type of malignant tumor of the thyroid is much better than is generally supposed. Sometimes these tumors will regress in size, become stony hard and remain in that state for a long period of time.

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CHAPTER XXIII

THYROIDITIS, RIEDEL'S STRUMA AND STRUMA LYMPHOMATOSA

GEORGE CRILE

THYROIDITIS is a comparatively rare disease. Kocher was the first to appreciate the etiology of this condition: "In the farsightedness of his genius, although at the time he did not have bacteriology to support his theoretical views, he claimed that every acute thyroiditis or strumitis was due to metastasis of an infectious agent located somewhere in the organism, or originating from the intestinal canal. Later bacteriological findings proved the correctness of such views" (Crotti[1]).

The cause of thyroiditis may not always be apparent, although a careful history will usually elicit the fact that the patient has had an attack of influenza or some other infectious disease. In the days when typhoid fever was prevalent, typhoid thyroiditis was occasionally encountered (Armstrong[2]). In many cases, however, no direct cause of the inflammatory condition of the thyroid can be demonstrated.

Acute inflammation of the thyroid gland is manifested by the usual symptoms of inflammation, namely, swelling, local heat, tenderness, pain, and fever. The process may progress to abscess formation or may become chronic. In the acute stage the treatment consists in the application of cold with incision and drainage, if fluctuation indicates the presence of pus (Fig. 110). Radiation may be applied as stated by Portmann (p. 345).

The inflammation may impair the function of the gland with resultant hypothyroidism. This impairment is usually temporary though it may persist for a year or more. Resolution may follow the acute stage, but it should be borne in mind that there is always the possibility that a collection of pus may become encapsulated as in one of our cases.

Thyroiditis may develop in a goitrous gland, usually adenomatous in character, the condition being called **strumitis.** The treatment

depends upon the cause in the individual case, but resection of the gland generally is indicated (Figs. 111, 112).

In cases of **chronic thyroiditis** partial resection of the gland is indicated but it should be borne in mind that the degree of hypothyroidism already present will be increased in direct proportion to the amount of gland that is removed.

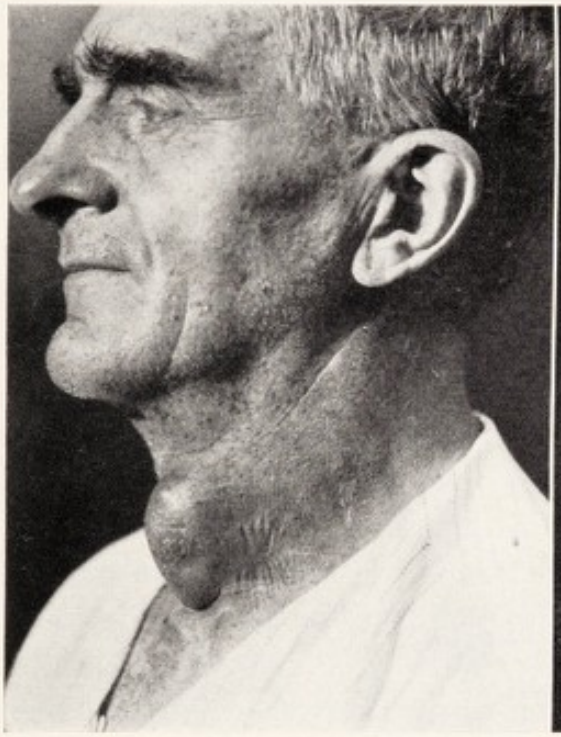

Fig. 110.

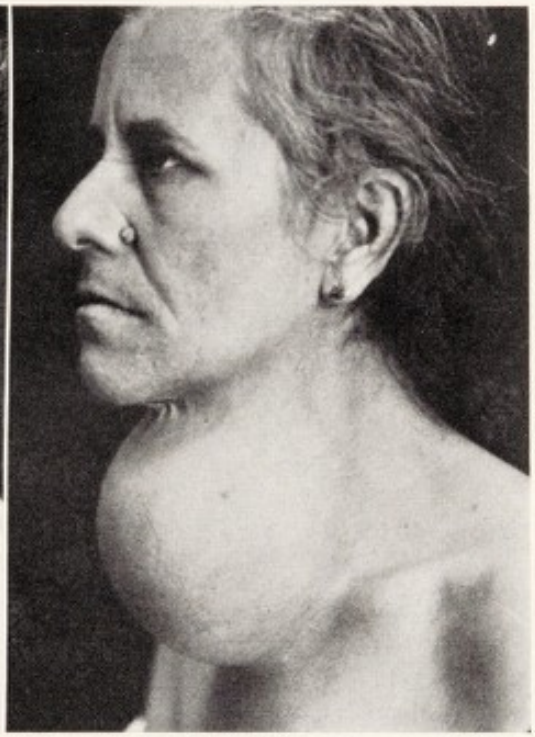

Fig. 111.

Fig. 110.—Thyroiditis. In this case, that of a man fifty-six years of age an abscess of the thyroid gland developed after a cold. On palpation the thyroid felt hard and woody and presented a fluctuant mass at the junction of the lower left lobe and the isthmus. The skin was somewhat reddened. At operation a large amount of grayish pus was evacuated.

Fig. 111.—Colloid adenoma with thyroiditis. The patient a woman forty-eight years of age had had a small goiter since adolescence which had gradually increased in size during preceding eleven years. Five months before she had had influenza. She showed moderate symptoms of hyperthyroidism. At operation a quantity of purulent material was encountered. The portion of the gland from which this came was necrosed and caseous. Some calcifications were found. Pathologic diagnosis: Colloid adenoma, subacute thyroiditis.

Tuberculosis and syphilis of the thyroid gland occasionally are encountered but the manifestations of these conditions do not differ pathologically or clinically from tuberculosis or syphilis encountered elsewhere and the usual treatment for these conditions is indicated. In cases of tuberculosis the thyroid may become infected by direct

extension from the cervical lymph nodes. We have seen 14 cases of tuberculosis of the thyroid.

Riedel's struma, the so-called **"ligneous thyroiditis,"** presents an interesting clinical picture. As the term "ligneous" implies, the gland becomes hard—even stony hard—in consistency. Usually the entire gland is involved although one lobe may escape. The blood supply is usually meager. The appearance of the gland suggests a malignant condition but the hardness involving the entire gland will usually suffice to establish the diagnosis, which may be confirmed at operation by the meager blood supply. In the case of a malignant growth which has involved the entire gland, usually the lymphatic glands are involved and this is not the case in thyroiditis.

Ewing[3] describes Riedel's struma as a benign granuloma of the thyroid. The outstanding characteristics of this tumor are described as follows by Graham and McCullagh: "In the majority of cases Riedel's struma occurs in persons under forty years of age; almost invariably the thyroid becomes adherent to surrounding structures and the cervical tissues are usually extensively involved, even to the point of complete encasement of the carotid sheath and its contents; practically always it is a deforming lesion, and the outlines of the thyroid lobes are lost; it is frequently a unilateral or localized process; it is generally surgically irremovable; it is usually associated with marked pressure symptoms; in many cases there are objective indications of long standing goiter, notably in the form of adenomatous nodules and adenomas."

As this condition is rarely operable the only applicable treatment is irradiation (p. 345).

Struma lymphomatosa is a term which in 1912 was applied by Hashimoto to a group of 4 cases "all in women forty years of age and over, who presented few and relatively insignificant symptoms, associated with uniform bilateral enlargement of the thyroid. The onset of the disease was insidious and its progress was slow. The enlarged thyroid gland was firm to hard in consistency (in one case malignancy was thought to be present); at operation the gland was found to be adherent to the trachea but not to the surrounding structures."[4]

Graham[5] distinguishes this condition from Riedel's struma as follows:

"1. The group of cases generally classified as Riedel's disease, ligneous thyroiditis, productive thyroiditis (exclusive of specific infec-

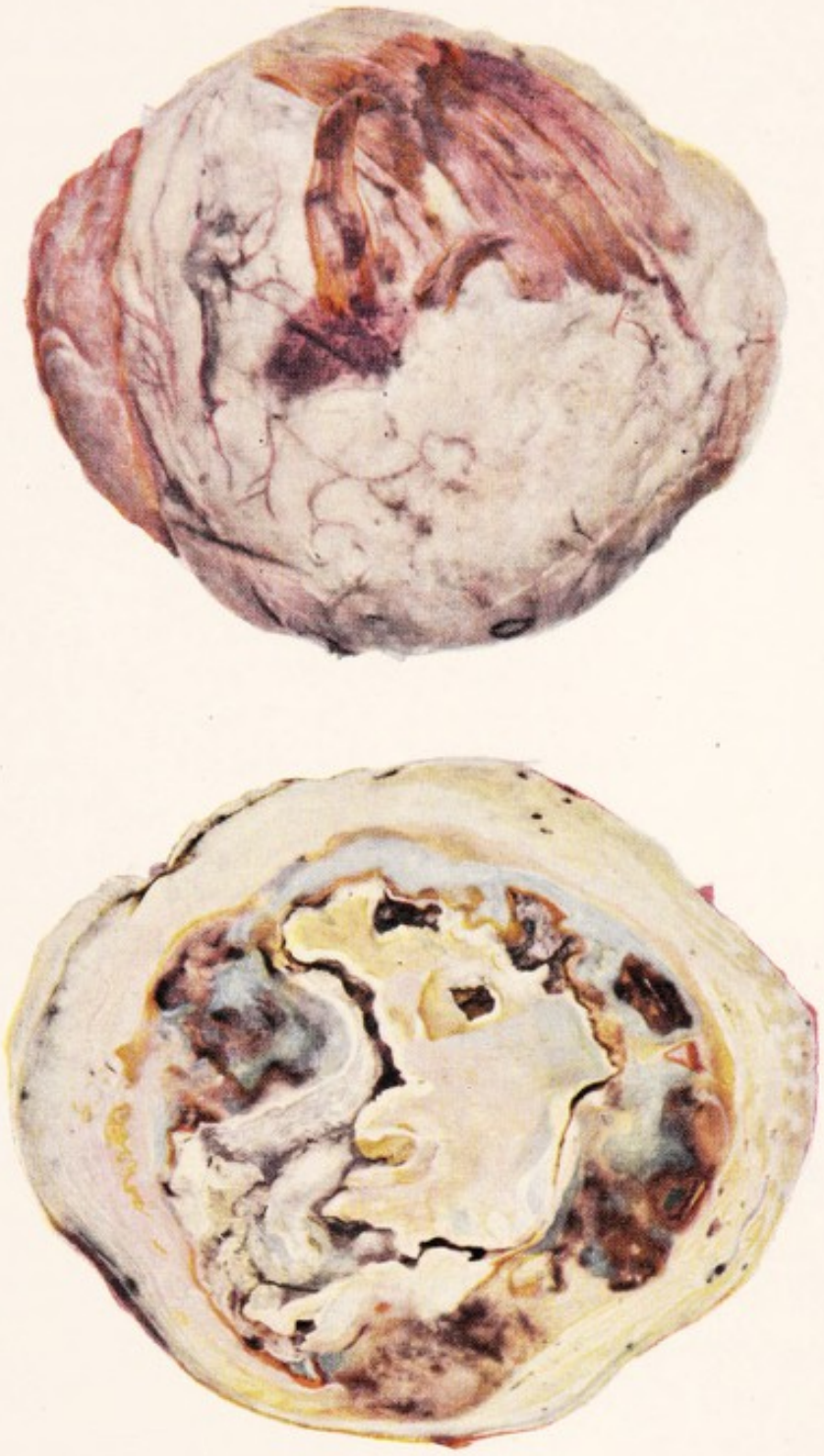

Fig. 112.—Subacute thyroiditis. Colloid adenoma containing abscess (Streptococcus hemolyticus). (See Fig. 104.)

tions, such as typhoid, tuberculosis, syphilis, actinomycosis, etc.) may be looked upon as having a local inflammatory process in the thyroid for which an etiological factor should be sought. In these cases the general body economy is affected only secondarily by reason of destruction of the thyroid, interference with respiration and deglutition, and injuries to important blood vessels and nerves. Such a process has its counterpart in other organs and tissues, and may be expected to behave in a similar manner, except for the fact that the thyroid gland is so situated that complications can occur readily.

"2. The changes which occur in the thyroid in the presence of the Hashimoto type of lesion may be considered primarily to be local manifestations of a constitutional disorder, the nature of which is as yet not understood. What the initial changes in the thyroid may be, is not known, but it seems clear that in the course of time these changes tend to become degenerative (rather than inflammatory) and sclerosing, and ultimately may be accompanied or complicated by more definitely inflammatory phenomena of a non-specific character. The lymphoid tissue, which is variable in amount and to a less degree in character, is non-specific for Hashimoto's struma."

As struma lymphomatosa in contrast to Riedel's struma is usually not adherent it can be removed surgically. As Portmann states (p. 346) radiation is apparently ineffectual. We have seen 74 cases of thyroiditis; 15 of Riedel's struma, and 5 of struma lymphomatosa.

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CHAPTER XXIV

THYROGLOSSAL DUCT CYSTS AND FISTULAE

GEORGE CRILE

UNDER ordinary developmental conditions, the thyroglossal duct, especially the suprahyoid portion completely disappears except for the foramen caecum of the tongue which represents the buccal opening of the duct.

In certain cases, however, due to some developmental error, the duct or some portion of it persists, and its secretion is retained, giving rise to cysts "lined by squamous or cylindrical cells and often containing thyroid follicles in the wall" (Ewing[1]).

It is probable that lingual thyroids such as we have described elsewhere (p. 411) are due to the hypertrophy of the accessory thyroid gland tissue which may be formed along the entire length of the thyroglossal duct. "The uppermost glands are very prone to hypertrophy at puberty and produce tumors presenting at the foramen caecum" (Ewing).

"All pathological conditions arising in the thyroglossal duct are caused by hyperactivity of the cellular and secreting elements in persisting parts of the duct. Any part of either the supra- or infrahyoid portion of the duct may persist separately, either as a solid glandular rod, or as a duct, or as a glandular mass, or as a cyst. Canalization may occur below the hyoid bone and result in the formation of a cervical cyst, which may open on the surface of the neck by a fistulous opening. The lumen always stops short just below the hyoid bone. Similarly we may have persistence of the canal in the suprahyoid region producing a cyst in the substance of the tongue, or leaving a long fistulous channel opening above on the surface at the foramen caecum, but blind below, just above the hyoid bone. There is no authentic case on record of the duct persisting as a patent channel throughout, from the foramen caecum above to the fistulous opening of the cervical cyst in the neck below" (Thompson[2]).

Technic.—We have performed ninety operations for the removal of thyroglossal duct cysts or fistulae.

Through a transverse collar incision the dissection is carried down to the hyoid bone. If the duct penetrates the bone, or if the duct divides and one branch passes behind the hyoid, then the hyoid is divided on each side of the thyroglossal duct tract. The tract is dissected out well up toward the base of the tongue, thus removing the cyst or fistulous portion and the tract above and below it.

The one essential point in the excision of either a thyroglossal duct, fistula or cyst, as Sistrunk[3] has emphasized, is that every vestige of the entire tract must be excised or the condition may recur, and if it does recur, the difficulty will be increased. In one case such a tract had been removed three times before our own attempt to remove it. Each time, according to the account given us, the recurrence gave increasing trouble. I felt, though it proved erroneously, that by a very wide excision including the greater part of the hyoid bone recurrence could be prevented. I found difficulty in defining the margin of the tract which was much widened, owing to previous operations. The pathologic report was that the tissue was benign, but the mass reappeared, and at the third operation, malignancy was clinically obvious and the pathologic report confirmed the clinical picture. This patient had six operations over a period of eight years, ultimately succumbing to malignancy.

We have seen a number of recurrences and in almost every instance they were found to be due to that unexpected phenomenon, the passage of the sinus tract or of one branch of it through the hyoid. This apparently occurs in the course of the fusion of the hyoid. In such an event, unless the middle section of the hyoid is removed in the course of the dissection, recurrence is quite certain.

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CHAPTER XXV

ROENTGEN RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE THYROID GLAND

U. V. PORTMANN

SINCE their discovery roentgen rays and radium not infrequently have been employed in the treatment of many diseases in order to avoid more radical procedures. Within recent years and with increasing knowledge of the physical properties of the rays and the biological reaction to them, radiation therapy has developed beyond the early period of empirical application, to a comparatively exact science. Careful analyses of the results which have been obtained by radiation therapy as compared with the results of other therapeutic procedures including surgery has established this method of treatment on a firm foundation. This branch of medical science requires special training, experience and technical skill. The mechanical technical details of the application of radiation, however, are of minor importance as compared with knowledge of the pathologic physiology and the clinical course of the diseases which are amenable to treatment. Training in surgery and pathology therefore, is especially valuable for a radiotherapist in order that he may appreciate the value of other methods of treatment as well as the limitations of his own.

Radiation therapy, as we understand it today, consists in the administration of roentgen rays or radium in doses of a predetermined intensity. These two forms of radiation have identical physical properties and biological reactions as far as therapeutic effects are concerned. The choice of the form of radiation to be employed therefore depends upon the availability of either and the experience of the radiologist. The reports would indicate that the results which are obtained by skilled radiologists are about the same whichever medium is employed, although far more cases have been treated with roentgen rays than by the use of radium.

THE BIOLOGICAL EFFECTS OF RADIATION UPON THE THYROID GLAND

It may be said in a general way that, according to our present knowledge, the effects of roentgen or radium rays upon any tissue are primarily destructive; that is, those cells which are sensitive to radiation are inhibited or destroyed. Such a reaction as direct stimulation of the cells does not occur though certain secondary stimulative effects may be produced in one tissue as the result of the inhibition of another. Also inhibitive effects upon certain types of radioresistant tissues may be secondary, resulting from the effects of the radiation upon adjacent or functionally related tissues which are radiosensitive.

Both experimental and clinical evidence indicates that the glandular tissue of the normal thyroid gland is quite resistant to roentgen or radium rays. Radiation of very great intensity will affect the normal thyroid when it is sufficient to cause necrosis but this intensity is as great or greater than that which will also destroy the skin. For example, when bare radon seeds are implanted in the thyroid gland they produce only a local necrosis with a sphere of fibrosis in a very localized area, and roentgen rays of great intensity may be applied without directly affecting the glandular structure or its function, although later when fibrosis develops there is a secondary inhibitory effect. However, the vascular system of the gland is just as sensitive to radiation as are the vessels of other organs and in the state of hyperthyroidism the blood vessels of the thyroid seem to be even more sensitive than under normal conditions. It is probable, therefore, that the main effects of radiation upon the thyroid are upon the endothelium of the vascular system, producing devascularization by reducing the lumen of the vessels. This primary reaction of devascularization is more or less temporary and reduces toxicity by diminishing the blood supply to the gland. If the radiation is carried to a sufficient degree either by high intensity or by prolonged treatment the devascularization will eventually be followed by the production of some degree of fibrosis, but it requires several weeks or months for the fibrosis to develop. This effect of radiation may be compared with the similar devascularization and fibrosis which follows ligation of the thyroid arteries, except that in the case of radiation this process develops very slowly and progressively while treatments are being administered.

The entire effect of radiation is to cut down thyroid activity so that function and toxicity are decreased either by inhibition of the

thyroid itself, or secondarily by some effect upon the endocrine interrelationship with which we are not yet familiar.

DIFFERENT TYPES OF GOITER

The types of goiter which can be successfully treated by radiation and those which should be selected for treatment depend upon the known effects of radiation upon thyroid tissue. It is important that radiologists should recognize the various types of goiter which are amenable to treatment, and should treat only these, as otherwise the method will be brought into disrepute through failures caused by ignorance.

The Hyperplastic Nontoxic Goiter of Adolescence.—This is a physiologic goiter which is successfully treated by a medical regimen which includes the administration of small doses of iodine and the more radical procedures are not indicated. Radiation may reduce the size of the gland to some degree but may also interfere with the physiologic processes which often eventually become balanced; therefore this type of goiter should not be treated by radiation nor by operation.

Simple Colloid Nontoxic Goiter.—This type of goiter is also more or less the result of physiologic processes which are not caused by disease of the thyroid gland itself. It is not benefited by radiation.

Nontoxic Adenoma.—This type of goiter is a progressively enlarging adenomatous thyroid gland. Medical treatment including the administration of iodine is usually ineffectual. In fact under certain circumstances this treatment may precipitate hyperthyroidism. Radiation is likewise contraindicated and does not decrease the enlargement to any appreciable degree. The surgical removal of the gland for cosmetic reasons or to relieve pressure is the only indicated treatment.

Toxic Hyperplastic or Exophthalmic Goiter.—That type of goiter, which is characterized by diffuse hyperplasia and symptoms of toxicity, is amenable to radiation therapy but the results which may be expected bear no relation to the severity of the symptoms. Some patients with mild symptoms may derive little relief, while others who are severely toxic may be greatly relieved. Naturally the exophthalmos will not be diminished to any great degree and a guarded prognosis in this respect should be given to the patient who is treated either by radiation or operation.

It may be stated in a general way that the *duration of the symptoms* is the most important factor on which to predict the results which

may be expected from radiation, as patients who have had symptoms for longer periods are less favorably influenced.

Toxic Adenoma.—The treatment of adenomatous goiters with toxic symptoms by radiation gives satisfactory results by reducing the toxicity but it may not diminish the size of the goiter. The benefits of the radiation of toxic adenomata are less spectacular and slower than the response to the treatment of exophthalmic goiter. Usually in the former the toxicity is of longer duration and therefore the cardiovascular symptoms are more pronounced. Tachycardia may persist after other symptoms of hyperthyroidism have disappeared and therefore it is sometimes difficult to determine if and when a cure has been effected. It is probable that radiologists sometimes prolong the treatment unnecessarily before they recognize that they will be unable to control completely some of the symptoms, especially residual tachycardia.

THE TREATMENT OF HYPERTHYROIDISM

The value of radiation therapy in the treatment of hyperthyroidism, toxic goiter, thyrotoxicosis, Basedow's disease or exophthalmic goiter as compared with surgical treatment is a debatable question. It is now generally recognized that this syndrome, which is given so many names, is not a disease which is caused primarily by dysfunction of the thyroid alone. The reduction of thyroid activity by any one of several therapeutic procedures, including radiation by roentgen or radium rays, may bring about a lessening of the symptoms. But it is difficult to be unbiased in one's opinion of any method of treatment which has been proved by individual experience to be successful in a considerable percentage of cases.

We know that a certain number of patients will be relieved by a strictly medical regimen of rest and supportive measures. A large percentage of cases are relieved by total or subtotal thyroidectomy. Roentgen and radium treatment in the hands of competent radiologists have also been proved to be efficacious in many cases. Therefore, in the light of our present uncertainty as to the etiology of this syndrome, it is unwise to formulate any fixed rule, adopt an inelastic routine, or advocate one method of treatment to the exclusion of all others.

Undoubtedly more of the severer degrees of hyperthyroidism are seen in institutional practice than are observed in the general practice of medicine. In institutions, surgical procedures are so highly de-

veloped that patients with even severe hyperthyroidism are operated upon more successfully than is the case in general practice. Therefore it is difficult for one in institutional practice not to be biased in favor of operative procedures in the treatment of hyperthyroidism. On the other hand, in localities where the surgical results have been comparatively unsatisfactory, other methods of treatment, especially radiation, are considered favorably.

Usually a discussion of this subject enters into a presentation of the various objections which are raised to each procedure. It is not my purpose to discuss these arguments against the use of radiation, some of which are academic, and many of which are now obsolete or untenable as the same objections may be raised to other methods of treatment.

Roentgen Therapy.—In the treatment of hyperthyroidism with the roentgen rays the tendency is toward moderation in dosage, the important control factor being the condition of the patient rather than any inelastic routine. The indications for the frequency or intensity of individual treatments or series of treatments should depend upon the lessening or the increase of symptoms as manifested by changes in the basal metabolic rate, in the pulse rate, loss or gain of weight, and changes in the subjective symptoms.

The technical and mechanical factors which are employed depend in some degree upon the personal preference or experience of the radiologist. These details are rather unimportant. Moderately penetrating rays are generally preferred, a peak voltage of from 90 to 140 kv. being employed with filtration by from 4 to 8 mm. of aluminum or its equivalent to produce an effective wavelength of from 0.28 to 0.29 angstrom. The milliamperage, time and focal distance from the skin are factors of choice by the individual operator and depend to a great degree upon the intensity of the output by the apparatus employed, of which no two are exactly alike. Most radiologists seem to prefer to administer to each field from 200 to 300 roentgen at each treatment the dosage being calculated to include backscattering from the skin.

In order to avoid any great amount of scattered radiation which might damage the larynx and trachea these organs should be carefully protected or should not be included in the field of radiation. It is customary to irradiate the right and left lobes of the thyroid separately although this is unnecessary from the standpoint of actual dose absorbed into the gland.

Some radiologists also treat the thymic area as a routine. The treatment of this area, although considered important by some radiologists would seem to be unnecessary in many instances, unless previous radiographs of the chest show the existence of a substernal goiter which might be active or show some evidences of the presence of abnormal lymphatic tissue within the mediastinum. Although thymic tissue may be found in the mediastinum especially in young individuals it is probably not active and does not contribute to the hyperthyroid state but it is a part of the generalized lymphatic reaction which is always associated with hyperthyroidism and therefore the necessity for the routine treatment of the mediastinum is debatable.

No goiter should be removed by operation or treated by radiation before the chest has been studied by radiographs with these points in mind. A substernal goiter is seldom reduced in size to any appreciable degree by radiation therapy.

The frequency of roentgen treatments depends upon the severity of the toxic state and the reaction in the individual case. In the beginning of a series of treatments, once a week is usually considered to be often enough, or the treatments may be spaced at longer intervals, the average being about two weeks, It would seem that the disease would be much more difficult to control if larger doses or smaller doses at more frequent intervals are used. Usually from six to eight treatments constitute a series. A careful record of the pulse rate, weight and subjective symptoms should be kept and the basal metabolic rate should be determined before each treatment, the course and dose being governed accordingly. The total intensity of radiation for a series should remain safely within the limits of skin tolerance. The number of series which may be given will vary with the indications in the individual case but it would seem advisable to discontinue treatment if decided improvement is not manifested within three months. If radiation therapy is carried too far the symptoms of hypothyroidism may appear but this condition is as easily controlled by the administration of thyroid extract as it is after thyroidectomy.

Radium Therapy.—The intensity of radiation with radium which is administered for hyperthyroidism will naturally depend upon the quantity of radium which is available. Usually radium packs are used and about one-third of an "erythema dose" is administered to each lobe at each sitting, the trachea being protected. For example,

with a 4 x 4 cm. pack at 2 cm. distance and a filter equivalent to 4 mm. of brass the dose would be 400 milligram hours.

The frequency and intensity of radium treatments should be governed in the same way as the roentgen-ray treatment.

A few radiologists have employed interstitial radiation by means of radon gold seeds or needles. Interstitial radiation, especially by means of implantation of radon seeds, is not advisable because of the necessity for the surgical procedure involved, this sometimes being attended by as much hazard as thyroidectomy. Moreover, the radiation effects cannot be accurately controlled when the seeds or needles are employed, because no one can judge the exact intensity of radiation which will be necessary to control the symptoms. If too much thyroid tissue is destroyed, hypothyroidism may be produced, and if too little is applied the patient will not be relieved or the treatment must be repeated.

Statistical Results of the Treatment of Hyperthyroidism by Radiation.—There are numerous reports in the literature on the results which are obtained by operation for hyperthyroidism and these far outnumber the reports on the results of treatment by radiation. Most of the surgical reports are made by surgeons connected with institutions in which goiter surgery is highly developed, and therefore these results, as far as operative mortality and recurrence of the disease and the incidence of other complications are concerned, are probably far superior to those which are obtained in general practice. Therefore the reports of the results which are obtained by operation may be said to represent the highest degree of operative skill and experience.

On the other hand, the results of the treatment of hyperthyroidism by radiation appear mostly in the radiological journals and therefore are seldom reviewed by the general reader. The reports of radiologists represent an average of what might be expected from radiation therapy because these therapists are rarely affiliated with institutions which have highly developed and special goiter clinics, and because they are from diversified localities, in many of which goiter surgery is probably not highly developed.

The failures of radiation therapy, like the failures of operation, may be attributed (1) to lack of cooperation on the part of the patient; (2) to coincident diseases such as cardiovascular complications; (3) to extreme toxicity. Another not infrequent cause of failure which may come under group 1 is undue haste and impatience when patients

do not show immediate improvement. It must be borne in mind that improvement is usually manifested very promptly after operation while the results of radiation therapy are somewhat delayed.

An extensive review of the literature shows that the average results which have been obtained by radiation therapy for hyperthyroidism may be arranged as follows:

	Per cent.
Cured and improved	75 to 80
Showing recurrences or unimproved	15
Mortality	5 to 10*

INFLAMMATIONS OF THE THYROID GLAND

Acute Simple Thyroiditis.—Acute inflammation of the thyroid gland is manifested by the usual symptoms of inflammation, namely rather rapid swelling, local heat, tenderness, pain, and fever. The process may progress to abscess formation. The treatment consists in the local application of cold and of small doses of roentgen rays which will have an analgesic effect and will shorten convalescence. If the inflammatory process has progressed to a preabscess stage the roentgen treatment will hasten the breaking down and drainage incisions may be made very promptly. Therefore roentgen treatment may be instituted with benefit at any stage of the inflammation, though it is hazardous to administer dosage of great intensity at one treatment.

Chronic Thyroiditis.—*Riedel's struma* or *ligneous thyroiditis* is a chronic inflammation of the thyroid gland which is manifested by a quiet painless swelling of fairly rapid growth. The gland is very hard and fixed. In about one half of the cases the condition is bilateral. The obstructive symptoms are prominent very early in the course of the disease. Because of the similarity of the signs and symptoms it is very difficult and sometimes it is impossible to differentiate this condition from malignant disease except possibly by the rate of growth. When a clinical diagnosis can be made, roentgen therapy is the preferred treatment. The intensity of radiation which should be applied is somewhat greater than that employed for acute inflammation; however, immediately after the treatment, swelling of the gland may

* The mortality rate shown in the above table includes all patients who have died of the disease after having been subjected to radiation therapy no matter in what condition they may have been when the treatment was administered. Thus it includes a large number of patients who were more or less moribund at the time or who had had postoperative recurrences or those for whom nothing else could be done.

occur which may be relieved by hot applications. When there is marked obstruction a tracheotomy may be necessary.

Tuberculosis of the Thyroid Gland.—This produces a more or less chronic inflammation of the thyroid which is seldom recognized clinically and is often difficult to diagnose even by means of microscopic sections. The pathologic process and its manifestations are the usual manifestations of tuberculosis. Tuberculous inflammation of the thyroid may involve adjacent lymphatics and other tissues and rarely may form a tubercular abscess. When tuberculosis of the thyroid is recognized it should be treated by small doses of roentgen rays as in the case of tuberculous lesions in other localities.

STRUMA LYMPHOMATOSA

This is a rare disease of the thyroid which is manifested by the presence of a large amount of lymphatic tissue in the thyroid along with some fibrosis and atrophy. Clinically there is a diffuse bilateral, quiet and rapid enlargement of the thyroid gland which in contrast to Riedel's struma or a neoplasm is not adherent. There are few symptoms and no evidence of hyperthyroidism or hypothyroidism but late in the disease some obstructive symptoms may develop because of fibrosis. The one patient (seen in 1924), I have treated, was diagnosed clinically as having an inoperable neoplasm of the thyroid but one year later in spite of intensive radiation the tumor had not decreased in size and the obstructive symptoms were somewhat increased. Subsequently an operation was performed and the true condition was recognized. It is probable that radiation treatment of this condition increases the fibrosis and from clinical evidences, at least, it is of no benefit.

It is recognized that struma lymphomatosa may develop into lymphosarcoma; when this occurs intensive radiation is indicated. In such cases radiation may result in relief or cure. Naturally the results which are obtained depend upon the type of neoplasm that is treated, as well as on the extent and duration of the disease and the presence of metastases.

MALIGNANT TUMORS OF THE THYROID GLAND

The treatment of a malignant tumor of the thyroid gland by radiation includes the use of roentgen rays and radium. There are individual indications for each, or for a combination of both, but there is no fixed rule which holds in every instance. Experience

and judgment are required in order to decide what method should be employed. Satisfactory results will be obtained from the treatment of most malignant adenomata and papillary carcinomata, but little can be expected from the treatment of scirrhous carcinomata or sarcomata.

Certain cases will be found which are obviously inoperable from the standpoint of surgical curability because of the size and extent of the tumor. In such cases treatment by radiation is indicated. If symptoms of tracheal pressure are apparent it is a wise precaution to perform a "decompression operation" or tracheotomy before radiation is instituted. The decompression operation consists in removing enough of the growth to relieve tracheal obstruction. In any case in which irradiation is being applied, a tracheotomy may be necessary because of the resultant edema and swelling which make it difficult for adequate respiration. Therefore, such patients should be under close observation for at least three weeks after the application of radiation.

For those patients in whom the condition is obviously inoperable the treatment should consist in the implantation of radium (interstitial radiation) preferably with radon gold seeds and occasionally with needles. Necessarily this is an operative procedure which is best carried out by making the usual incision through the skin, and carrying the dissection to the thyroid gland when implantation can be made into the diseased area under direct vision. The number of seeds or needles, or the dose which will be necessary depends upon the size and conformation of the diseased area so that no fixed dosage can be established. Of course care should be taken not to puncture the large thyroid vessels or to place large radium containers immediately adjacent to them or to the trachea or esophagus unless these organs are involved. In about three weeks after the radium reaction has taken place the area should be thoroughly irradiated with roentgen rays.

When an unsuspected malignancy is encountered at operation for a supposedly benign thyroid disease, radon seeds or needles should be used at once or as soon as practicable and should be followed by treatment with roentgen rays.

Roentgen treatment alone is sufficient to relieve many inoperable thyroid malignancies (about 20 per cent will remain cured for five years). However, it is good judgment to apply as much radiation by radium and roentgen rays together as the area will tolerate safely.

The **roentgen technic** which has proved useful in our experience consists in dividing the cervical area into two or three fields including the upper mediastinum. We have found that irradiation of this latter field is important in order to take care of metastases or extensions into this area which frequently cannot be discovered clinically or radiographically. The cervical, thyroid and supraclavicular areas should be cross-fired from the right and the left side, as well as posteriorly, the trachea being carefully excluded from the field unless it is involved by the disease process. It is our experience that radiation may produce ulceration within the trachea with subsequent healing, but the skin of the neck is comparatively sensitive and therefore it is wise to limit the roentgen intensity applied at the first treatment to from 800 to 1000 roentgen, to include backscattering with short wavelengths (0.16 angstrom). We have found that this intensity may be safely applied again within three months; however, a third application is seldom advisable and should not be considered within less than eight months.

The natural duration of life for a patient suffering from malignant disease of the thyroid is about eighteen months. It is our experience that among cases which are definitely inoperable about 30 per cent are definitely relieved and their life period extended to three years. Fortunately the largest group of cases, those of malignant adenomas, seem to be comparatively radiosensitive so that when operation followed by radiation can be employed from about 25 to 35 per cent live for from three to five years.

Metastases and Recurrences.—I have called attention to the fact that occasionally one sees a growth which has developed following thyroidectomy for a supposedly benign condition and that one must suspect the presence of a neoplasm. However, it is conceivable that normal thyroid tissue may be stimulated to develop under certain physiologic conditions. We have also observed a few cases with obvious malignancy of the thyroid (malignant adenoma) in which adenomatous tissue seemed to grow after the neoplastic activity had apparently ceased. The condition is manifested by small local nodules within the thyroid area which, when excised, present more or less the morphology of the previous neoplasm. In such cases distant metastases do not occur. This peculiar circumstance has raised the question in our minds as to whether this is a true recurrence of the malignancy or is a physiologic answer to demand of the organism for more thyroid secretion.

When an obvious local recurrence of a neoplasm occurs in spite of radiation it should be removed by as wide an excision as possible. This may also be said of a single distant metastatic lesion as, for example, in bone; however, the occurrence of such a single metastasis is very rare indeed.

Metastases from neoplasms of the thyroid may occur in almost any tissue of the body; however, they are manifest and most frequently observed in the lungs and bones. They have the same morphological structure as the parent tumor. The malignant adenomata are more prone to be the cause of distant metastases than are the other types of thyroid neoplasms because the former invade the blood vessels and form thrombi, and detached cells lodge as emboli after passing through the circulation. This explains why the most frequent locations of metastases are the lungs and long bones. Therefore it behooves a surgeon who operates upon a malignant thyroid to deal gently with the tissues in order not to dislodge cells which lie within the blood vessels. Unquestionably metastases have occurred from harsh manipulation of the thyroid, not only at operation but also during clinical examination by too vigorous palpation.

In the literature of the past there are reports of a sort of so-called "aberrant thyroid" discovered in various distant tissues, the structure of which has the same morphological characteristics as a benign adenomatous gland. In many instances these thyroid nodules were undoubtedly metastases from unrecognized malignant adenomata. In such cases, therefore, the thyroid gland should be carefully searched as a primary source of the neoplastic tissue when unexplainable pulmonary or bone lesions are discovered.

Scirrhous and papillary carcinomata and fibrosarcomata seldom metastasize except to the adjacent lymphatics. They slowly involve the local tissues and usually destroy life before distant metastases occur. Sometimes, however, they invade the mediastinal lymphatics from which they extend out into the pulmonary tissues.

Carcinoma-sarcomata and lymphosarcomata metastasize but are usually so rapid in their growth that the patient succumbs before the metastases are manifest.

When thyroid metastases are discovered they should always be irradiated by radium, roentgen rays, or both, according to the location and the indication in the individual case. They are as amenable to treatment as is the parent tumor. The treatment is usually only palliative but from an economic standpoint it is worth while.

CHAPTER XXVI

THE PREOPERATIVE MANAGEMENT OF PATIENTS WITH HYPERTHYROIDISM

JOHN W. SHIRER

THE preoperative management of any surgical condition of necessity cannot be so stereotyped as to apply to any large group of patients, particularly those in whom the clinical syndrome of hyperthyroidism is present. Rather, the preoperative treatment must be planned for the individual patient bearing in mind such factors as the severity of the disease, its duration, the associated organic changes presented, and the psychic make-up of the individual. Rational preoperative treatment must be practical and must be readily available. It must in no way jeopardize, but rather must better the patient's general condition and promote his peace of mind.

It is obvious that the patient suffering from only a moderate degree of hyperthyroidism will require only a minimum amount of preoperative preparation. There is a special group of cases, however, which we can call the "bad risk group," in which a more careful analysis of the individual must be made in order to insure a smooth postoperative course.

For all patients with hyperthyroidism, whether or not they are in the "bad risk group," the following conditions should be assured:

1. **Rest.**—To make sure that the patient shall have sufficient physical and mental rest, absolute rest in bed should be insisted upon, and this rest must in no way be disturbed by the hospital routine. Records are valuable but the patient's rest is more valuable.

2. **Environment.**—The environment of a patient suffering from hyperthyroidism should be such as to induce his confidence in all those who come in contact with him. Cheerful surroundings are made possible only by the *esprit de corps* of the institution. A spirit of enthusiasm, willingness, and cheerfulness should be manifested by all those who come in contact with the patient. Perhaps no patient is more emotionally unstable than the patient with hyperthyroidism.

Because of this fact every attempt should be made to allay any fear, worry, or anxiety concerning the operation itself. The house surgeons should recognize the fact that this operation is perhaps the most vital experience the patient has ever had. The many questions asked by the patient should be answered intelligently but diplomatically.

The average period of preoperative hospitalization for patients with hyperthyroidism is from ten to twenty-one days, depending upon the patient's response to preoperative therapy. To secure the maximum benefit from Lugol's solution a period of from seven to fourteen days is necessary, but whether or not Lugol's solution is used, no patient with hyperthyroidism should be operated upon immediately after his admission to the hospital.

No preoperative management is complete without a careful and searching analysis of the symptoms referable to the various systems. This procedure has an important bearing upon the postoperative course, a fact which is exemplified by our findings in a study of a group of patients over fifty years of age. Every system should be so analyzed as to identify to the examiner the salient points in the complete medical history of the case. This is particularly true of the pulmonary or respiratory system, in the analysis of which we may find a history of repeated infections of the upper respiratory tract, of repeated attacks of influenza, of pneumonia, of a productive cough which is worse in the morning, and of inability to cough and produce sputum. The genito-urinary system should be carefully studied, especially in the case of male patients as prostatic hypertrophy may be present without producing marked obstructive symptoms. A searching inquiry as to the personal history may reveal attacks of acute exanthemata or of infectious diseases, especially scarlet fever, as a result of which the renal function has become definitely impaired.

Following such a study of all the systems, a careful analysis of the laboratory data is of paramount importance as these findings indicate the measures to be taken for immediate elimination of the complicating factors; at least, they aid in the direction of the postoperative management. A careful analysis of the symptoms referable to the various systems and of laboratory data makes it possible to prognosticate the type of postoperative convalescence.

The following laboratory data are desirable: Basal metabolism estimation; a roentgenographic examination of the chest to rule out substernal or intrathoracic extension of the goiter, tracheal compression or deviation of the trachea, evidences of old pulmonary fibrosis

or chronic bronchitis, and inactive pulmonary tuberculosis; electrocardiographic tracings in the presence of any cardiac irregularities; determination of renal function by blood urea estimation, phenolsulphonephthalein intravenous test, and the Mosenthal test, the last being of special importance in the case of patients over fifty years of age.

Diet.—The object of any phase in the preoperative management should be to diminish the drive or metabolism of the individual. This applies especially to the diet, which should be so planned as not only to diminish metabolism but also to furnish sufficient calories for the maintenance of the body weight. An analysis of the various types of food shows that the carbohydrates will furnish the individual with an adequate supply of food and with the least amount of metabolic disturbance. Various workers have indicated that a high caloric diet is indicated in cases of hyperthyroidism and many have described certain types of diet. The diet employed in the Cleveland Clinic furnishes between 3500 and 4500 calories per day, mostly from foods rich in carbohydrates, sufficient protein being given to maintain the protein balance. The most highly organized proteins, however, are eliminated from the diet.

Fluid Balance.—In the presence of hyperhidrosis, diarrhea and increased urinary output, which are characteristic symptoms of hyperthyroidism, the maintenance of the water balance is of special importance. This is accomplished by forcing fluids if necessary and by maintaining a fluid intake of between 3000 and 3500 cc. daily. The fluid intake can be maintained by the use of citrous fruit juices to which glucose has been added.

Care of the Bowels.—The care of the bowels is a very difficult problem in any case of hyperthyroidism. It has been shown that a definite hypermotility of the entire gastro-intestinal tract with spasticity of the colon is associated with hyperthyroidism. In most patients with hyperthyroidism the barium may be seen in the sigmoid and even in the rectum three hours after its ingestion. This marked hypermotility associated with a spasticity of the colon may explain both the diarrhea and the constipation which characterize different cases of hyperthyroidism. In view of these observations, the administration of cathartics would seem to be contraindicated in the average case. In many cases the administration of cathartics has caused diarrhea. We have found that when the hyperthyroidism is controlled, the hypermotility of the gastro-intestinal tract is diminished and the

spasticity of the colon is likewise diminished. This finding indicates that the logical and rational way of caring for the bowels in a case of hyperthyroidism should be along entirely different lines from that ordinarily practiced in health. Often a course of treatment with paregoric together with the administration of a small amount of belladonna will sufficiently slow the peristalsis to relax the spasticity of the colon so that the diarrhea will cease and there will be daily normal evacuations of the bowels. It would seem that this method of clearing the bowels should be considered first rather than a resort to the use of any kind of cathartic. A small clear-water or saline enema perhaps is the method of choice for the relief of constipation if the suggested management fails to produce satisfactory results.

General hygienic measures should be carried out as in the preoperative management of any surgical case. The care of the teeth and oral hygiene are of paramount importance. This is particularly true of cases in which there is a marked pyorrheal infection of the gums. These patients should be examined by the dentist for the application of temporary prophylactic measures. The patient should be instructed to brush his teeth after each meal.

Therapy.—The preoperative medications are relatively few in number. Lugol's solution is administered daily to every patient with definite hyperthyroidism from the day of admission to the day of operation. In cases of adenomatous goiter in which there is no evidence of hyperthyroidism at the time of examination, Lugol's solution is not administered unless the patient's history indicates that there have been definite cycles of hyperthyroidism. The dose employed is 15 minims, given three times a day, grape juice being used as a vehicle.

Sedatives.—Many patients require sedatives for the first few days after their admission to the hospital until they become completely orientated. Much has been written about the use of various barbituric acid compounds in the preoperative care of patients with hyperthyroidism. Luminal at bedtime, in doses of $1\frac{1}{2}$ grains, allonal at bedtime, in doses of $1\frac{1}{2}$ grains, luminal sodium given intramuscularly in doses of 2 grains, and occasionally veronal at bedtime in doses of 5 grains have been employed. We have observed, however, that the continuous use of the barbituric acid compounds over a prolonged period of time produces a number of discouraging symptoms particularly in aged patients in whom one often sees the development of a definite intolerance to these drugs with the appearance of psychoses.

It has been our practice, therefore, to limit the administration of allonal and luminal to the first three or four days after admission. The complications which may arise following the use of the barbituric acid compounds should be constantly kept in mind. We have observed the typical rash in many cases, psychoses in a number of cases, and acute urinary suppression in several others following the administration of these drugs. If the patient's hyperthyroidism is severely active, morphine and hyoscine are the drugs of choice. Sufficient sedatives should be used to insure the patient's having the necessary amount of rest.

Digitalis is used primarily in all cases in which there is evidence of myocardial weakness. It is of questionable value in cases of hyperthyroidism without myocardial insufficiency. In very severe cases of auricular fibrillation, digitalis is used. Tincture of digitalis is given in doses of 2 cc. every four hours for six doses, following which 1 cc. is given three times daily. To obtain the maximum effect of the drug the Eggleston method is used. In cases in which there is nausea and vomiting, the digitalis is administered per rectum, or digifolin is given subcutaneously, in doses of one ampule.

Transfusion.—The patient who is emaciated, prostrated, restless, even delirious, whose extremities are swollen, whose abdomen is distended with fluid, whose heart and lungs are embarrassed by the presence of free fluid in the chest, whose heart is dilated to the point of decompensation, whose kidneys are failing, is often strikingly benefited by the transfusion of blood. The transfusion of whole blood carries needed oxygen and fluid to the cells by the most direct route and restores to the normal status the altered serum-albumin and serum-globulin. Not only in these extreme cases is this procedure of value. It should be employed in every case in which there is any doubt whatever as to the ability of the patient to withstand the operative procedure. That is, the transfusion of blood both before and after operation should be employed in advance of the emergency.

CHAPTER XXVII

THE RÔLE OF THE NURSE IN THE PREOPERATIVE AND POSTOPERATIVE CARE OF THE PATIENT WITH HYPERTHYROIDISM

ABBIE PORTER

SINCE patients with hyperthyroidism are in a very abnormal mental state—frightened and apprehensive, the first duty of the nurse is to gain their confidence and to reassure them in every possible way.

The general preoperative routine to which all patients are subjected on admission to the hospital must, of course, be applied to patients with hyperthyroidism, but special management is required so that the various examinations will scarcely be obvious to them. Thus, as a rule, patients are weighed, measured, et cetera, as soon as they enter the hospital. The patient with hyperthyroidism, however, is put to bed at once and at any time during the first day, as favorable opportunities are presented, the weight, temperature, pulse rate, respiratory rate, and blood pressure, both diastolic and systolic, are taken.

As soon as these patients have been seen by the resident surgeon, a special preoperative routine is instituted which consists chiefly in rest and quiet in bed. Absolute rest in bed is essential. In addition to the daily bath the patient is given a sponge bath each evening. Sodium bromide (20 grains) is given in the evening to insure a good night's rest, provided no other sedative has been ordered. A high carbohydrate diet is given and tea, coffee, and highly seasoned foods are eliminated from the diet.

Sodium bicarbonate ($4\frac{1}{2}$ grains) is given in a capsule every morning and evening. On the evening before and on the morning of the operation, thyroid extract (2 grains), is placed in the capsule so that it will not be noticed by the patient.

The best policy for the nurse to follow during the first few days is to say as little as possible; first, in order to avoid the possibility

of contradicting anything which may have been said at the doctor's office previous to the patient's admission to the hospital; and second, because it is always wiser to study a patient's temperament before talking much. The first few days should therefore be spent in observing the patient, noting just where to break away from the regular routine; just what to concede. The nurse must bear constantly in mind the peculiar need of these patients for comfort and peace of mind. Seemingly trivial things annoy patients with hyperthyroidism. They are often irritated by the operating-room clothes and in such cases they are not put on until the operation is completed and the dressings are applied and not at all if the patient objects.

Each morning an inhalation "treatment" is given by the anesthetist with the nitrous oxide anesthesia apparatus. This is explained as part of the treatment.

One attractive and seemingly tractable young girl absolutely refused to cooperate with the anesthetist when the latter came to administer the inhalation "treatment." Baffled by this unexpected action, the nurse studied the patient in order to discover the difficulty and found later in the day that this girl's hair was her special pride and the fact that it was not becomingly arranged in the morning had made her unreasonable. On the next morning her hair was arranged as she desired and no further difficulty was encountered.

As stated above, during the preoperative period absolute rest in bed is required. The patient is not awakened for medication and the number of visitors is limited. Temperature, pulse rate and respiratory rate are taken every four hours. The maximum systolic and minimum diastolic blood pressure is determined daily. Fluids are forced until the daily fluid intake is between 3000 and 4000 cc. In severe cases glucose and orange juice are given. Lugol's solution, 1 cc. in grape juice, is given three times a day until the day of operation, and immediately after the operation, 3 cc. in milk is administered by rectum, and 1 cc. by mouth and 2 cc. by rectum is given at 6 P. M. on the day of operation.

On the morning of operation the regular routine is not broken. A capsule containing morphine and atropine is given by mouth before the operation which is performed in the patient's room.

All essential articles are assembled in the corridor outside the room (see Chapter XXVIII). The anesthetist who has given the inhalation "treatments" enters with the nurse in charge and explains that a treatment is to be given (see Chapter XXIX). After the

patient's eyes have been covered with a cold compress and the anesthetist has signalled that the patient is ready, the necessary articles are brought into the room (Fig. 113).

Just before the close of the operation the patient's nurse should be in the room ready to remove everything which was not there before the operation and to have the shades drawn so that the room will be darkened. A cold compress is placed over the forehead and eyes and the patient is placed in a comfortable position with the back rest elevated.

The postoperative care then begins. A hypodermic injection of morphine sulphate ($\frac{1}{6}$ grain) is given and 2000 cc. of normal saline

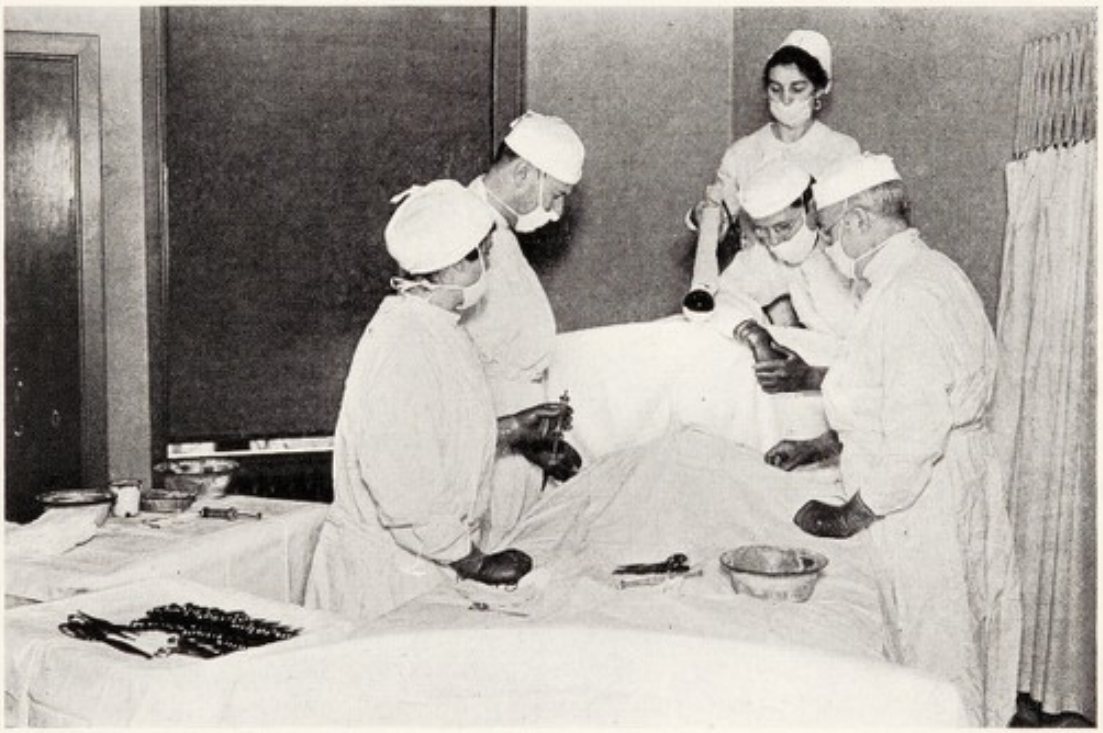


Fig. 113.—Thyroidectomy in patient's room.

solution is given by hypodermoclysis. The hands and face are sponged and a general sponge bath is given as restlessness may demand. The temperature, pulse rate, and respiratory rate are watched carefully, the temperature being taken every two hours and any rise reported immediately to the resident surgeon. Six or nine ice-caps are placed round the patient if a temperature of 101° F. or over is reached. If the temperature rises to 103° F. the patient is put in an ice-pack under the supervision of the ward surgeon. While the patient is in the pack the pulse and respiratory rates are recorded every fifteen minutes and any increase or irregularity is reported at once.

The blood pressure is taken every four hours under the direction of the ward surgeon. Sufficient sedatives are given to keep the patient mentally and physically quiet. Intravenous medication may be required but it is given only on the order of the resident surgeon.

An ice-cap is placed over the heart unless an order to the contrary is given. Inhalations may be used if they add to the comfort of the patient.

An emergency tray set up for tracheotomy is kept ready for use but not in the patient's room. An oxygen tent also must be ready for use. The blood of all patients is grouped upon their admission to the hospital and the supervising nurse must have a donor ready, as a transfusion may be required.

To relieve postoperative nausea, 1 ounce of a solution of sodium bicarbonate with bismuth may be given every half hour. If there is no nausea or as soon as nausea ceases orange juice with glucose is given to the patient. A little lemon juice may be added to make the mixture more palatable. During the day of operation 500 cc. of orange juice is given and 500 cc. during the following night. The administration of this mixture is continued until the patient is able to take other food. The daily fluid intake should be from 2500 to 3000 cc.

During the postoperative period the number of visitors is restricted as before operation. The patient is kept in bed until 10.30 A. M., she must return at 9 P. M. and must rest in bed between 12 and 5 P. M.

The successful care of the patient with hyperthyroidism requires the closest cooperation between the surgeon, the resident staff and the nursing staff. The private nurse in charge of such a patient must be unusually tactful and resourceful, for mental and physical rest are as essential for the cure of hyperthyroidism as is the operation itself.

CHAPTER XXVIII

THE RÔLE OF THE OPERATING-ROOM NURSE IN OPERATIONS ON THE THYROID GLAND

EMMA M. BARR

THE duties of the nursing staff during an operation on the thyroid gland are many and varied. When a number of operations are done in immediate succession it is the responsibility of the head nurse so to outline the nursing procedure as to facilitate an uninterrupted schedule. When, as in the Cleveland Clinic Hospital, these operations are performed on the thyroid gland in the patient's room, the duties

Fig. 114.—Supply table set up for operation in patient's room.

of the head nurse become more complicated. The patient must be kept unaware that an operation is to be performed, but no routine measure for the safety of the patient or the convenience of the surgeon can be neglected.

To accomplish these two ends the following procedures are necessary:

All preparations for the operations are made in the operating room and everything is in readiness before the first operation is started. All

supplies necessary for all the thyroidectomies to be performed during the morning are assembled and set up on the tables (Fig. 114) and the instrument trays (Fig. 115). These tables and trays are set up by graduate "scrub-up nurses" with the assistance of unsterile graduate nurses and are then sent to be placed in the corridors outside the rooms in which the operations are to be performed. Sterile operating gowns and sterile gloves also are sent to the various floors that they may be at hand for a change after each operation. A dressing carriage with the additional supplies that may be required is prepared and is taken to each room by a graduate nurse as the operating schedule progresses. It is very essential to have sufficient supplies on hand in order to avoid the necessity for a return to the operating room—a needless waste of time and energy.

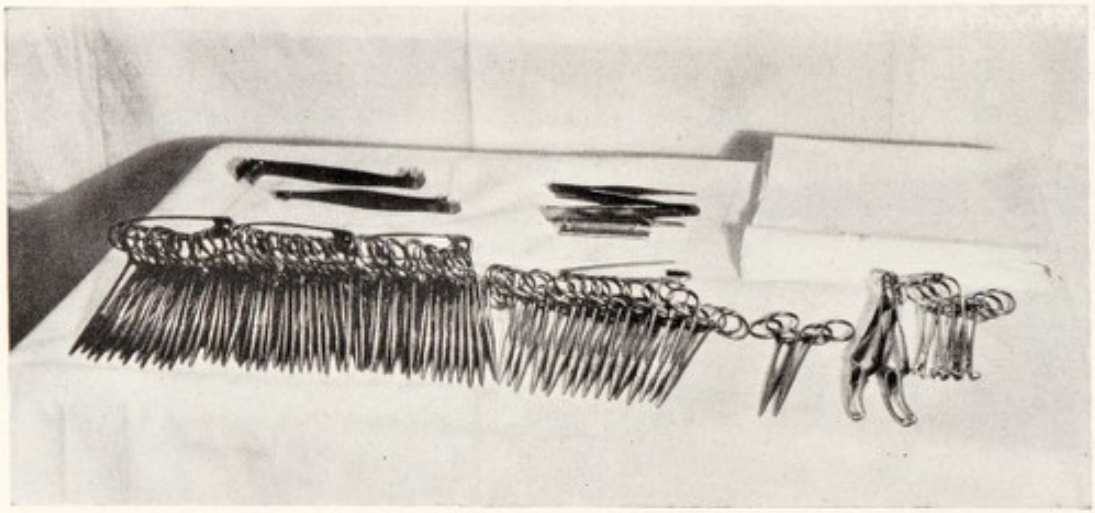


Fig. 115.—Instrument tray set up for operation in patient's room.

An unsterile nurse is present at every operation and her duties are very important. She must be alert to see that the table used by the "scrub-up nurse" is well supplied with novocaine, sponges, catgut; she must have tracheotomy tubes sterilized and ready to give to the "scrub-up nurse" should an emergency arise; she must watch the instrument tray closely to see that enough instruments, especially hemostats, are available. In different operations the number of hemostats required varies considerably, the average number used being about sixty.

Operations on the thyroid gland vary considerably. Sometimes only one and sometimes both lobes are removed. Sometimes the wound is dressed open and the unsterile nurse must have neutral acriflavine gauze (1 : 1000) ready with the other dressings.

The efficient performance of a thyroidectomy in the patient's room requires close cooperation between the operating-room staff and the floor nurses.

It is the duty of the latter to prepare and have ready outside the patient's room the extension light (Fig. 116), ether, iodine (2 per cent), alcohol (70 per cent), ice compresses, a goiter pillow to place under the patient's neck, blocks to be placed under the wheels of the bed to keep it from moving, and a small bedside table on which to set the instrument tray. When all these articles are at hand, only a minute or two is required to place them in the patient's room after the anesthetist has signalled that the patient is ready.

After each operation is completed the operating-room orderlies promptly return the used tables to the operating room. Thus by the time the operations in the rooms have been completed all operating-room supplies have been returned to the operating room. The instruments are immediately washed and sterilized by the instrument nurses so that when the doctors and nurses return to the surgical floor everything is in readiness to carry on the operations scheduled for the operating rooms.

The "scrub-up nurse" plays a very important rôle in the performance of a thyroidectomy. She is expected to anticipate the needs not only of the operator but also of his assistants. In this clinic a spirit of complete cooperation has been developed among the surgeons, the assistants and the "scrub-up nurses." This cooperation is of vital importance to the operating-room nurse whose duty it is to supervise all preparations for the operations, bearing in mind always the necessity for shortening the duration of the operation especially in severe cases of hyperthyroidism.

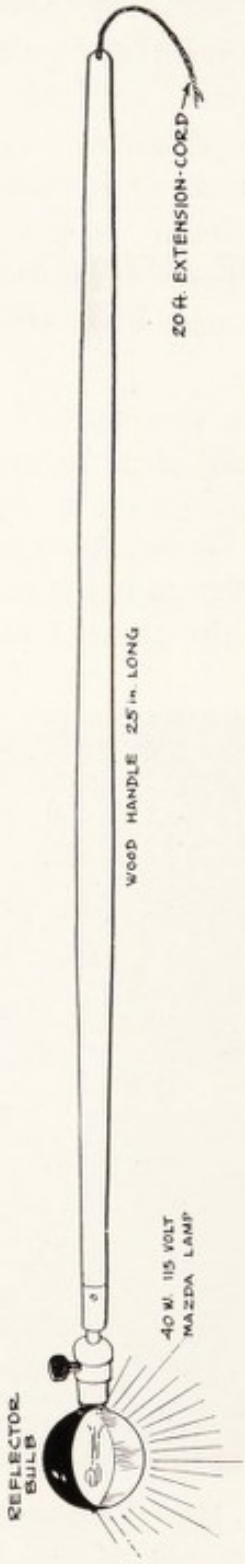


Fig. 116.—Extension reflector for illumination of operating field.

CHAPTER XXIX

THE ADVANTAGES OF NITROUS OXIDE-OXYGEN ANALGESIA FOR OPERATIONS ON THE THYROID GLAND

LOU E. ADAMS

IT has been conceded for some time that nitrous oxide-oxygen analgesia is the anesthetic method of choice for all types of operation on the thyroid gland. In particular the more serious the physical

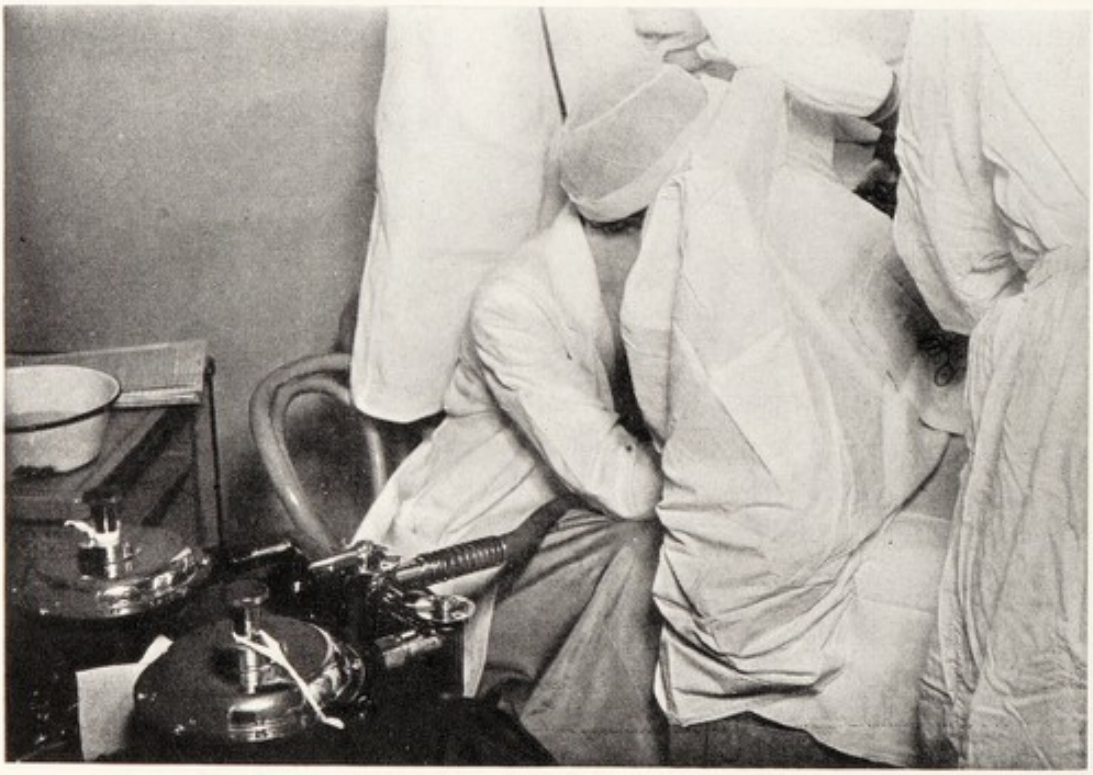


Fig. 117.—The position of the anesthetist and arrangement of apparatus for operation in patient's room.

condition of the patient the greater is the necessity for analgesia which obviates the mental anxiety of the patient without interfering with any vital function.

COLLOID OR SIMPLE GOITER

The colloid goiter may be removed in the routine surgical manner in the surgery, if the general condition and mental attitude of the patient present no contraindications.

The patient may be carried to complete surgical anesthesia, if it seems advisable, for the difficult part of the dissection. At any time the stage of analgesia may be restored with ease to determine the condition of the voice. Either the anesthetic or the analgesic stage may be produced at any moment according to the demands of the operation.

The possibility of compression and collapse of the trachea must be borne in mind by the anesthetist during the dissection of the gland. The use of oxygen under pressure will overcome most of the resultant respiratory trouble unless the obstruction becomes complete. An air-way is always kept in readiness and inserted if necessary after which oxgyen is again given under pressure.

HYPERTHYROIDISM

The anesthetist must always bear in mind that patients with hyperthyroidism are hypersensitive to every stimulus and that fear is ever present. Therefore, the first aim of the anesthetist is to establish a friendly relation. As these patients are always in the hospital for a week or more before the operation, an attempt is made during that time to establish a suitable line of approach for each. If the anesthetist has not visited the patient before operation it is necessary to analyze her reactions as soon as the introduction is made. Suggestions for her comfort and welfare make a good lead. The operation should never be spoken of but the patient should be advised that the inhalation of oxygen will be beneficial. A subject of special interest to the patient is sought—a hobby, her family or business, and conversation is directed in such a way as to make the patient feel the interest of the anesthetist in all that pertains to her.

As soon as the position of the head is arranged for a good exposure of the neck, a cold compress is placed over the eyes and nitrous oxide-oxygen analgesia is started. It is fortunate that during the first five minutes nitrous oxide-oxygen exhilarates most people and puts them in a very cooperative state of mind so that it is easy to gain their confidence. While the novocaine is being injected much encouragement is needed. It may be necessary to induce a little deeper stage of anesthesia for the first few novocaine injections in order that the morale of the patient may be sustained.

In some of the more difficult cases inhalations of oxygen are given to the patient daily for some days previous to the operation in order that the patient may become accustomed to the position of the neck, the face mask, and the cleansing of the neck. The first time this is tried the pulse rate may be increased, but later no change is noted. This maneuver reduces the excitement on the day of operation.

We try to avoid the excitement stage of anesthesia. To avoid commotion and confusion all noises including talking are eliminated. Often the smallest amounts of nitrous oxide will cause excitement and oxygen alone must be used and it may be necessary to resort to the so-called "vocal anesthesia."

We depend upon the facial expression and eyes to a great extent for these supply the first indications of mental disturbance. Sometimes the pulse and respiratory rates may not be affected but the morale of the patient is poor. If this poor morale continues it is reported to the surgeon. Often a word of encouragement from him is a help or it may be wise to change the surgical procedure, to deepen the anesthesia, or to discontinue the operation. Each patient must be treated individually.

The object of analgesia is to get the patient in a receptive mood, to prove to her that you are there for her comfort and that you will do everything possible for her—at all times encouraging, cheering, sympathizing, and agreeing, all but crying with her in order to gain control. The pulse and respiratory rates are often changed by the mental state. A close watch is kept to avoid mental disturbance.

If there has been some excess bleeding the surgeon will ask the patient to cough as this is a good test of hemostasis. This offers another argument for the superiority of analgesia to anesthesia.

Analgesia alone or local anesthesia alone is not sufficient but the combination is ideal. One takes care of the physical state, the other of the mental state.

It must be borne in mind by everyone concerned in the operation that the state of analgesia cannot be successfully established by the anesthetist alone—the cooperation of the entire organization is necessary.

INTRATHORACIC GOITER

Nitrous oxide-oxygen analgesia is the anesthetic method of choice for the removal of an intrathoracic goiter as the danger signals may be recognized at once if the patient is able to converse and to respond

to suggestions. Thus, if considerable mucus is present, the patient is conscious enough to clear the throat thus avoiding the necessity for aspiration. The chief difficulty in these cases is the interference with respiration and when this becomes marked the administration of oxygen under pressure gives good results.

Thus, under nitrous oxide-oxygen analgesia, at no time is the patient in danger of respiratory failure. With the cooperation of the patient the situation is always under control.

THYROIDECTOMIES IN CHILDREN

The administration of analgesia to children requires a great deal of patience and much preliminary work on the part of the anesthetist.

As an example of the difficulties that may be encountered and the way in which they can be met, the case of a child four years of age may be cited. This child was admitted to the hospital with a pulse rate of 160. She was a physical wreck and was afraid of everyone, clinging constantly to her mother or grandmother. The first visit of the anesthetist was very discouraging but repeated visits were made, until a source of interest was established. It was discovered that the child was delighted with paper dolls cut from colored paper. We played with such dolls for some days and then brought in balloons which pleased her. From these balloons to the gas machine with its rubber rebreathing bags was an easy step. These bags were dilated and collapsed by exhalation and inhalation and after two weeks of labor and pleasure came the test with the trial ligation. By this time confidence and friendship had been established and the child would stop any play in order to blow up the "balloons."

On the day of the operation a small amount of nitrous oxide was added to the oxygen in the bags until the little patient was in a dazed condition, when she was placed in position and the novocaine block was established. As soon as this was done the child was brought back to the talking stage and the ligation was performed. Every trace of the procedure was removed, the mother came in and the anesthetist went out. The child had been warned against falling out of bed. To account for her discomfort after the operation she was told that she had fallen out of bed. That afternoon the anesthetist went back to call and took the machine so that the child could blow up the "balloons." She did this gladly and at no time did she connect the anesthetist with her "sore neck." The same procedure was repeated for the second ligation and for the lobectomy with the same

results. After three months the patient returned for a second lobectomy in a much improved condition. She remembered the anesthetist as her friend and playmate and the "balloons" were again given to her. This time the gas machine was not used as frequently as it was not such a novelty.

On the day of the last lobectomy the administration of the nitrous oxide-oxygen was started while the patient was sitting on her mother's lap; first the mother blew into the machine and then the child. When a sufficiently dazed condition was induced the procedure was as before. These four operative procedures were all done with the patient under analgesia. She talked and sang all the time. Sometimes a little deeper stage of anesthesia was induced as when there was to be a pull on the gland but at no time was the patient completely anesthetized.

Another child of twelve years was persuaded to inhale the oxygen in order to have red lips like the adults she knew.

The real secret of the successful administration of analgesia to children is to be well acquainted with their likes and dislikes, to keep them interested, and to make it a game. Often gifts will help, and they are well worth while when one sees the pleasure the children get from them. Any promise made to these children must be scrupulously kept. The cooperation of the nurse in charge is a great help. The plan of procedure in each individual case and the part the nurse is to play should be explained to her. Haste is prejudicial. Each child must be studied first and the familiarity with the procedure worked up gradually.

CONCLUSION

In a case of hyperthyroidism the patient is in an extremely nervous and apprehensive condition. A little tact on the part of the anesthetist will save much trouble. Nitrous oxide-oxygen analgesia offers the best anesthetic method for all goiter operations in both adults and children.

The outstanding characteristics of analgesia are the following:

1. It provides perfect safety and protection.
2. It is pleasant to take.
3. It covers mental anxiety.
4. It gives no bad after-effects.
5. The internal respiration is not disturbed.
6. Oxygen under pressure may be given at any time.
7. It enables the surgeon and the anesthetist to cooperate at all times.

CHAPTER XXX

LIGATION

GEORGE CRILE

A MOST searching examination into the end-results of our operations upon the thyroid gland has convinced us that ligation plays a vital rôle in selected cases. It would be easy enough to refuse operation in the case of a very bad risk on the ground that because of broken compensation, edema, ascites, pleural effusion and an extremely emotional state, there could not be enough possible gain to warrant the procedure. On the other hand, the most extreme case is most in need of help, even though final recovery seems almost past belief.

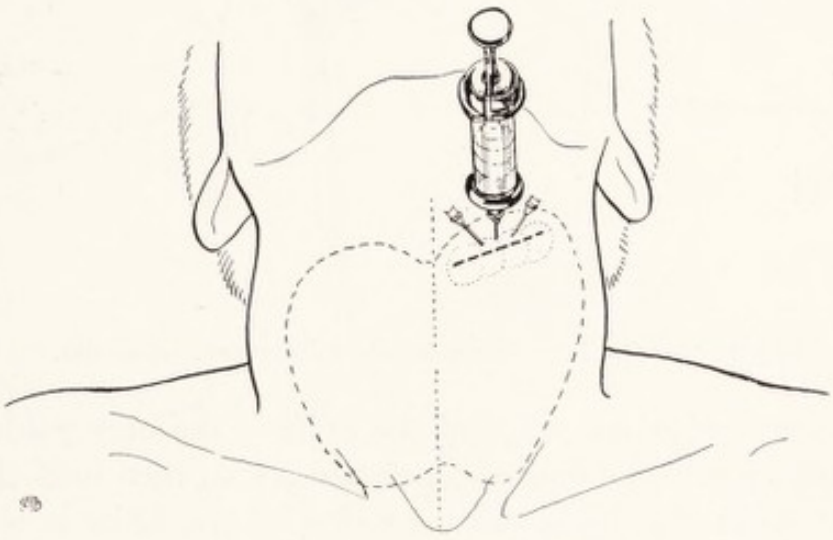


Fig. 118.—Ligation of superior thyroid artery. Infiltration with novocaine.

However, we have a number of such patients who are living useful lives many years after operation. If the patient has the desire to make a courageous effort to hold on to life, the surgeon should be no less courageous.

The indications for thyroidectomy are based entirely on individual experience. Every surgeon soon discovers for himself which patients he feels will be cured. In case of doubt as to the outcome of a thy-

roidectomy a trial ligation is indicated. We perform this trial ligation under local anesthesia with the patient in bed.

The skin and all the tissue overlying the upper pole are infiltrated and then the needle of the syringe is passed into and around the pole, a stream of novocaine being emitted as the needle penetrates this territory (Fig. 118). The needle, of course, is guided away from the great vessels. The first puncture is made with a very small needle which is replaced by a large one after the skin is infiltrated.

After the infiltration an incision is made through the skin parallel to the folds in the neck, the flaps being under-cut for a short distance upward and downward just enough to allow for a vertical incision through the platysma and the cervical fascia (Fig. 119). Once the

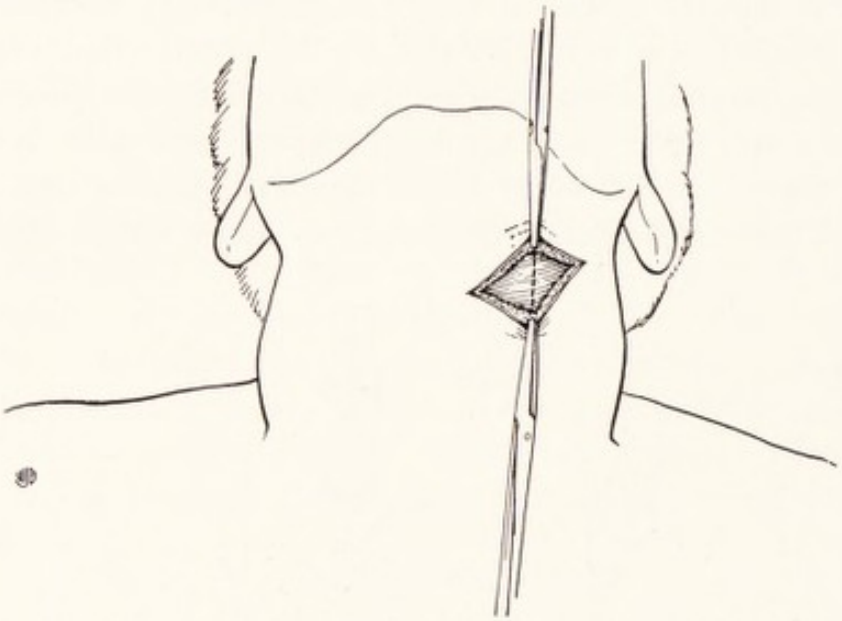


Fig. 119.—Ligation of superior thyroid artery. Incision.

skin has been incised the edge of the knife is the only guide in the further dissection. The operator feels the fascia, then feels the knife divide it. After the fascia has been divided the knife is laid aside and a pair of forceps introduced and opened to widen the wound sufficiently for the introduction of the blade of the special retractor. The assistant then inserts a retractor on the opposite side and with blunt dissection separates the fibers of the anesthetized muscle (Fig. 120). The deeper planes are exposed successively until the glistening capsule of the thyroid gland is reached.

The superior thyroid artery, or at least the anterior branch of the first bifurcation, usually lies at the bottom of the wound. This vessel with some surrounding tissue is grasped with the forceps and

the mobility of the upper pole is tested. At this point a specially made needle is used which has a full curve and a round, not a cutting edge, and a shank so strong that it will not break while being passed

Fig. 120.—Ligation of superior thyroid artery. Separation of longitudinal fibers of muscle with hemostat.

around the deeply placed artery (Fig. 121). The needle must be just large enough to be passed around the upper pole and maneuvered until it emerges at the end of the exposed gland. The purpose of

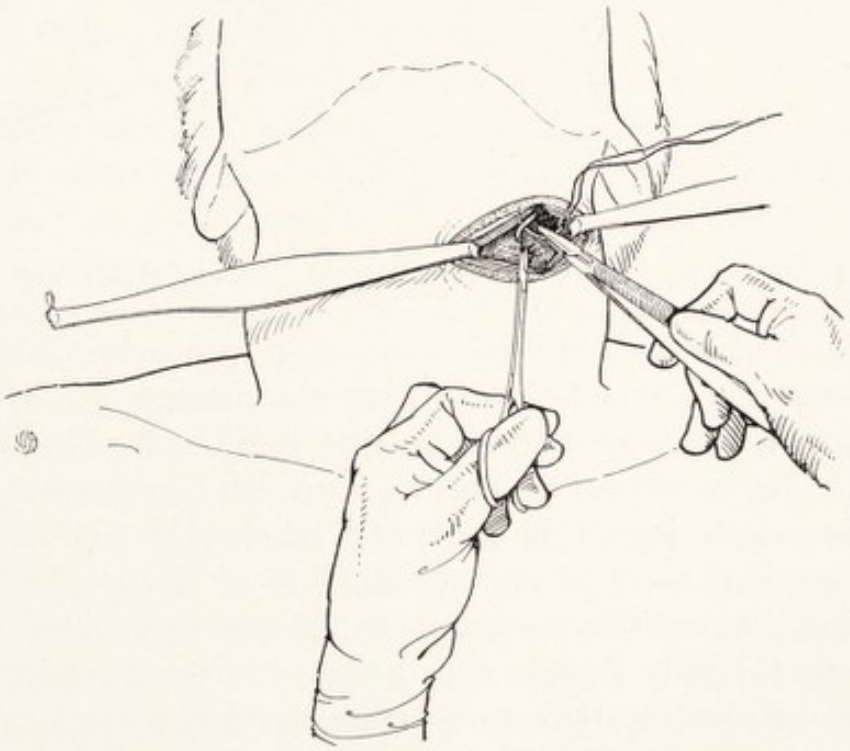


Fig. 121.—Ligation of superior thyroid artery. Passing of ligature around artery.

the needle is twofold: Less dissection is required, as the point of the needle is made to pass beneath the posterior branch of the artery which is elevated above the recurrent nerve.

Silk is always used as a ligature as it is intended to remain until the thyroidectomy is performed. The deeper part of the wound is not sutured, and the skin is closed with clips (Fig. 122). The entire time consumed by the operation is usually only two or three minutes.

There are several special points which are worth mentioning: A separate and special set of instruments is needed for a ligation, consisting of two-bladed retractors, the needle described above, and the light mounted on a long handle for the illumination of the field (Fig. 116). Another point is important, namely, that it is simpler and quicker to perform the ligation than to hunt for the landmarks. As is evident, ligation means no more than the administration of a subcutaneous infusion. If ligation required the taking of the patient to the operating room, if it required a formal operation, if it required a

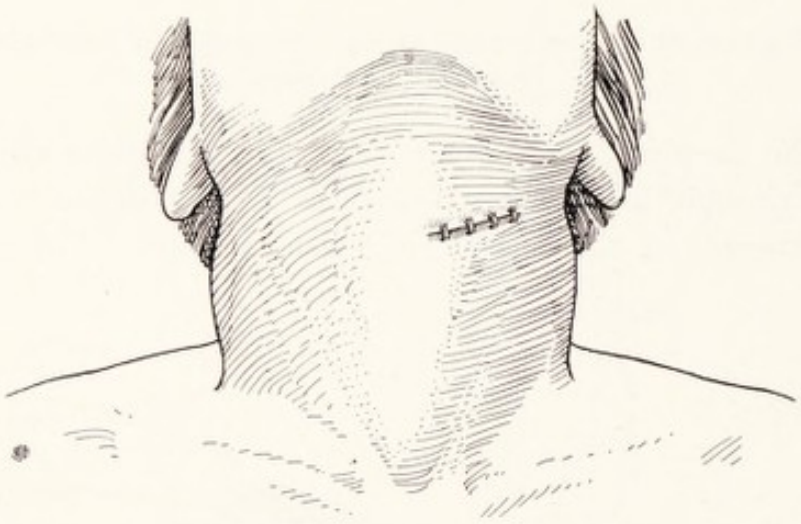


Fig. 122.—Ligation of superior thyroid artery. Closure of skin with clips.

considerable dissection, in other words if it approached in formality and in area of injury and dissection the performance of a lobectomy, the slight residual benefit to the patient would be hardly worth considering. In the mind of the patient a ligation becomes but a trivial procedure, something on the order of a subcutaneous infusion.

If there were no other evidence in favor of ligation the fact that even this slight operation is occasionally followed by a violent reaction, demonstrates clearly that, in such a case, a larger operation such as thyroidectomy or lobectomy would quite certainly prove fatal. Thus the indication for ligation, as we have already stated, is doubt as to whether or not the patient would be able to undergo a thyroidectomy. A trial ligation is analogous to the military procedure of testing the enemy's line to learn the strength of the resistance.

If the ligation causes but little disturbance, then in several days a thyroidectomy or a lobectomy may be performed. If a sharp reaction occurs, then a second ligation is made and the patient is sent home to wait for several months before thyroidectomy is done. In almost every instance there is marked improvement during this interval and even in those cases in which there is only moderate improvement the patient is able to undergo a thyroidectomy safely.

A review of our cases in which ligation has been done shows that the loss of time during the interval between the ligation and the thyroidectomy is more apparent than real, as the patient is constantly progressing toward his final reconstruction. In some instances the patient feels that he is normal and requires no further operation. Among our cases, ligation has been so beneficial that the period from the final thyroidectomy until the complete restoration at home is shortened almost to the extent of the interval between ligation and the thyroidectomy.

Ligation in Cases of Adenomata.—We no longer make any distinction between the treatment of hyperthyroidism associated with a hyperplastic gland or with an adenomatous gland. We have found that a patient may die from a hyperactive adenomatous goiter as readily as from a hyperactive hyperplastic gland.

The results of operation in cases in which hyperthyroidism is perhaps associated with adenomata are ultimately perhaps not quite so brilliant as in cases in which hyperthyroidism is associated with hyperplasia but death is as certainly averted and invalidism is as certainly overcome.

In the preparation for an operation for adenoma associated with hyperthyroidism, Lugol's solution is just as effective as in the presence of hyperplasia. Likewise, in desperate cases, while ligation does not affect the disease in cases of adenoma as strikingly as in cases of hyperplasia, ligation does help to make thyroidectomy possible.

It should be emphasized that if ligation is made an ordeal, then the disease is given an acceleration, and the beneficial effects are lessened by so much. For example, suppose an extremely sick patient were subjected to an intense emotional strain, a great fear, and at the same time received a lacerated wound of some magnitude, is it not certain that the condition would be made worse? If a ligation is to offer a maximum benefit then every adverse factor must be subtracted from the procedure.

CHAPTER XXXI

INDICATIONS FOR THYROIDECTOMY IN CASES OF HYPERTHYROIDISM

GEORGE CRILE

WE believe we now have sufficient data on which to base the conclusion that in the treatment of hyperthyroidism, important as is the rôle of a partial rest cure, radiation, any form of iodine, thyroid extract, general medication, general hygienic regulation, the overcoming of auto-intoxication, dietary control, or the removal of foci of infection, no one of these measures and not all combined approach the certainty and efficiency of surgical treatment as the primary mode of attack, this being supplemented, however, by the above-mentioned lesser methods of attacking this protean disease. Our conclusion is based not only on the immediate but also on the remote mortality; it is based on the expectancy of life no less than on the conservation of organic function and the general well-being of the individual. From an economic viewpoint, it provides the shortest road to recovery.

In hyperthyroidism the thyroid gland is a druggist—a tireless druggist, one that is ceaselessly manufacturing and turning into the circulation the exciting hormone—thyroxin.

It follows that the problem presented by the patient with hyperthyroidism is precisely the same as that which is presented by a patient who is taking thyroid extract or iodine in such amounts as to cause definite symptoms of hyperthyroidism. In such a case is it better to control the racing heart and overworked myocardium by a rest cure, sedatives, digitalis, bromides, diet, change of scene, by any or all of these lesser expedients—or is it better first to stop the drug and then supplement the restoration by these valuable adjuncts?

In order to justify our conviction that surgical treatment is the primary mode of attack against hyperthyroidism, it is essential to show that the immediate mortality is less than from nonsurgical treatment; that the end-results are better. The mild cases may be

excluded, for in these the surgical risk is negligible. The crucial test is presented by the fully developed case which has reached the terminal stage characterized by emaciation, cardiac decompensation, swollen extremities, ascites, vomiting, acidosis, prostration—the case that is nearing final dissolution or that shows repeated periods of, or continuous delirium.

The crucial fact in these cases is the state of the internal respiration. The surgical problem is to determine whether or not the condition is one of hopeless dissolution in which case even if it were possible by a miracle to wish out the thyroid, death still would be inevitable. In other words, can we differentiate between the quick and the dead? This we have found can be done almost with certainty by the application of the following biologic test.

Restore the water-electrolyte equilibrium of the desiccated cells by subcutaneous infusions of normal saline to which 1/30 per cent novocaine has been added (Bartlett's solution), amounting to from 2000 to 4000 cc. in twenty-four hours.

Digitalize the failing myocardium, whose feeble effort is not sufficient to assure the circulation of the blood in the essential organs—the myocardium, the brain, the liver, etc., leaving these organs at this critical time in a state of relative anemia.

Through blood transfusion supplement the damaged blood serum by good blood. This applies especially to the altered serum albumin-serum globulin ratio (Haden and Shirer).

Modify and control the ceaseless, exhausting restlessness and nervous tension—physical and mental—by sedatives, and especially by the service of nurses fitted by natural endowment and special training to assuage, cajole, and quiet.

If after these measures have been applied, the downward course of the patient continues unchecked, as happens in only about one out of 500 cases, then dissolution and death are inevitable. On the other hand, if the vomiting ceases and the delirium gradually disappears, then the patient is viable and operable.

In other words, whether the hyperthyroidism is associated with simple hyperplasia, with an adenoma, or with a colloid goiter; whether it is the only pathologic condition present or is associated with tuberculosis, with diabetes, with hypertension, with pregnancy; whatever the age of the patient; whether or not the legs are swollen; whether or not there is fluid in the abdomen or in the chest; whether the condition is chronic or acute; whether or not there is exophthalmos—

providing vomiting has ceased and delirium has lessened, the patient is submitted to operation. The one positive contraindication to operation is persistent delirium.

OPERABILITY IN THE PRESENCE OF PREGNANCY

In cases in which pregnancy is associated with hyperthyroidism, what shall be done? In our earlier experience after consultation with obstetricians, we at first thought it was best to terminate the pregnancy, but we soon found that this procedure is strongly contraindicated because of the violent thyroid crises that follow and may result in death. We then tried to let these patients go on through the term of pregnancy but we found that while some patients went through satisfactorily, severe crises often developed in the course of the delivery —in one case death occurred. As the result of this experience, we have performed thyroidectomy regardless of the stage of the pregnancy and have secured most gratifying results. There have been no deaths, the patients have gone through the operation very well and there has been no tendency to recurrence of the disease. Furthermore, we have seen nothing unusual in the growth and development of the offspring.

GENERAL CONSIDERATION OF THE OPERABILITY IN CRITICAL CASES

In the great majority of cases, operation is completed in one stage, but in a minority group of cases in which because of old age or early childhood, of damaging delay, or of complications, one would feel disposed to advise against operation, operability may be established by performing the operation in two or more stages.

Not only may the operation be performed in multiple stages, but each stage may in turn be divided by interrupting the operation at any point according to the indication of the moment, the wound being packed with flavine gauze until the negativity of the patient is restored and the continuation of the procedure is safe.

It should be noted that, although it would perhaps appear that the gradations in the plan of management described above are to be applied in the presence of certain clearly defined phases of the disease, the *possibilities, not the probabilities*, guide the management in every case, for in any patient with hyperthyroidism an acute crisis may develop at any moment.

In every case, therefore, a state of negativity is approached; in every case hydration of the cells is promoted; in every case interference with internal respiration by the inhalation anesthetic is

reduced to a minimum by not allowing the patient to pass beyond the stage of analgesia induced by nitrous oxide-oxygen—*never by ether*. In every case the operation is performed in the patient's room in order to avoid the psychic and physical stimuli incident to the removal from bed and transportation to the operating room. In every case we hold ourselves ready to stop the operation at any point.

This plan presumes an accurate estimate of the operability at every stage, in other words, the ability to decide whether delay or action is best; it presumes the advantage of a permanent organization of the hospital, medical, and nursing staff, with mobile operating units which make easy the performance of operations in any room, with the patient undisturbed in his bed; it presumes the prevention of fear, worry and anxiety, the preoperative use of iodine, the assurance of an adequate water intake to maintain the optimum water balance, the avoidance of ether anesthesia and the priceless service of an anesthetist skilled in maintaining in the patient a contented, even, happy frame of mind under nitrous oxide-oxygen analgesia; it presumes safe judgment as to how far to venture at a given moment, to ligation, to lobectomy or to bilateral partial thyroidectomy; the maintenance of tranquility during the operation; complete flexibility in the operative approach, in the extent of the operation, and in the final disposition of the wound, whether it shall be temporarily left open, closed with drainage, or closed without drainage; an operative technic so planned that the operation can be stopped abruptly at any point; the prompt use of blood transfusion; the support of a failing myocardium by digitalization; postoperative care by skilful nurses who have developed a special understanding of the peculiar needs of these volatile patients; accurate judgment and prompt action on the part of the resident surgical staff, each member of which is himself trained and able to perform successfully every type of operation on the thyroid gland. These are the requisites that have so minimized the mortality rate of operations on the thyroid gland that death, when it does occur, is due to secondary causes such as sudden heart failure, hemiplegia, uremia in cases of diabetes of long standing, and occasionally pneumonia or pulmonary embolism.

Under such conditions the mortality from lobectomy or from bilateral partial thyroidectomy is no higher, perhaps in extreme cases is even not as high as that incident to the transportation of these highly excitable patients to the hospital. A ligation performed

in a few minutes, without moving the patient from his bed and without mental disturbance, causes even less reaction than the admission of the patient to the hospital. The second ligation, performed the second day after the first, is followed by a still slighter reaction; and the marked improvement which results from the ligations makes the reaction following lobectomy in the case of a stabilized patient no more severe than that following ligation in the case of the frail, excitable, emaciated patient.

The decision as to whether a bilateral thyroidectomy or a single lobectomy should be performed depends entirely upon the condition of the patient. If the patient has been sufficiently stabilized by the preoperative management, then in many cases a bilateral resection may be performed with no more risk than that which attends ligation or even admission to the hospital in the case of a sicker patient.

The surgical team, like a football team, has many plays which it can execute to meet the many and often swiftly changing indications presented by the patient. There are principles in accordance with which each play is planned, but no rules: in case of doubt the play is deferred.

CHAPTER XXXII

ROUTINE TECHNIC OF THYROIDECTOMY

ROBERT S. DINSMORE

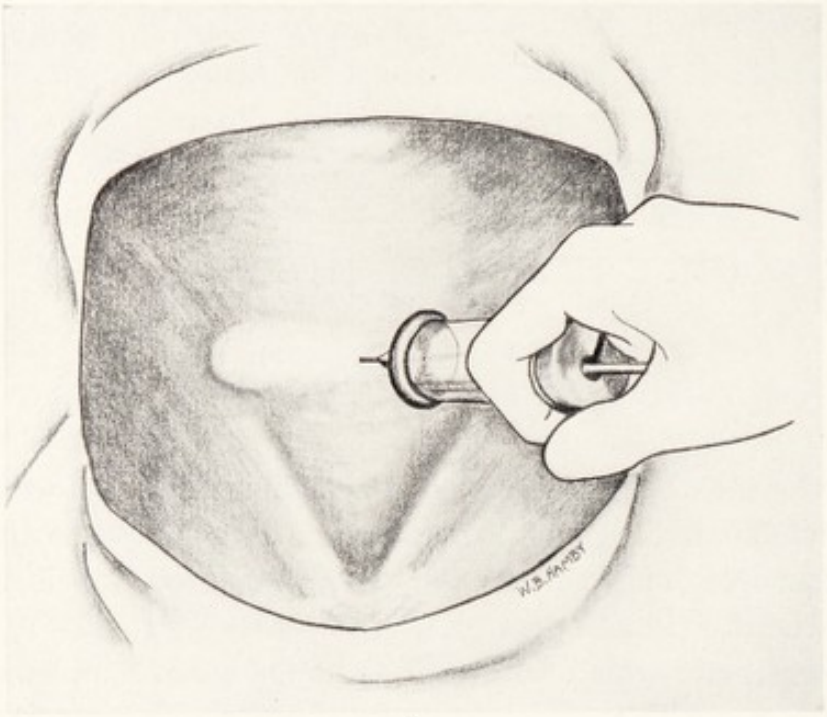
IN reviewing the literature on the technic of thyroidectomy, we must conclude that there are many variations and that the fundamental principles of all are the same, the method varying more or less with the individual operator.

The anesthetic which we use is light analgesia supplemented by local infiltration with novocaine in three-fourths of 1 per cent dilution. The infiltration is carried out in three steps, a small wheal being made intradermally with a fine needle placed at the midpoint of the projected incision line (Fig. 123). From this point the novocaine is introduced, the skin and subcutaneous tissue being infiltrated over a wide area. No attempt is made to infiltrate beneath the cervical fascia or preglandular muscles. It is important that the neck be placed in extension without any rotation of the head.

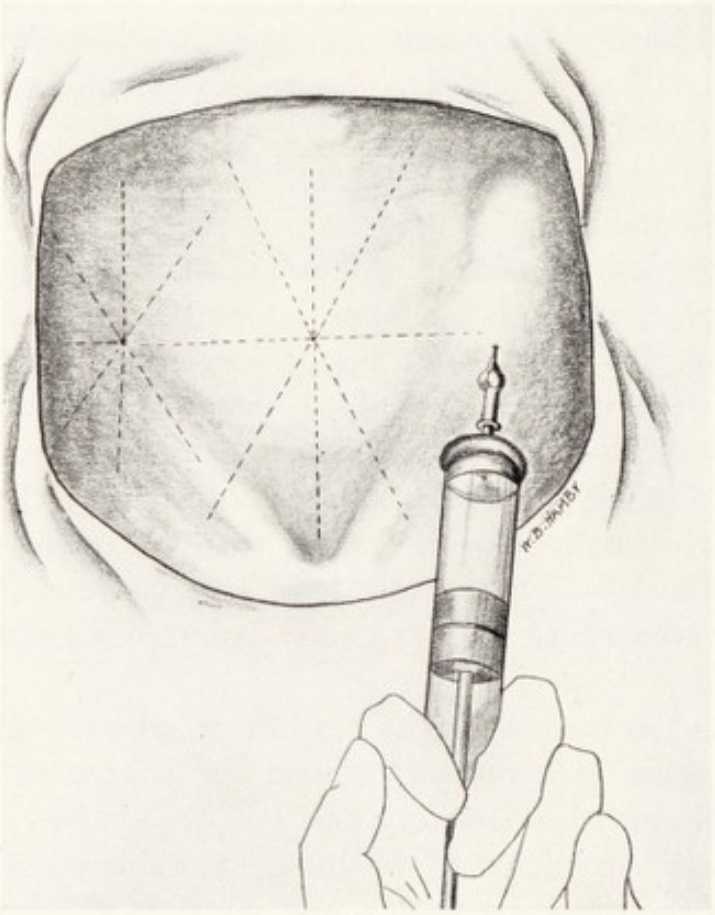
A transverse incision is made, no attempt being made to make it elliptical (Fig. 124) (Richter). For practical purposes the incision is made at a point midway between the episternal notch and the cricoid cartilage,[1] as we have found that by this procedure the most satisfactory scar is produced. Generally speaking, the unsatisfactory scars are usually too low rather than too high. If an elliptical incision is made, frequently it is observed after the scar has formed, that the ellipse is much more exaggerated than had been anticipated.

The incision is made with the head extended backward and when the neck is again in a normal position the transverse incision will give a slightly curved satisfactory scar.

The incision is carried directly through the skin and subcutaneous tissue across the platysma muscle and down to the cervical fascia, making a full-thickness flap. The flaps are then dissected upward and downward, care being taken to carry the dissection down to the episternal notch and upward to the level of the cricoid cartilage



A



B

Fig. 123.—Technic of thyroidectomy. Infiltration of skin and subcutaneous tissue with novocaine. At this time no attempt is made to infiltrate beneath the fascia. Lines in B show direction of infiltration.

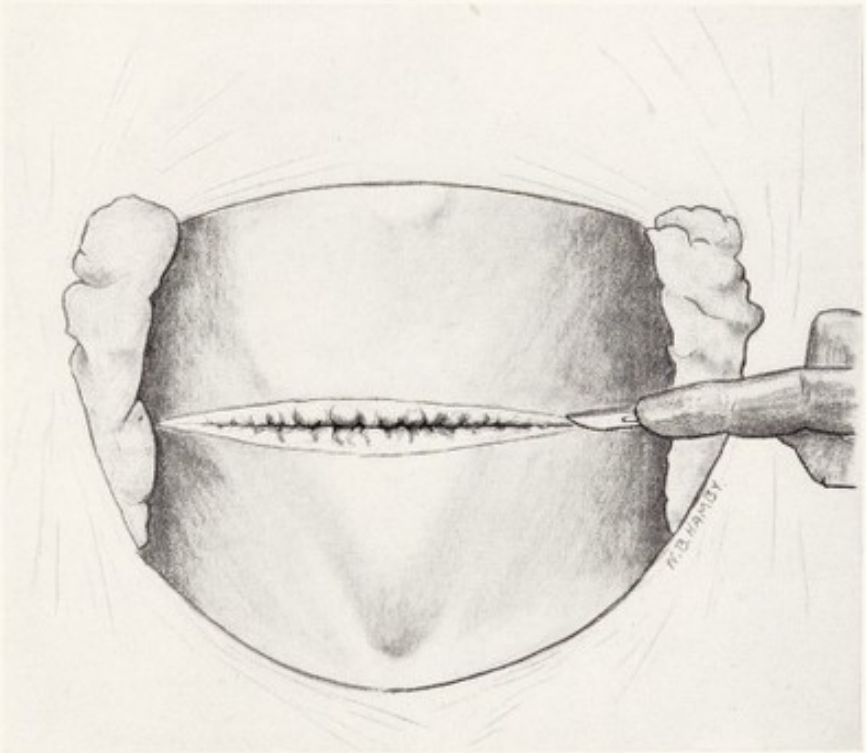


Fig. 124.—Technic of thyroidectomy. Straight transverse incision across neck. The dissection is carried through the subcutaneous tissue and the platysma muscle down to the cervical fascia, thus making a full-thickness skin flap.

(Fig. 125). It is essential that the dissection be fairly wide as the preglandular muscles are not divided transversely.

After the dissection of the skin flaps, the second step of the infiltration is carried out, the novocaine being injected into the immediate

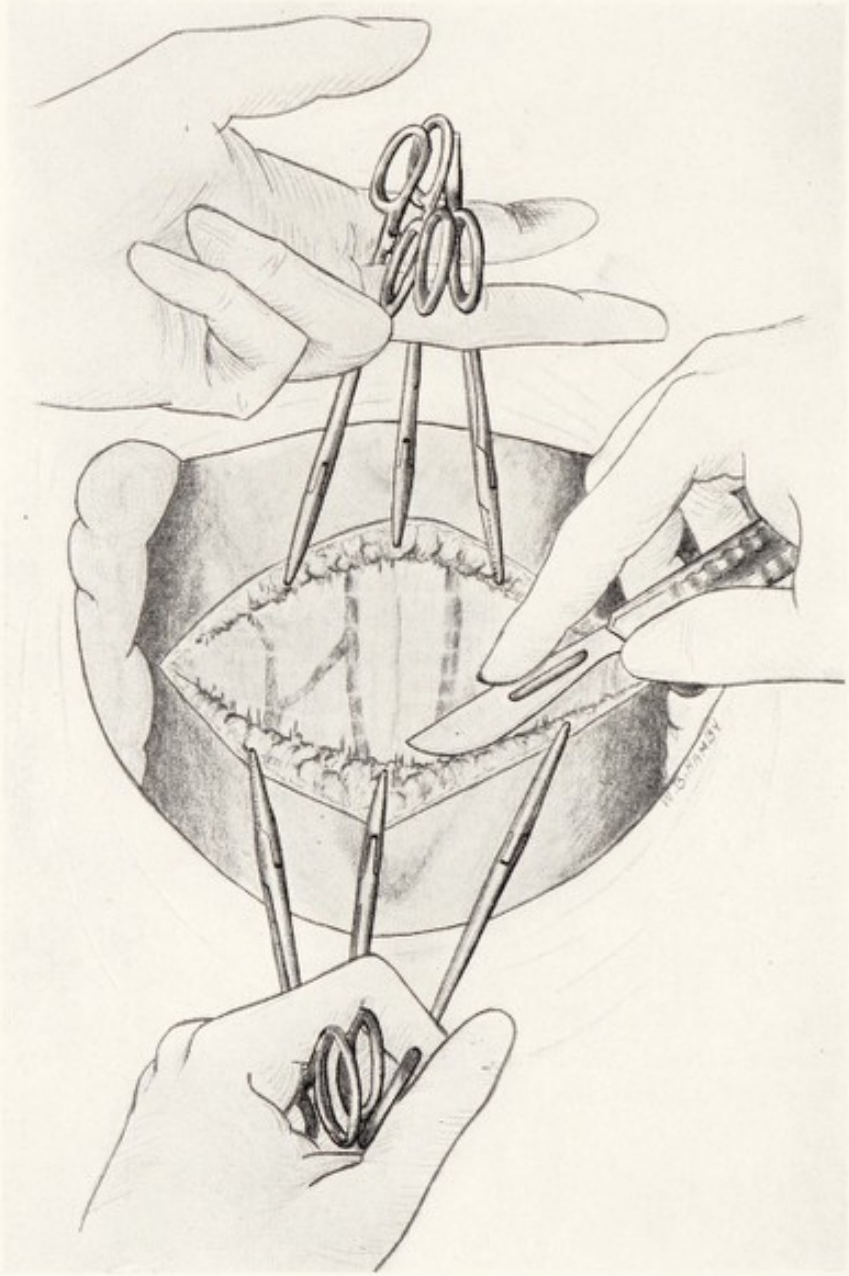


Fig. 125.—Technic of thyroidectomy. Skin flaps dissected upward and downward, below to the episternal notch and above to the level of the cricoid cartilage.

cervical fascia, and the preglandular muscles (Fig. 126). After the high and low dissection of the skin flaps it is possible to make a long vertical incision through the fascia and preglandular muscles, down to the capsule of the gland, which is also divided in the same line, and

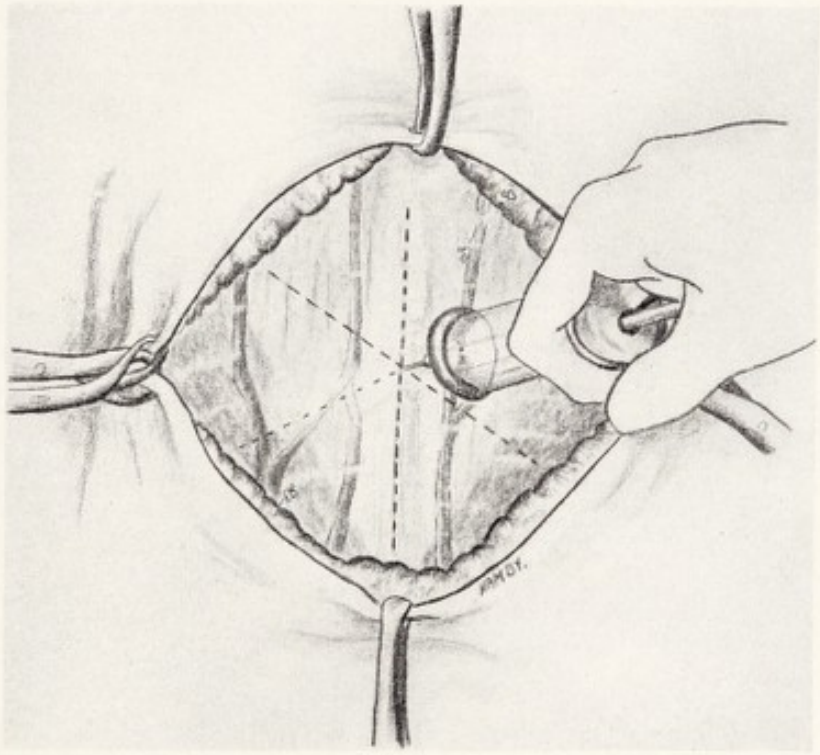


Fig. 126.—Technic of thyroidectomy. Infiltration with novocaine beneath the cervical fascia and into the preglandular muscles.

to expose the gland (Fig. 127). The capsule is then dissected free and as much of the surface of the gland exposed as possible (Fig. 128). We have tried various sorts of clamps for elevating the gland and have finally resorted to the use of hemostats, three of which are usually used. They are placed just within the true capsule of the gland.

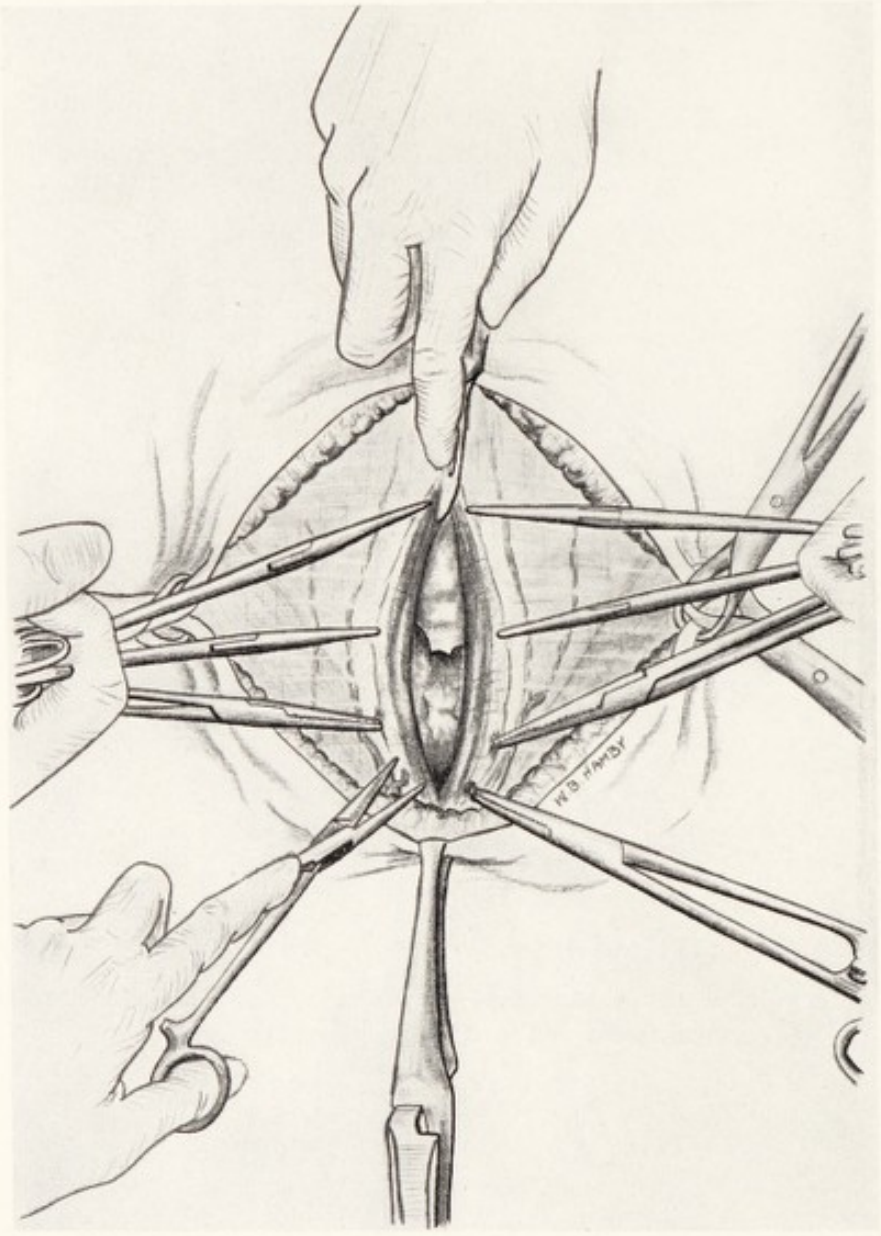


Fig. 127.—Technic of thyroidectomy. Longitudinal incision through the fascia, preglandular muscles and capsule of the gland. This dissection is carried from the level of the cricoid cartilage well down into the episternal notch. With a long incision it is not necessary to divide the preglandular muscles transversely.

The third step of the anesthesia is the infiltration of the gland itself with novocaine. Ordinarily this infiltration can be carried out with from 10 to 15 cc. of novocaine, the greater portion of which

is injected into the superior pole (Fig. 129). After the gland has been exposed and infiltrated it can then be lifted up and the superior pole exposed. I prefer to remove the right lobe first, but this is simply a matter of personal choice.

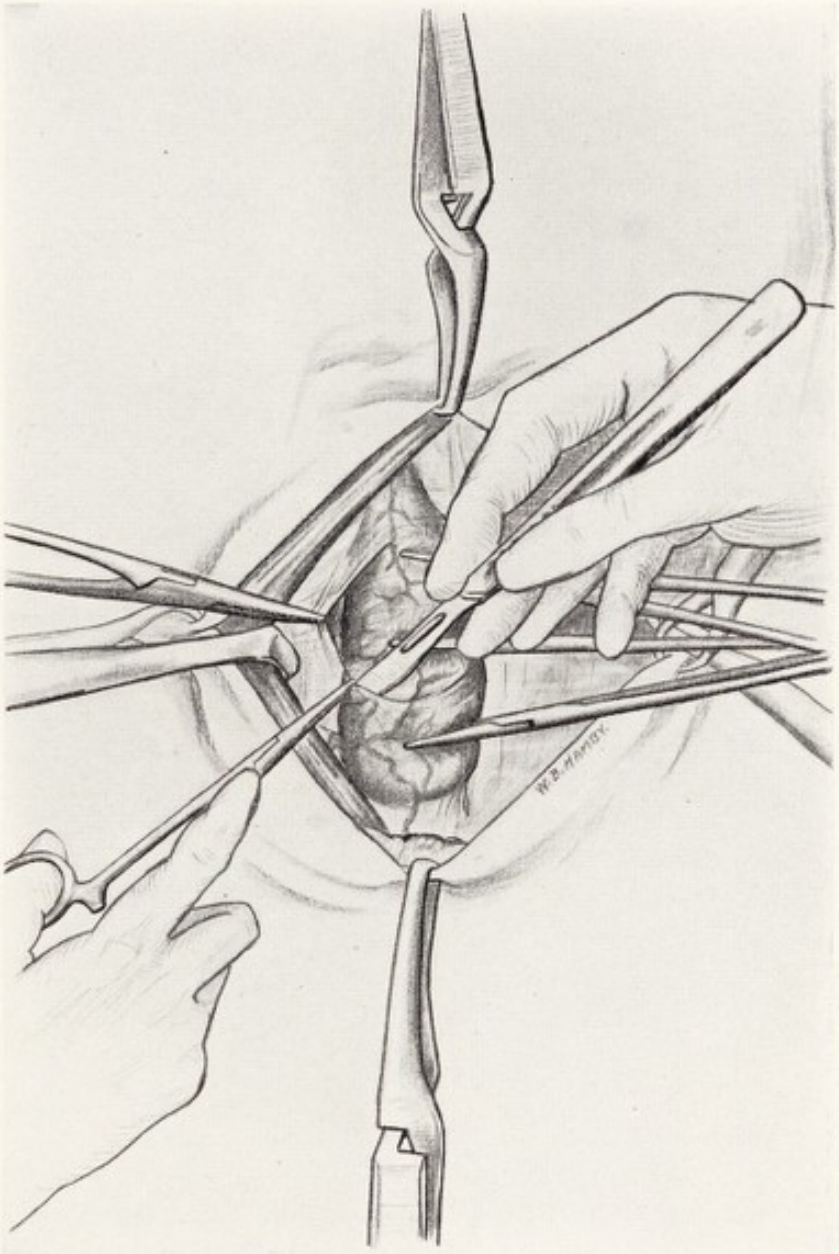


Fig. 128.—Technic of thyroidectomy. Dissection of the capsule of the gland laterally to the level at which the gland is to be divided. None of the capsule is removed.

Two clamps are placed on the superior pole after it has been lifted up and it is absolutely certain that the upper pole is free from the fascia connecting it with the larynx (Fig. 130). Pemberton is always careful of this point and places his index finger beneath

the superior pole. This is an important step because the clamps must be applied always from within outward. If the clamps are applied from the outside of the gland it is easy to pass by it and catch the terminal branch of the recurrent laryngeal nerve as it passes into the

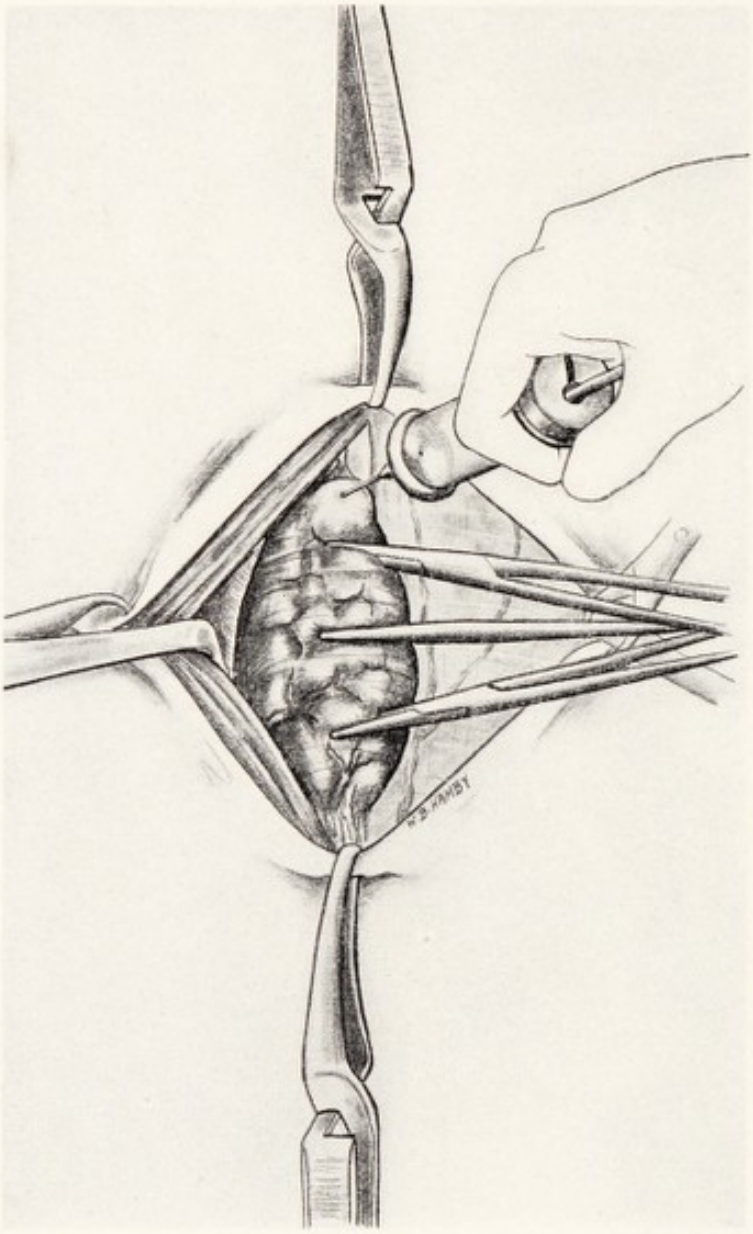


Fig. 129.—Technic of thyroidectomy. Infiltration of gland with novocaine and application of hemostat for traction.

larynx. This observation is not a theoretical one as I have been unfortunate enough to see it demonstrated in the autopsy room. It is quite true that the upper pole is not always directly opposite the larynx but in the majority of instances this is an anatomic finding.

A second hemostat is then applied to the lateral vein of the thyroid

which is ordinarily at the outer surface at the juncture of the middle and lower thirds of the gland (Fig. 130). Hertzler[2] considers this one of the important steps in any thyroidectomy, stating that the

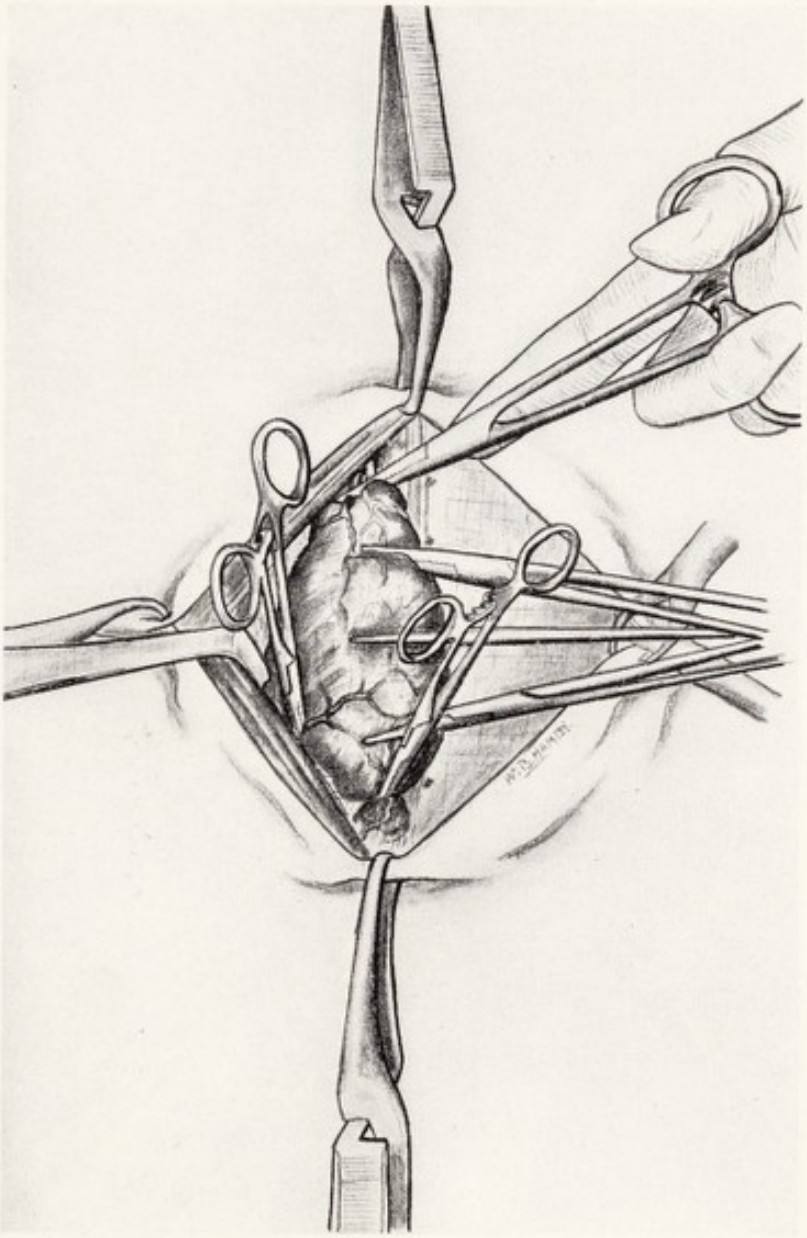


Fig. 130.—Technic of thyroidectomy. Application of three "pilot" hemostats. The upper pole is dissected free and lifted up, the hemostat always being directed from within outward. The lateral vessels are caught with the second hemostat. The inferior pole is then caught, the clamp being applied so as to take up some thyroid tissue with it and to have the clamp standing erect.

line of cleavage is often lost at this point because of the fact that the fascia planes divide here, one sheath going over the carotid and the other to the gland. Guthrie routinely ligates this vessel first. The third clamp is then applied at the inferior pole. I have always made

it a point to leave some thyroid tissue at the inferior pole, and I prefer to place the clamp in such a position that after it has been applied it will stand erect in the wound (Fig. 130). I think that a great deal of the difficulty with bleeding which is encountered

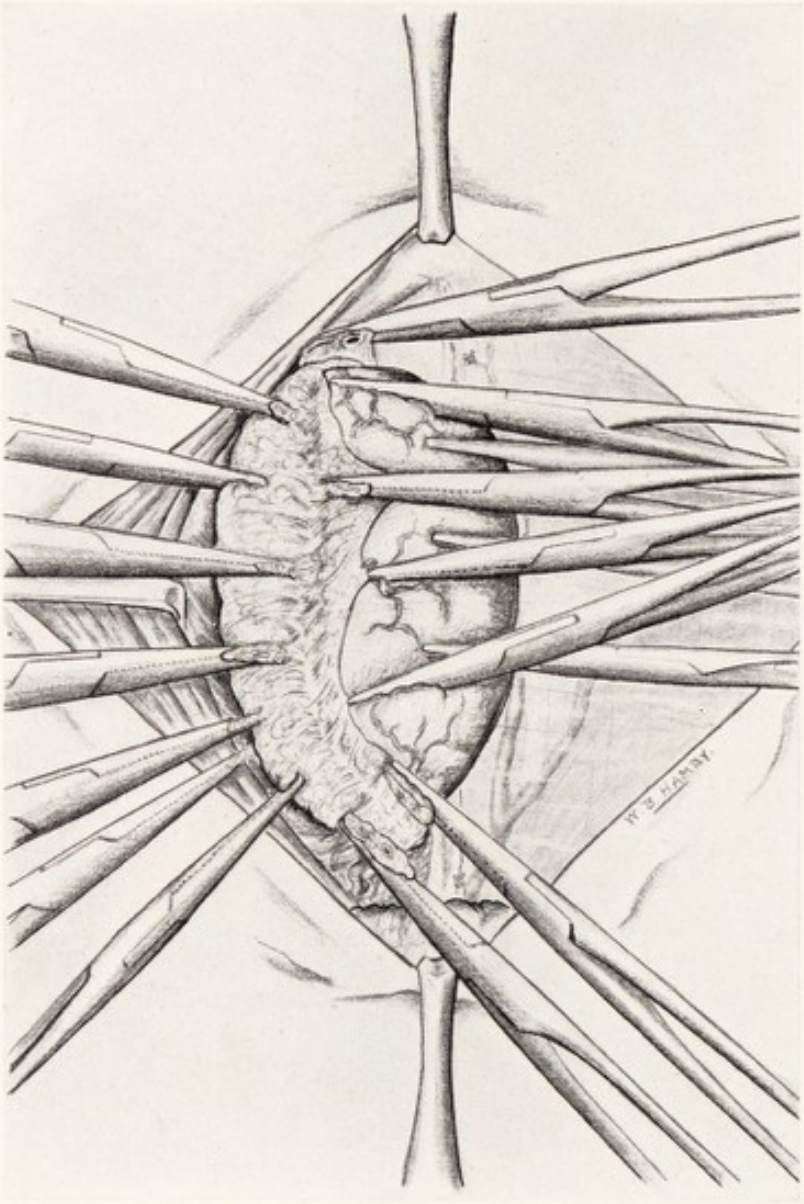


Fig. 131.—Technic of thyroidectomy. Dissection of gland. After the points within the primary clamps have been divided the dissection is carried inward from the outside of the gland for about one third of its extent.

in thyroid surgery can be lessened if these three pilot hemostats are consecutively applied. The poles and the lateral thyroid fascia can then be divided and an incision made through the lateral posterior border at the point at which the gland is to be divided. This incision can then be carried in for a short distance, approximately 1 cm.

After this has been done it will be noted that the gland can easily be lifted forward. From this point the gland is turned outward and the dissection carried from the tracheal side (Fig. 131).

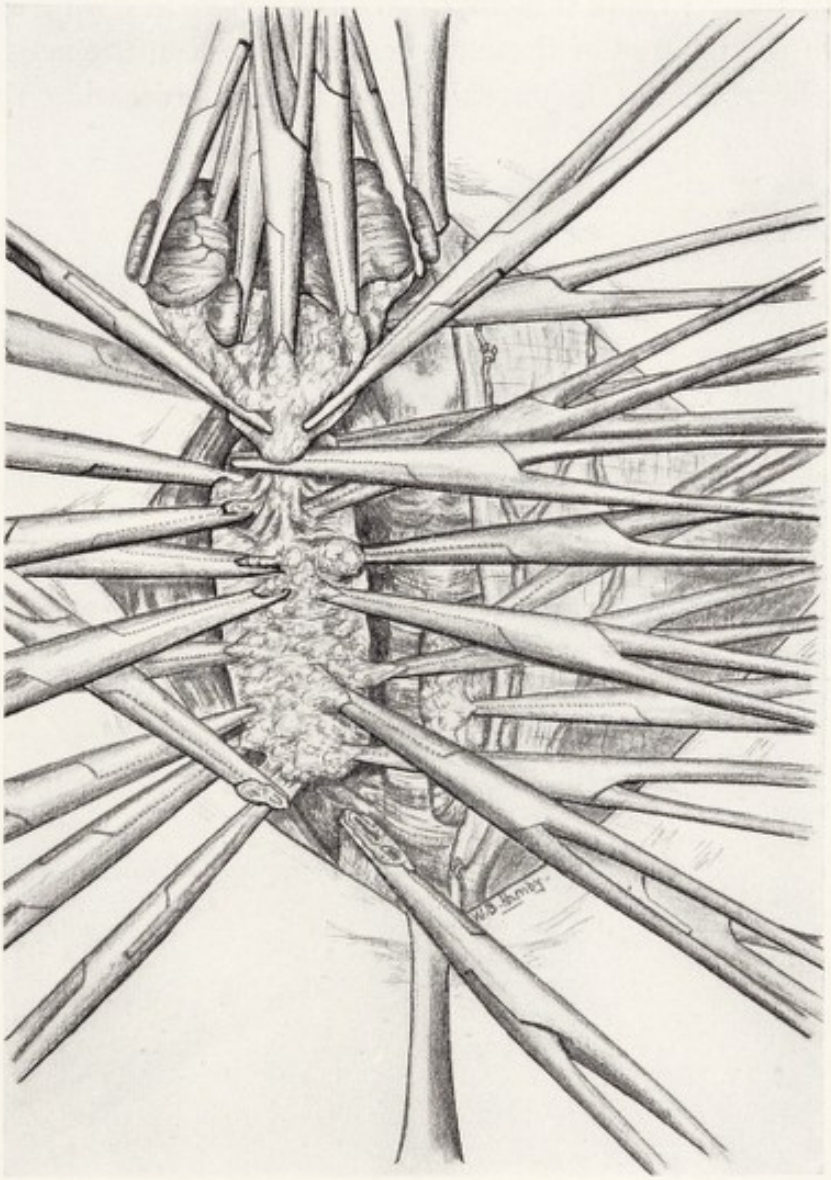


Fig. 132.—Technic of thyroidectomy. Gland lifted forward after division of isthmus. After the superior pole, the lateral veins and the inferior pole have been divided and the lateral incision into the gland substance has been made, the gland is turned outward and the isthmus divided. The gland can then be lifted well forward and the clamps applied nearly transversely; that is, away from the tracheo-esophageal groove.

Sistrunk always advocated this procedure and it has been a great help to me. The clamps can now be placed nearly transversely above the trachea and the dissection carried from that point outward (Fig. 132). This procedure does away with the difficulty of placing the

clamps down along the side of the trachea which is directly along the tracheo-esophageal groove and is a common site for injury to the recurrent laryngeal nerve (Fig. 133).

After the gland has been removed, the tissues are ligated with fine catgut ties. I think it is important that as little sewing as possible be done in the ligation of these tissues. I have seen the needle passed through the recurrent laryngeal nerve actually bisecting the nerve.

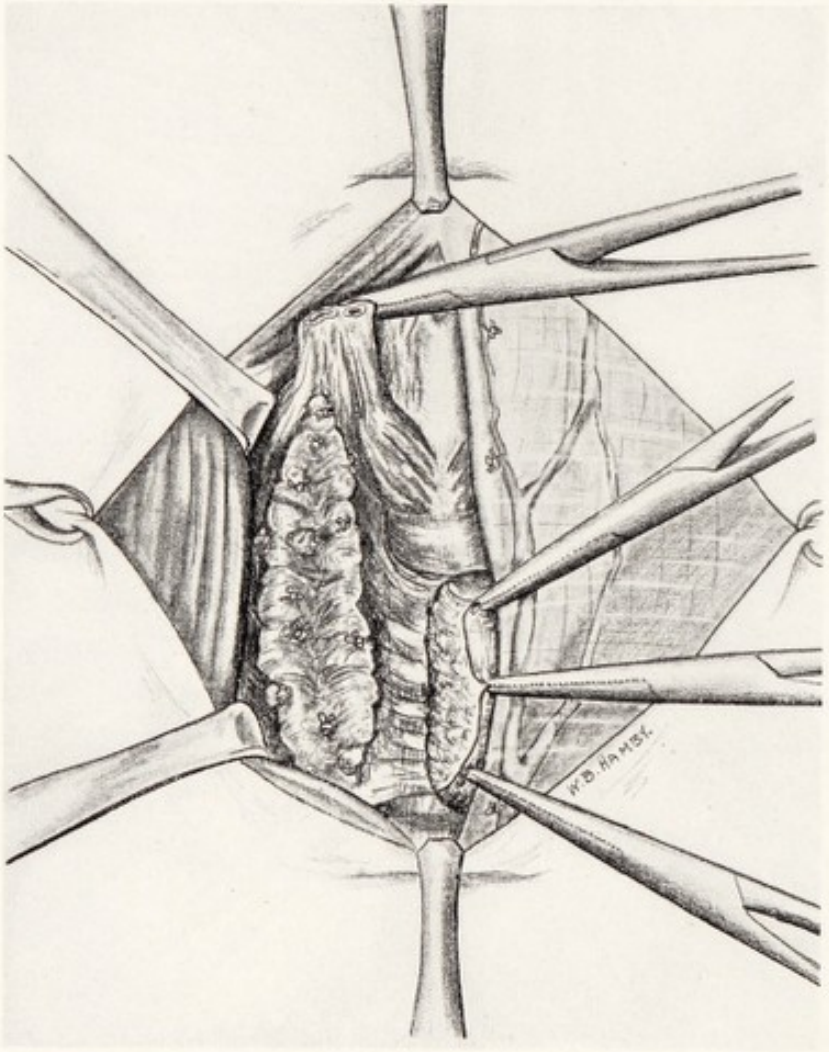


Fig. 133.—Technic of thyroidectomy. View of thyroid bed after removal of right lobe.

I prefer to ligate the upper pole with a double catgut suture, inserting it from the same direction as that in which the clamps were applied, that is, from within outward (Fig. 134). After the hemostasis is complete the same procedure is carried out on the opposite side (Figs. 135, 136). After the ligation has been completed on the opposite side the wound is carefully inspected and the patient

asked to cough in order to make sure that the ligatures have been accurately applied. It has been our practice routinely to place a small rubber tissue drain or a small tube in the wound. Recently I have been using a Y tube the ends of which project into the cavities caused by the removal of the lobes.

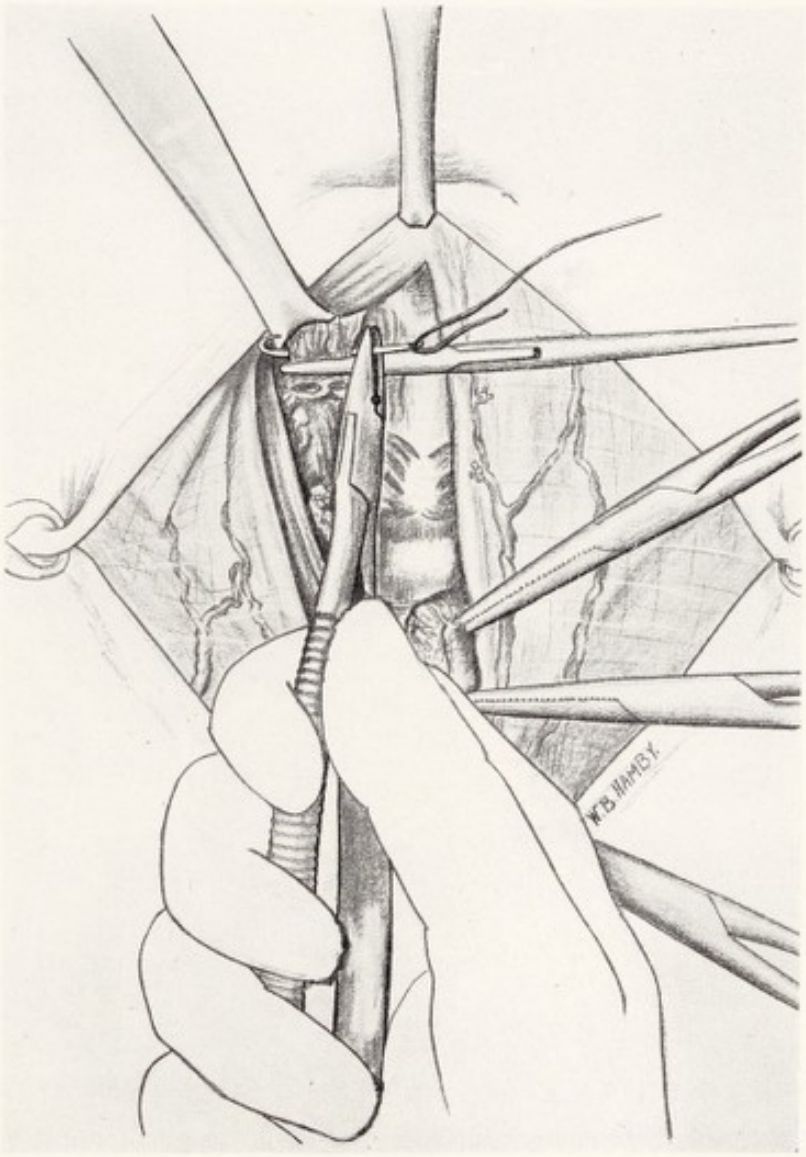


Fig. 134.—Technic of thyroidectomy. Ligation of upper pole with a double catgut ligature. The pole is lifted up and the ligature always passed from within outward.

An accurate closure following a thyroidectomy is of the utmost importance. One of the most distressing complications is an adherent scar or a small adhesion, which moves with swallowing. This is uncomfortable for the patient and is always noticed by his friends. I have dissected out a fairly large number of these postoperative

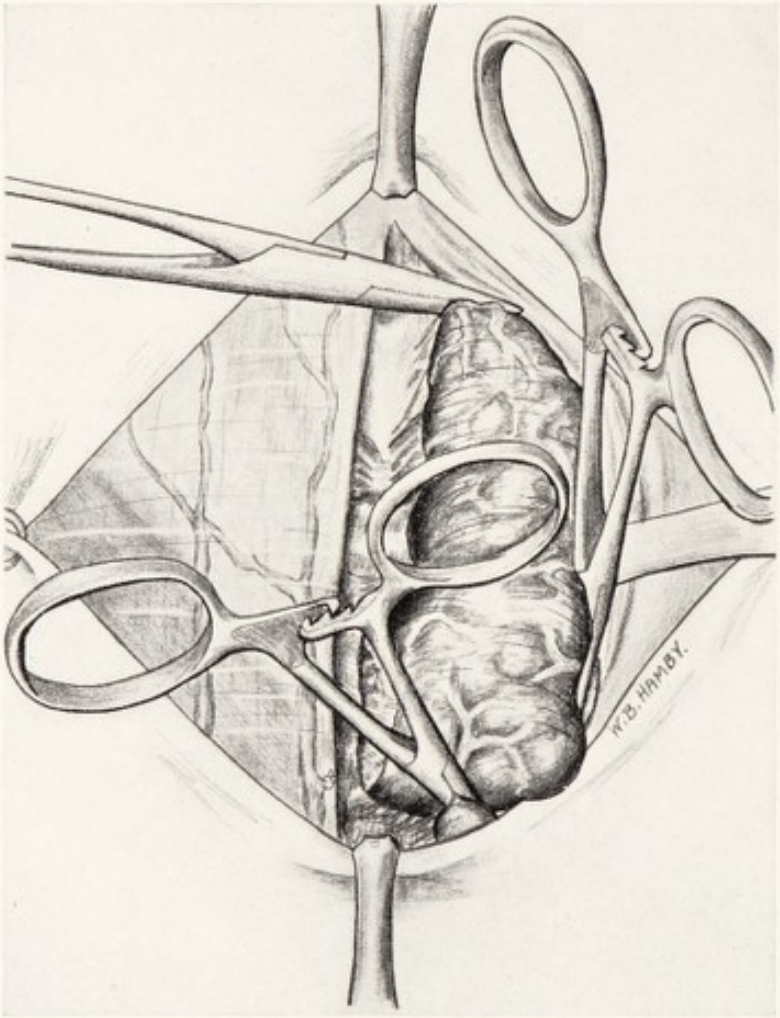


Fig. 135.—Technic of thyroidectomy. "Pilot" hemostats in left lobe.

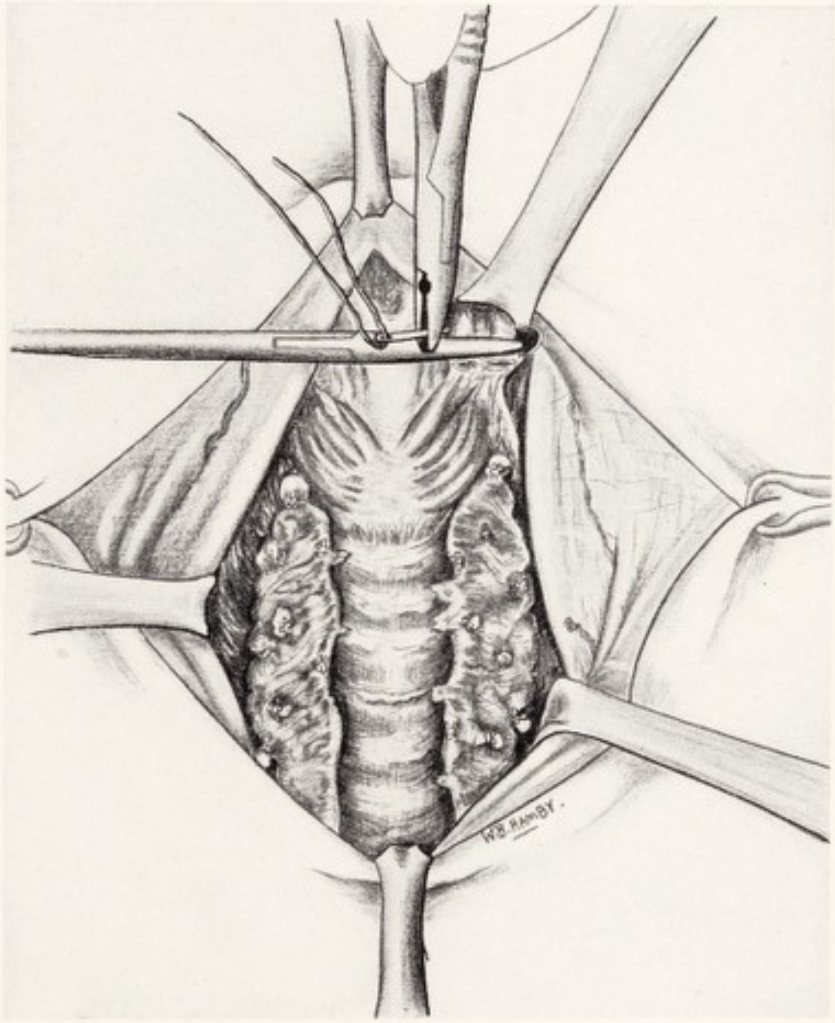


Fig. 136.—Technic of thyroidectomy. Ligation of left superior pole with view of thyroid bed.

adhesions and in most instances I have found that they are caused by a retraction of the preglandular muscles. After dissecting down to the cervical fascia I have found the fascia to be adherent to the trachea, the muscles having retracted. The correction of this condition is not a simple procedure as a very much wider dissection may be necessary than one would suppose, in order to get the muscle and fascial layers again in approximation. All layers are closed separately.

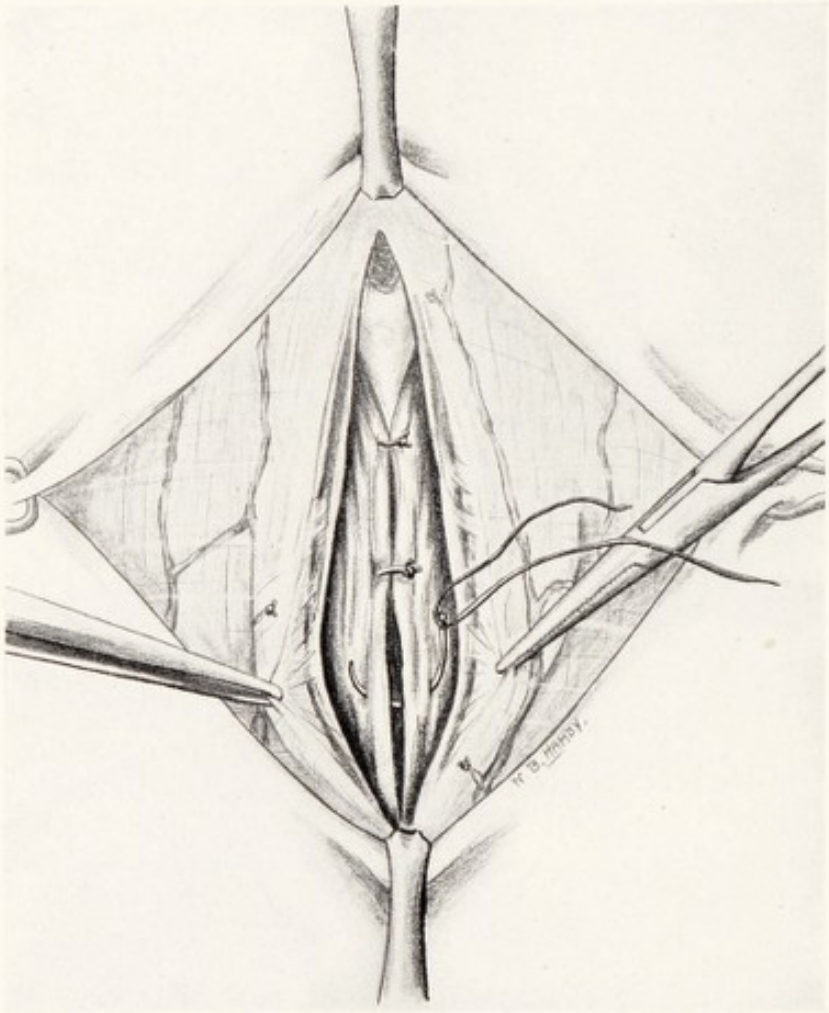


Fig. 137.—Technic of thyroidectomy. Closure of capsule with interrupted sutures of fine catgut.

Interrupted sutures are placed in the capsule of the gland (Fig. 137); the preglandular muscles are then approximated with fine catgut sutures (Fig. 138) and the fascia is closed with a running suture of fine catgut, a small opening being left near the lower angle of the wound for the insertion of a drain (Fig. 139). No effort is made to close the platysma, but the full-thickness flaps are closed with skin clips (Figs. 140, 141). If a satisfactory scar is to be obtained with

skin clips it is most important that they be placed accurately and inserted directly over the incision line and at right angles to it. It is a very common error to apply these clips from the side so that they appear at many different angles when the incision line is completely closed. The clips should not be applied too tightly and should always be removed in from forty-eight to seventy-two hours to prevent the formation of small scars which may result if the clips are left in place too long.

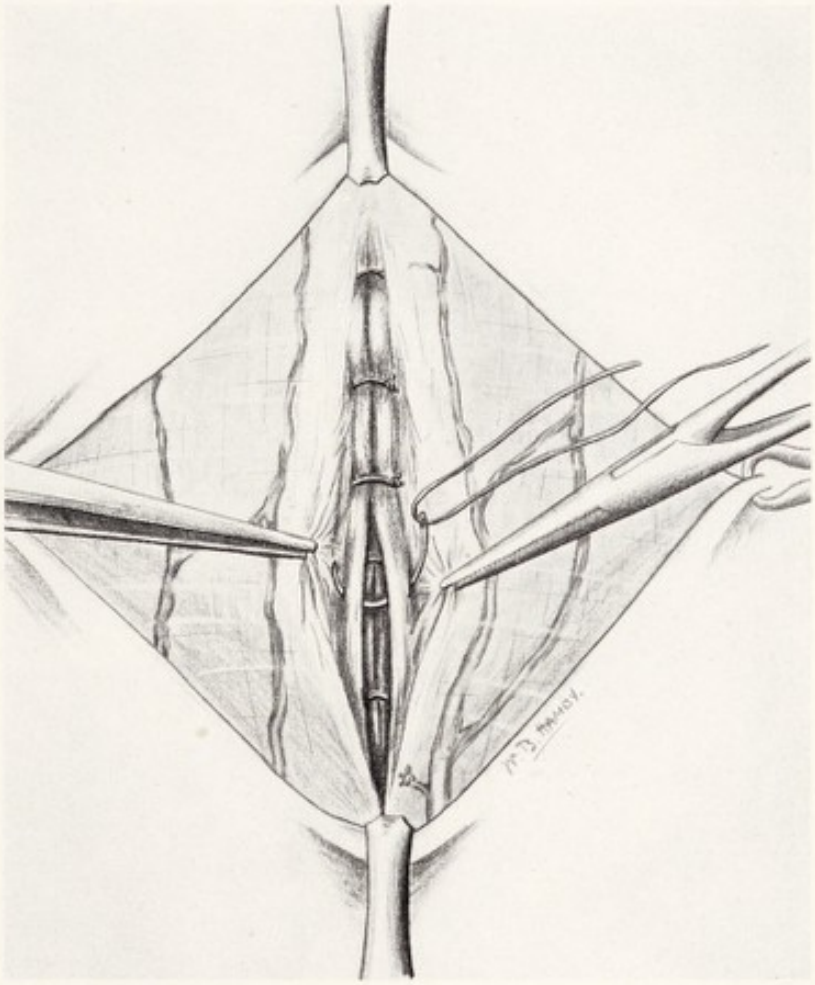


Fig. 138.—Technic of thyroidectomy. Closure of preglandular muscles with interrupted sutures.

In my own hands, the technic described above has been the one in which I have seen the smallest number of injuries to the recurrent laryngeal nerve. The most common sites for injury of this type have been the superior pole, the inferior pole, and the tracheo-esophageal groove at about the middle point between the level of the inferior and superior poles. If the superior pole is free and the clamps are inserted from within outward I believe that injury at the upper

pole is of rare occurrence. Injury at the inferior pole is also rare if the hemostats are kept within the gland.

After the gland has been divided at both poles and another incision has been made through the posterior lateral border, and the gland has been lifted up, the dissection can be carried across the gland in such a manner that a triangular piece of thyroid tissue is always left covering the tracheo-esophageal groove. I do not believe that

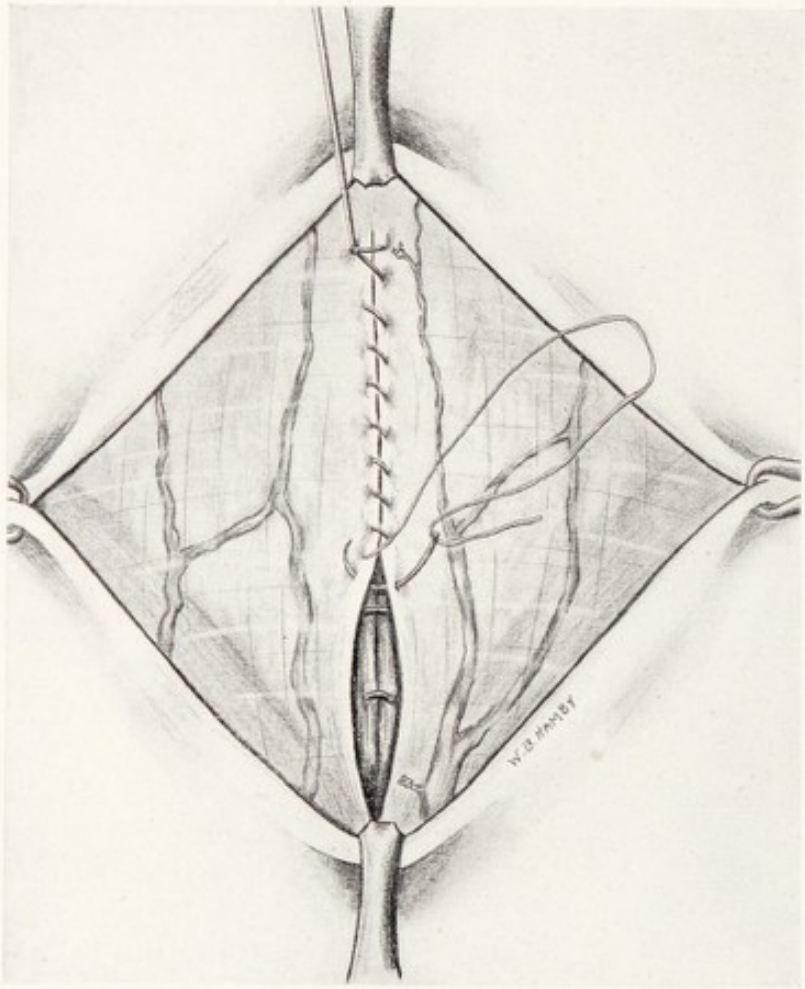


Fig. 139.—Technic of thyroidectomy. Closure of fascia with fine catgut running suture. A small opening is left in the lower third for drain.

this can be accomplished by complete removal of the gland from the outside inward as it is very easy to rotate the trachea forward, in which case it will suddenly be found that a great deal of thyroid tissue along the lateral surface of the trachea has been removed, and there are small bleeding vessels almost in line with the recurrent laryngeal nerve.

Anatomical studies have shown that the most constant site of

the superior parathyroids is in the posterior capsule of the thyroid gland at the juncture of the upper and middle thirds. The inferior parathyroids lie usually at the juncture of the middle and lower thirds but their location is not so constant as that of the superior parathyroids. Millzner,[3] Lahey,[4] and Terry and Searls[5] have called

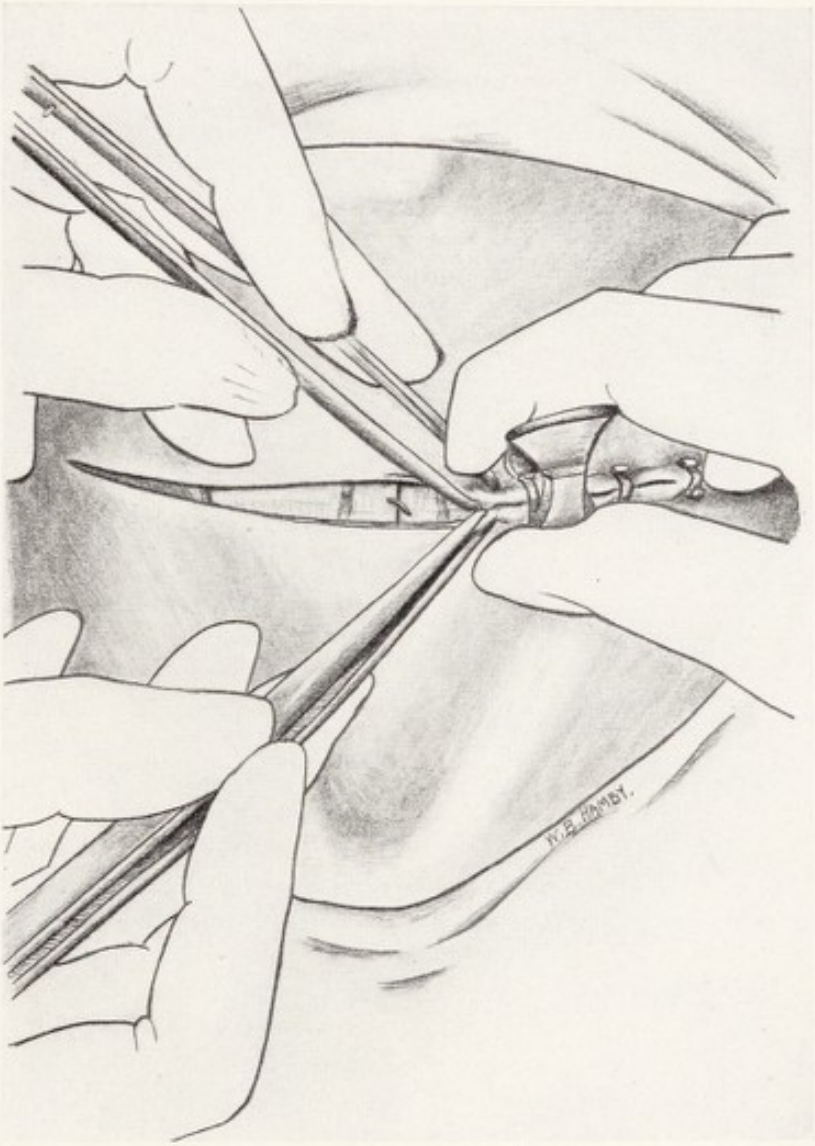


Fig. 140.—Technic of thyroidectomy. Closure of skin with clips. It is essential that the clips be inserted at right angles to the incision line. To accomplish this they must be applied from directly above the incision and not from the side as this invariably twists the clip.

our attention to the fairly high incidence of the removal of parathyroid bodies which lie on the anterior surface of the gland. This observation coincides with our experience in this clinic. Graham states that the most common site of parathyroid bodies, found in pathologic specimens here, is the lateral inferior border of the gland. Lahey[4] and

Terry and Searls[5] have advised the routine search for the parathyroid glands and reimplantation of them if possible.

We have had no experience with the radio knife, although Jackson,[6] Mock,[7] Tinker,[8] and Bartlett and Bartlett[9] have used it. Jackson[6] has summarized the advantages and disadvantages of the procedure,

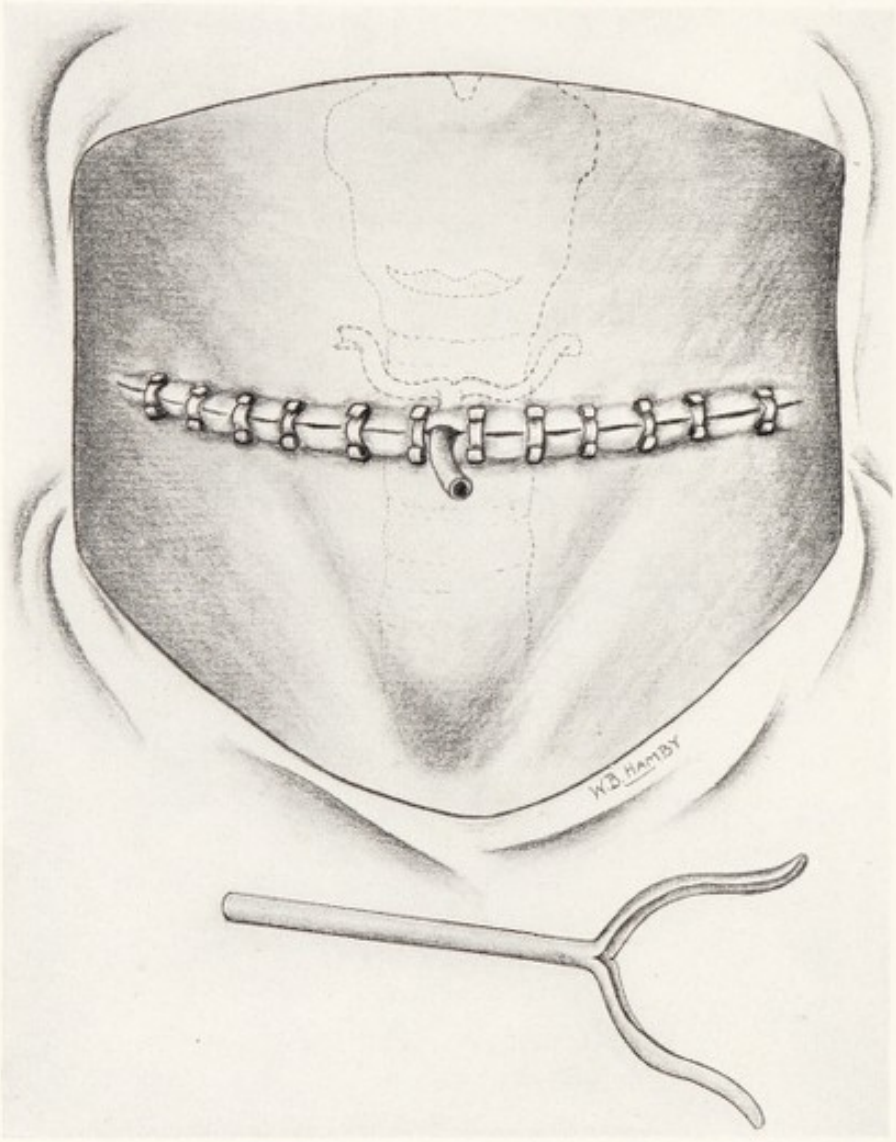


Fig. 141.—Technic of thyroidectomy. Drainage of wound with small-molded rubber drain which is removed in from twelve to twenty-four hours.

the chief advantages being the time-saving factor, better hemostasis, and less catgut in the wound. He points out that it is especially advantageous in operations on hyperplastic glands and for malignant tumors of the thyroid. He has pointed out that the radio knife should never be used for the skin incision or near the skin as necrosis may result. He feels that it increases the danger of postoperative

hemorrhage and that it is of no particular advantage in the case of large adenomatous goiters.

A satisfactory technic for thyroidectomy, then, is one which can be carried out within a reasonable length of time, under some form of light anesthesia or analgesia augmented by local anesthesia; one in which the proper amount of gland is removed without injury to the recurrent laryngeal nerve or parathyroid bodies, one in which the result is satisfactory from a cosmetic standpoint, and above all, one which brings about the cure of the patient.

Donald Guthrie[10] has made a very pertinent statement, in which he says: "One can never afford, even though his experience in thyroid surgery becomes large, to be careless or rough in his operations upon the thyroid gland, nor can he disregard the importance of meticulous postoperative care, for it is attention to these details in the management of goiter patients that spells success."

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CHAPTER XXXIII

SPECIAL PIONTS IN THE TECHNIC OF OPERATIONS ON THE THYROID GLAND

GEORGE CRILE

GENERAL CONSIDERATIONS

Operability is estimated on the basis of the experience of the individual operator. It cannot be estimated by the size of the gland or the basal metabolic rate alone, the pulse alone, the age, the degree of emaciation, the morale, the presence of complications such as diabetes or nephritis, or the blood chemistry, but by a chastened judgment which takes into account all of these factors. No judgment should be final and if in the course of the operation doubt appears, then the operation should be terminated with a single lobectomy in order to give time for confirmation. In such a case the wound should be dressed but left open. If the warnings were superficial and not real the other lobe may be removed on the following morning. It is wiser to get the answer at the cost of a lobe than of a life. In other words, the surgical treatment may be a single or a distributed procedure.

If experience has taught us anything it has taught us that, on the whole, with the diagnosis of hyperthyroidism, thyroidectomy should be performed. There is but one definite and final contraindication, namely irremediable delirium. Every other grave condition or complication can be conquered.

The Anesthetic.—Since the earliest days of surgery the prevention of pain and the allaying of fear have been supremely important to the surgeon. Freedom of action in carrying out a delicate technic is the gift of full surgical anesthesia. After the discovery of anesthesia, chloroform and ether were employed for a long time. Relentless criticism drove chloroform out of the operating room but for many years ether was the anesthetic of choice. Ether is now under similar criticism and is at last giving way to the use of local, regional, and spinal anesthesia which have been steadily making their beneficent

way against general anesthesia, while the agencies for the production of general anesthesia certainly have changed.

When general anesthesia is indicated the inhalation anesthetics, such as nitrous oxide and ethylene combined with narcotics such as morphine, are used, and also the various kinds of intravenous, subcutaneous, and rectal anesthetics. But even these forms of anesthesia have been followed by evil results similar to those that followed the use of the heavier anesthetics, namely, uncertain effects, postoperative depression, interference with the function of organs, lessening of the factor of safety. In many cases these effects have been prolonged unduly, and in serious risks with a low margin of safety the mortality rate has been increased.

It would seem obvious that if the patient can be carried through the operation painlessly, without emotional disturbance, without general anesthesia and without the serious strain of being taken to the operating room, the operative risk will be greatly reduced. Under such conditions, moreover, there will rarely be vomiting. Vomiting not only disturbs the patient and violently disturbs the wound in the mobile neck, but it tends to produce hemorrhage, occasionally contaminating the wound, and lastly, and most important of all, it is only the symbol of a serious body-wide depression which involves every organ—every cell of the organism and represents a state which sometimes ends in death.

Were any inhalation anesthetic prolonged sufficiently, it would inevitably cause death. Operation under general anesthesia is in effect an operation under partial or temporary death. We believe that the bad risk patient with hyperthyroidism can be operated upon more safely under local anesthesia, combined with some form of analgesia, the more evanescent the better, than with any general anesthetic. We believe also that nitrous oxide is an ideal agent for the production of analgesia when it is administered by a trained anesthetist who is gifted with high intelligence and intuition.

Position of the Patient.—With the patient completely draped, leaving exposed only the neck, it is easy for the surgeon to fail to note the precise position of the head. The correct position of the head is the special function of the anesthetist. Unless the head is in the correct alignment the line of incision may fail to be symmetrical.

The Skin Incision.—In an operation for goiter it is important to remember that the scar descends during the first year and that too often it will be found conspicuously on the sternum. We have tried

the low or necklace incision and found that the larger the goiter the more the scar descends. Nothing should be more condemned than the lateral vertical incision. No plastic operation can overcome this error for fundamentally it is wrong to divide the elastic fibers in the skin at right angles, as the scar subjected to the continuing elastic pull progressively widens and deforms and embarrasses the patient.

In making the skin incision the two important facts to consider are the direction of the elastic fibers in the skin, an anatomical fact, and the fact that a scar, however long, is not noticed if it lies along the lines and in the direction of the normal folds of the skin, a psychological fact. The scar should lie inconspicuously among the normal wrinkles. The line of incision, therefore, should be anywhere in the region of the natural folds or wrinkles of the skin and parallel to them, and the incision is less conspicuous if it is long like its neighboring wrinkles rather than short.

What determines the normal line of wrinkles and how is the surgeon to recognize it when the skin is stretched doubly by the goiter and the back-tilted head? No wrinkle need be seen to know its normal course as the wrinkle is the creation of the position of the jaw and skull above and of the clavicle and the bony chest below, and the incision should be parallel to either one. When making the incision, the skin should not be held, for by holding it, the skin becomes easily displaced, thereby making a distorted line. The knife should, of course, be keen and a free incision should be made.

Platysma.—I have tried disregarding the platysma, reflecting it upward and dividing it, but having noted the results, it soon became clear that the skin incision should not pass through the platysma, and that the platysma need only be divided vertically. The delicacy of the expression of the neck in temperamental women will thus be preserved while otherwise an expressive face and the upper portion of the neck will reach a surgical deadline at the incision. The motor innervation of this delicate muscle comes from above downward and these motor nerves, if divided, cannot be restored.

Division of the Muscles.—In some thousands of cases I divided freely the muscles overlying the goiter and even devised a pair of clamps to facilitate the execution of this error. In the follow-up of these patients I was struck with the progressive recession and immobility of the neck just above the clavicle—a zone of physiologic death. The obvious truth was that the motor innervation coming from above downward was unwittingly divided with the muscles

and the division of these motor nerves made inevitable the complete atrophy of the distal section of the muscle that was divided.

It is not to be denied that the transverse division of the muscles gives a perfect approach by revealing the posterolateral aspect of the thyroid gland and this is just what the surgeon likes. However, we found two compensations for not dividing the muscle. One is the prevention of a deformity; the other, greater certainty of the preservation of the recurrent nerves and the parathyroid glands. Therefore, we make a long vertical incision in the anterior midline through the platysma and the fascia, and through the muscle in the median line, this being made possible by reflecting the skin flaps.

Skin Flaps.—The skin flaps should be reflected by a simple maneuver of the knife—a maneuver that might be called a "push-cut." The flap should include the subcutaneous fat down to the platysma. If the knife is allowed to come right up to the skin, the skin will adhere to the scar, which will cause annoyance to the patient. The only purpose of the skin flap is to give the opportunity of making the long vertical incision.

Control of Hemorrhage.—Is it necessary to expose the superior and the inferior thyroid arteries as a first stage in the thyroidectomy? This maneuver will certainly diminish, although it will not completely arrest hemorrhage as the blood vessels will still bleed and the field will still be obscured. Unless the superior and the inferior arteries are tied at a point beyond the first branch that leads to the thyroid gland, the bleeding for practical purposes will be but little reduced. The superior thyroid arteries are at best small arteries and as such demand no formal treatment. Their importance attaches not to their prowess as bleeders but to their position in the upper and the lower recesses of the neck where they shed their blood on important structures in obscuring profusion—notably on the recurrent nerves. If the thyroid arteries were freed from the tragedies of the recurrent nerves, their evil reputation would be gone.

THE PREVENTION OF ABDUCTOR PARALYSIS AND PROTECTION OF THE PARATHYROIDS

Unilateral abductor paralysis is unfortunate; bilateral abductor paralysis is a tragedy. It is scant comfort to the surgeon, and certainly no comfort to the patient, to have the paralysis appear several days after the operation, or after she has left the hospital. Frazier,[1] Sir Charles Ballance,[2] and others have made contributions to nerve

anastomoses, but much further investigation must be made. No method of treatment—massage, electricity, local applications—yields more than a meager result; prevention is the ideal.

Dr. C. C. Higgins[3] made many dissections of the recurrent nerves showing their inconstant position. The prevention of abductor paralysis, however, has little to do with a knowledge of anatomical landmarks. Every student of surgery knows the general position of the recurrent nerves, and yet the greatest tragedies which follow thyroidectomies pertain to these structures. Even the surgeon who has had much experience in operations on the thyroid gland reviews the position of the recurrent nerves as an evil memory. The hazard is not due, however, to the anatomical location of these nerves but rather to the vulnerability of their structures, to the neighborhood of fixation, to adhesions, and to certain characteristics of the nerve conduction.

The Vulnerability of the Recurrent Nerves.—As compared with the peripheral nerves, the recurrent nerves are exceedingly soft. In this respect they more nearly resemble the nerves of the spinal cord and of the abdomen—nerves which have had phylogenetic protection. The peripheral nerve fibers can undergo almost any degree of trauma without resultant motor or sensory disturbance, but the naked recurrent nerves are almost as sensitive as is the naked brain or the spinal cord, and the slightest direct, or even indirect pressure on a recurrent nerve interferes with nerve conduction and immediately changes the voice. Struggle and survival probably had no effect upon such vital organs as the larynx and trachea—the avoidance of death demanding their complete protection, so that in their vulnerability the recurrent nerves must be classed with the brain, the spinal cord, the optic and the auditory and the splanchnic nerves and it is this extreme vulnerability that is the first and the most important factor in the production of abductor paralysis.

The Fixed Point of the Nerve.—The soft recurrent nerve enters the box of the larynx and ends in a fixed attachment to the abductor muscles, its trunk lying in physical contact with the gland which is to be removed, the goiter having overgrown and overlaid the nerve and in some cases become attached to it. Here we have an ideal setting for trouble—a slender, loose-lying, highly vulnerable nerve, one end rather indifferently secured by the ramifications of the cervical fascia, one part attached by adhesions to a goiter which is movable and the other end fixed to the larynx.

Another fact of importance—and in this we have the setting for most of the tragedies of the recurrent nerve—is that because the direction of the growth of a goiter is determined by its growth pressure and the resistance presented, the goiter—like soft wax injected under pressure—is distributed above the larynx, behind the larynx, behind the trachea, and between the trachea and the esophagus, and in all

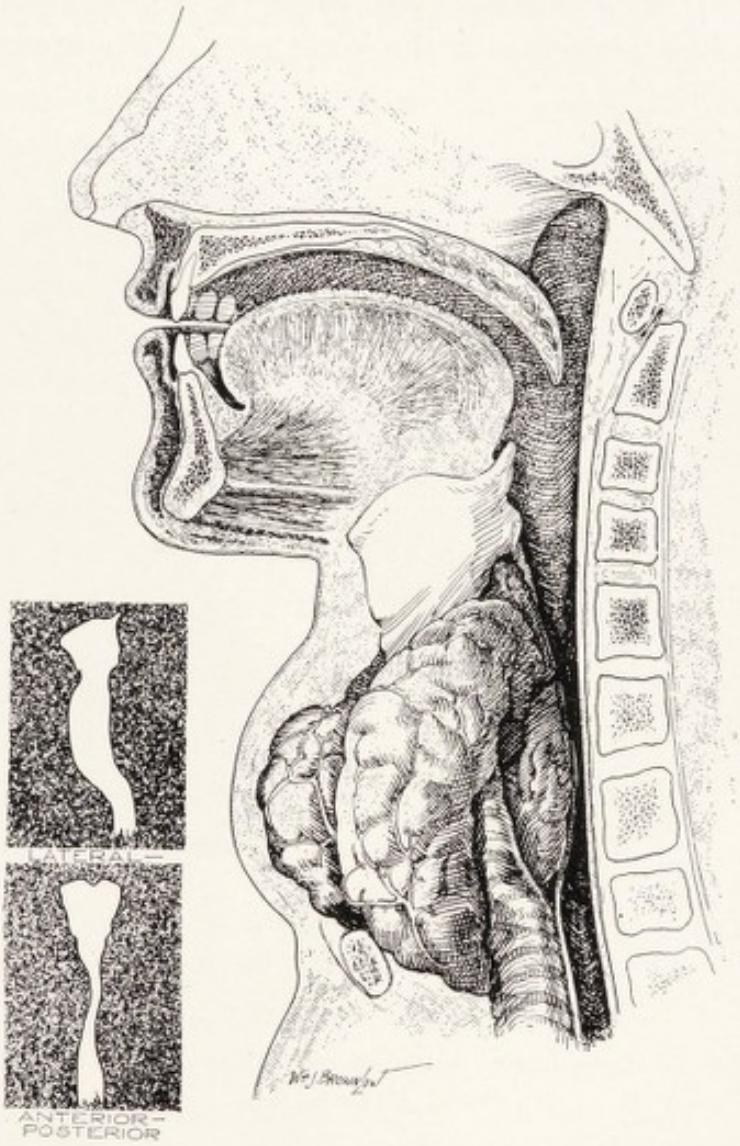


Fig. 142.—Goiter extending behind the trachea. A schematic drawing illustrating the position of the gland and resultant compression of the trachea.

of these instances, it overlies and surrounds the recurrent nerve. Therefore, if these extensions are brought out into the wound by rolling or by pulling the gland, if the slightest pull downward is made, the recurrent nerve breaks at its attachment and the tragedy occurs. The most common direct cause of abductor paralysis is the pull on the nerve which may occur when rolling out the goiter. The

most disastrous effect is produced when the nerve is disturbed by the dislodgment with the finger of an upper lobe which has thrust itself behind the larynx. Such direct pressure and pull on the laryngeal nerve have probably caused more paralyses than either forceps or knife. Any pull on the nerve may cause partial and temporary, or complete and permanent paralysis. How rarely is there a paralysis of the recurrent nerve due to extraction of the thyroids from the chest or from the deeper recesses in the lower neck. The upper backward

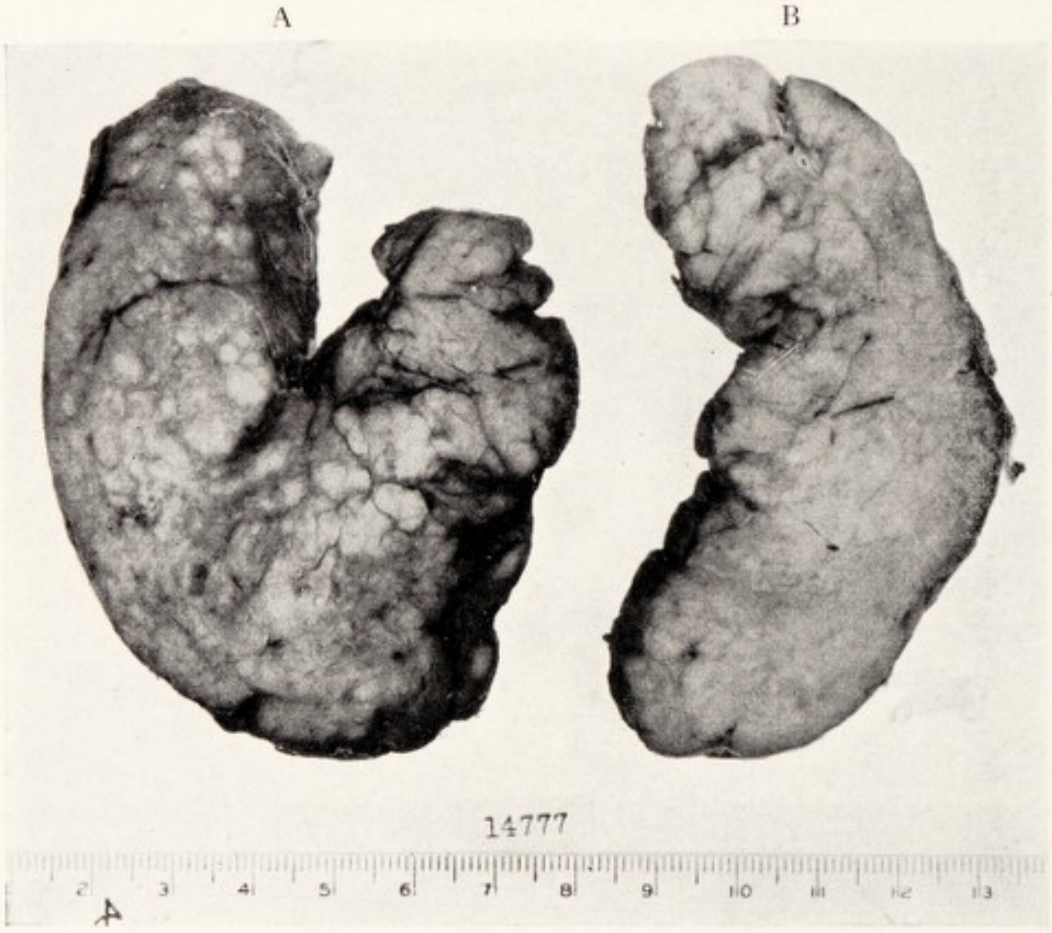


Fig. 143.—Lobes of thyroid removed from case illustrated in Fig. 142. A, Right lobe. B, Left lobe.

thrusts of the thyroid gland bring the train of trouble, although I do not mean to imply by this that the recurrent nerve is never injured directly by forceps or knife, by rough sponging, or by packing to control bleeding, but rather that abductor paralysis is probably most frequently caused by traction.

Neighborhood Changes.—A most important neighborhood change made by a goiter is the formation of adhesions between the capsule of the thyroid gland and the neighboring structures, including the

recurrent nerves. Such adhesions are frequently seen in cases of hyperthyroidism, of thyroiditis and of malignant tumors of the thyroid. The rôle which adhesions play in the production of abductor paralysis will be referred to later.

Late Paralysis Due to Scar Formation.—It is certain that if the nerve trunk is directly exposed in the course of the operation, the exposed nerve will be covered by scar tissue. Scar tissue is capable of producing a block of the action current, hence of causing a physiologic severance of the nerve. Permanent paralysis from a scar is just as great a tragedy as direct division of the nerve. In either case no ideal plastic operation has yet been devised, although the successful work of Frazier has brought us nearer than any other to its satisfactory solution.

The Parathyroid Bodies.—The posterolateral border of the thyroid gland is also the danger zone for the parathyroids. The parathyroids, as Terry[4] and Millzner[5] have shown, may appear on even the anterior aspect of the goiter but the posterolateral aspect, especially in its upper and lower portions, is the common location of the parathyroid bodies. It is so difficult to recognize the parathyroids that not only may the surgeon be uncertain during the operation as to whether or not any of the parathyroid bodies have been removed, but also the assistant who follows the useful suggestion of Lahey and searches the excised tissue may be equally in doubt, and may be obliged to turn to the accurately trained pathologist, who, in the quiet of his laboratory, may even require the confirmation of his microscope. Should the surgeon or his assistant recognize the parathyroid bodies in the excised thyroid tissue, they should be immediately transplanted into a muscle, as advised by Lahey.[6]

Technic of Transplantation of Parathyroid.—We obtained temporary relief from tetany when we transplanted the parathyroid itself, free from thyroid tissue, but it occurred to me that since the parathyroid bodies always bear a close anatomical relation to the thyroid glands, there might be some sort of mutual advantage, that is, an unknown symbiotic relationship between the two. To preserve this relationship, I carefully refrained from injuring the anatomical connection between the thyroid gland and the parathyroid glands by avoiding any physical injury of the tissue to be transplanted, and with a sharp knife transplanted a unit of thyroid-parathyroid tissue, thus transferring, as it might be, the parathyroid with its anatomical, perhaps nervous, and perhaps biochemical environment.

The functional integrity of the recurrent nerve and the parathyroid bodies depends on their safety not only from trauma, but also from swelling, edema and retraction, and therefore, the preservation of the small margin of thyroid tissue, with its capsule covering the nerve and the parathyroids by the method described above, is the best possible protection against these dangers.

We have now stated enough of the leading facts pertaining to injury of the recurrent nerve and the removal of the parathyroid bodies to serve as a foundation for the description of a technic that will effectively prevent, or, at least greatly minimize, these grave accidents.

TECHNIC FOR THE PROTECTION OF THE RECURRENT NERVES AND OF THE PARATHYROID BODIES

In the case of a simple goiter, or of a colloid adenoma, the preservation of the recurrent nerves and of the parathyroid bodies is simple and easy. But we have our real problem in the case of a hyperplastic gland which is as vascular as a nevus, is as soft as cheese, and is adherent to the surrounding tissues, when the patient is feeble and time important—a case in which unless the pound of flesh is completely removed, the patient will not be cured; and these are common cases.

The first requisite is a free exposure of the gland by a long vertical division of the preglandular structures from the larynx to the sternum, the lower part of the incision being made with a forefinger slipped behind the ribbon muscles so as to protect the vessels on the surface of the goiter and the veins in the lower neck. If the long vertical incision does not give enough exposure, then a transverse incision must be added.

If both lobes are of about the same size, adherent and set deeply in the lateral aspect of the neck, the mode of attack is by a vertical division of the gland in the midline, the division being carried not to the wall of the larynx and trachea, but to a point just short of the rings and the laryngeal box, that is, the incision should pass just through the thyroid tissue and no further. Then with thin accurate hemostats without barbs or hooks at the end, the attachments of the goiter to the trachea and larynx are caught and divided point by point, the division including the attachments of both the upper and lower pole. As soon as opportunity offers, the superior and the inferior thyroid arteries are picked up and divided. The gland is now free to be lifted gently, little by little, from its position deep

in the neck, each resisting point being caught with the slender blades of the forceps until the outer margin of the gland comes into the range of operation, when the hemostats are attached to the outer margin.

Since the nerves lie in the tracheo-esophageal space, the dissection is not only carried downward and outward but, until the deep capsule is reached, it is kept within the gland where there is no danger of approaching the nerve. When the deep capsule is reached, the forceps are so placed that a margin of thyroid tissue is left behind for the protection of the recurrent nerve during the operation and for another and equally important reason, namely, the protection of the nerve against scar formation. Always, from the beginning to the end of the operation, the point of each hemostat is directed inside the capsule of the gland.

By this technic neither the recurrent nerves nor the parathyroids will be exposed to view, nor subjected to trauma, not even by direct pulling. As the patient is under analgesia and can talk throughout the operation, the surgeon is made all too clearly aware if there should be any transgression against the nerve by either direct or indirect injury.

After one lobe is excised, the hemostats are tied off. The bed of the final wound—looking like Topsy's head—will show many small buds of thyroid tissue at the point of the ties. It may be argued at first thought that the ligation of these small masses of thyroid tissue is not so desirable as the ligation of the blood vessels singly, but a moment's consideration will show the advantage of tying these small masses. The great difficulty is the removal of enough of the thyroid tissue without injuring the nerves or the parathyroids. By the ligation of these small masses the tissue included in the ligature is destroyed. Some of these knobs of tissue are clipped off, but most of them remain as they are tied. To search out and tie single vessels leads to many accidents because of their fragility and if one is broken then the precise position of the rest becomes obscured. The bleeding vessel, like the squid, obscures the field and the securing of a vessel thus hidden in obscurity in close proximity to the recurrent nerve is in itself a hazard. It therefore is a safer and an easier method to catch many vessels in a safe zone within which the danger of retraction or mischance is limited. This method has one objection, but it has two outstanding advantages. The objection is that the small tufts of thyroid tissue will be absorbed with the catgut ligature and in this process there will be created an added amount of serum. This serum rarely requires drainage but in some cases enjoins on the patient

several added days of quiet during its absorption. It almost never eventuates in infection. The two advantages in the tuft tying are minimizing postoperative oozing and lessening the time of the operation. The excessive vascularity of the thyroid makes it difficult

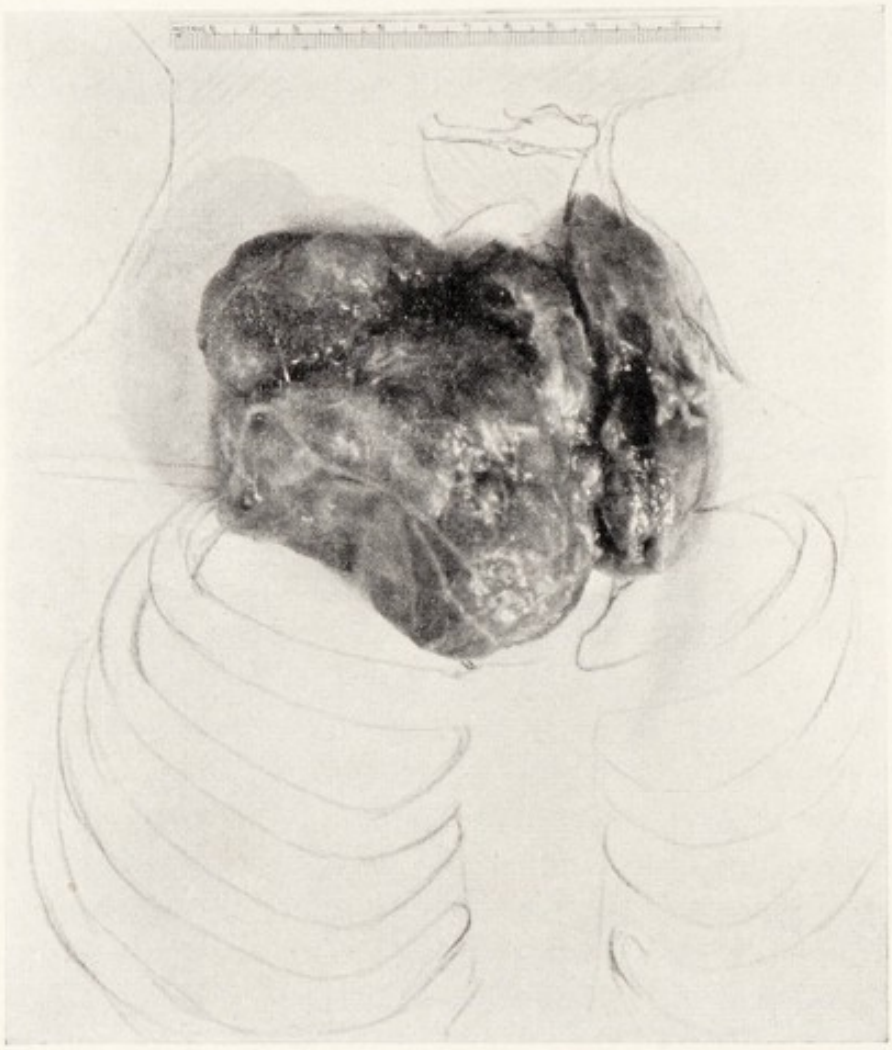


Fig. 144.—Intrathoracic goiter with hyperthyroidism. In this case, that of a woman sixty-three years of age, the patient presented symptoms of hyperthyroidism with marked dyspnea. At operation the right lobe of the gland was found to extend into the chest, an extension from the lower lobe passing over the midline to the left side. Pathologic diagnosis: Fetal adenomata.

to seize and tie every potential oozer. The objections seem but a trivial price to pay for a safer operation.

If the goiter is retrolaryngeal, then when its attachment to the larynx is completely severed, the retrolaryngeal portion will slide out almost without aid and the voice will not even be changed in pitch.

If the goiter is substernal, the process of delivery resembles the laying of an egg (Fig. 144).

If the goiter is behind the trachea, it is easily drawn out. It matters little into what recesses the goiter has thrust itself, once its attachment to the larynx has been divided it will tend to extract itself because of the severing of this attachment and the release of the pressure.

Protection of the Nerve Against Scar Formation.—The posterior margin of the thyroid, that part lying between the capsule and the nerve, is "No Man's Land." It is not palpated; it is subjected to the least possible traction, and no division of tissue is made, so that no paralyzing scar can form during the healing of the wound.

By these precautions temporary and permanent injury of the recurrent nerve may be completely eliminated, except in the occasional case in which a technical emergency arises.

AMOUNT OF THYROID TO LEAVE

How much thyroid tissue should be left? From the standpoint of end-results the surgeon must steer a difficult course between the Scylla of myxedema and the Charybdis of failure to cure the disease.

The most permanently satisfactory results are secured in the cases in which such an amount of thyroid tissue is removed as to produce a temporary, mild hypothyroidism which is characterized by a gain in weight, a slight feeling of coldness in the extremities, some dryness of the skin, and subnormal reaction to ordinary excitation, that is, the condition which is associated with a slightly subnormal basal rate. When this condition follows the thyroidectomy the patient usually passes through a definite cycle, progressively increasing in weight for from four to six months, then gradually losing in weight until the pregoiter normal is regained. All the psychical and physical processes participate in this cycle. It is during this stage of "overcure" that the internal, fundamental reconstruction takes place which leads to a permanent cure. Only occasionally is it necessary or indeed wise to give thyroid extract and when such medication is indicated, it should be given intermittently.

On the other hand, the patient, who after the operation still has even a slight residuum of the symptoms of hyperthyroidism, is likely to grow worse, not better. His course is just the opposite to that of the patient in whom mild myxedema develops.

In our earlier experience, our anxiety to assure the safety of the parathyroids and laryngeal nerves led us to leave too much thyroid tissue in too many cases. What constitutes too much? The right

amount to leave in the case of an aged patient with colloid adenoma would be enough to continue the disease in a young patient with a hyperplastic gland.

When hyperthyroidism is associated with a unilateral adenoma at any age, it is safest to perform a bilateral resection. In some of our cases in which we left the apparently unaffected lobe untouched, because we thought it was normal and quiescent, after a number of years a large goiter developed, and in these cases not only was there a new goiter, but there was also a new hyperthyroidism. Another reason for resecting the apparently normal lobe is that, until it is actually exposed to view, its size cannot be exactly ascertained. More than once I have been on the point of leaving such an apparently innocent lobe, but on further investigation have found a surprisingly big mass of thyroid tissue tucked away as if by trickery, in the deep recesses of the neck. The lobe in ambush is often larger than the lobe in the open.

The amount of thyroid which should be left depends also upon the aggressiveness of the disease. In the case of a goiter whose drive against the organism of its victim gains momentum slowly, running a steady course without violent fluctuations in its severity, more thyroid should be left than in a fulminating case of hyperthyroidism.

The amount of tissue to be left depends not only on the age of the patient and on the duration and the intensity of the disease, but it depends also upon the temperament of the patient, upon his economic and social status, and upon his psychic environment. In the case of a temperamental young married woman with a faithless husband, a sickly child, insufficient income, a quarrelling family, and infected tonsils, hyperthyroidism may continue in the presence of a small amount of thyroid tissue. Such a patient is not safely cured unless there is removed all of the gland that can be safely removed without laying bare the recurrent nerves and damaging or excising the parathyroids. Such a temperament multiplied by embitterment, fears, worries, anxieties, and despair causes almost any fragment of thyroid to grow to formidable size.

On the other hand, an unexpected outcome of thyroidectomy is sometimes observed in such a case as we have been describing; following the operation the patient's physical and mental condition is immediately and greatly improved, and the tranquillity and sound judgment which supplant the former abnormal irritability, bring

about a readjustment of the very difficulties which either caused or aggravated the disease.

The question as to the amount of thyroid tissue to leave must be settled before the final stage of the technic is entered. As a guide I have considered several criteria. I know now that the basal rate is a weak reed upon which to lean. The total mass of the gland is no safe guide, for mild hyperthyroidism may be associated with a rather large goiter in an elderly subject in which case a relatively larger amount should be left. On the other hand, very severe cases of hyperthyroidism in a younger individual may be associated with a gland which is too small to be readily palpated, in which case but little should be left.

The amount to be left is a matter of developed personal judgment, continually checked by a close follow-up of cases and the discipline of error. In the case in which there has been a rapidly acute onset of the hyperthyroidism more of the gland must be removed than in the chronic cases; the younger patient requires the removal of more than the older one; certain races and intense temperaments more than the placid types; the patient in whose domestic, financial, and social status there is irremediable distress needs a wider excision than the patient who has undergone a single but passing crisis. Regardless of all other considerations, the larger the gland the more mass is left, and *vice versa*. If it were possible, a logarithm would be determined expressing the intensity, size, etc., of the gland, but although there is no such mathematical formula, there is one important guide which may be considered as a living expression of such a logarithm, that is, the characteristic appearance of the gland itself. Its vascularity, its softness or brittleness, its fixity in position due to adhesions between its capsule and the adjacent tissue—in short, the entire picture presented by this hard-worked gland represents the physical havoc wrought upon it by every emotion and fear, by every impulse that comes over the sympathetic innervation to goad it on to more work. The gland carries on its face the strain which is the most accurate of all criteria, although, unhappily its message is empirical. The other important point is that none of this residual mass of gland should be wasted by being left where there are neither parathyroids nor recurrent nerves to protect but the calculated mass should be left along the lateral posterior boundaries of the gland. The lateral margin and the margins of the upper and lower poles contain the parathyroids, and cover the recurrent nerves.

The ideal operation would be to extract by some magical process the portion of the gland to be removed, leaving the entire capsule and a uniformly thin margin along the posterolateral surface and around the upper and lower poles, and a protecting film for the comfort of the trachea and the larynx.

THE HIDDEN GLAND

The most common cause of the so-called recurrences of hyperthyroidism is the inadvertent failure to remove a tongue of thyroid tissue whose growth energy has thrust it into a curiously soft, nonresistant cove behind the larynx just at the upper margin of the larynx but below the pharynx. This error is due largely to the appearance of the cove, as the surgeon thinks this cove is the end of the gland. The result of failing to remove this tongue of the gland is that in a short time, sometimes immediately after the patient has left the hospital, as the result of the release from pressure from in front, the thyroid mass usually though not always slowly emerges from its cove and becomes apparent at the side of the larynx. The patient herself notes the mass and the final result is inevitable residual hyperthyroidism. In these cases a second operation is clearly needed.

When the technic we have described is used, in which the operation proceeds from within outward all the attachments first being severed, such an error is not made, as this tongue of the gland will be drawn out into view.

CLOSURE OR DRAINAGE

If a simple single adenoma has been removed, then one may close without drainage. But when a hyperplastic gland has been removed, if the surgeon has planned the excision with the purpose of protecting the parathyroids and the recurrent nerves and has balanced this consideration against the decision as to the correct amount of gland to remove, then if the capsule cannot be closed, in order to maintain in a normal thyroid balance, it is rarely advisable not to drain.

Drainage.—Some years ago I for the last time committed the error of making a counter drain through a low point in the flap, with the idea that the lowest point of gravity should be used since such a point gives the best drainage, but it puts the mark of Cain on the patient's neck.

In most cases a rubber drain is used as it occupies but a small space and can be withdrawn painlessly at the end of the same day

or on the next morning, without distorting the line of union and without leaving any permanent scar.

Closure of the Deeper Part of the Neck.—Since the muscles have not been divided transversely they are brought loosely together by interrupted stitches, the fewer the better, two usually being enough. Special care should be taken to bring together and to reestablish the reciprocal relation between the ribbon muscle and the up and down excursions of the larynx in speaking, swallowing, and coughing.

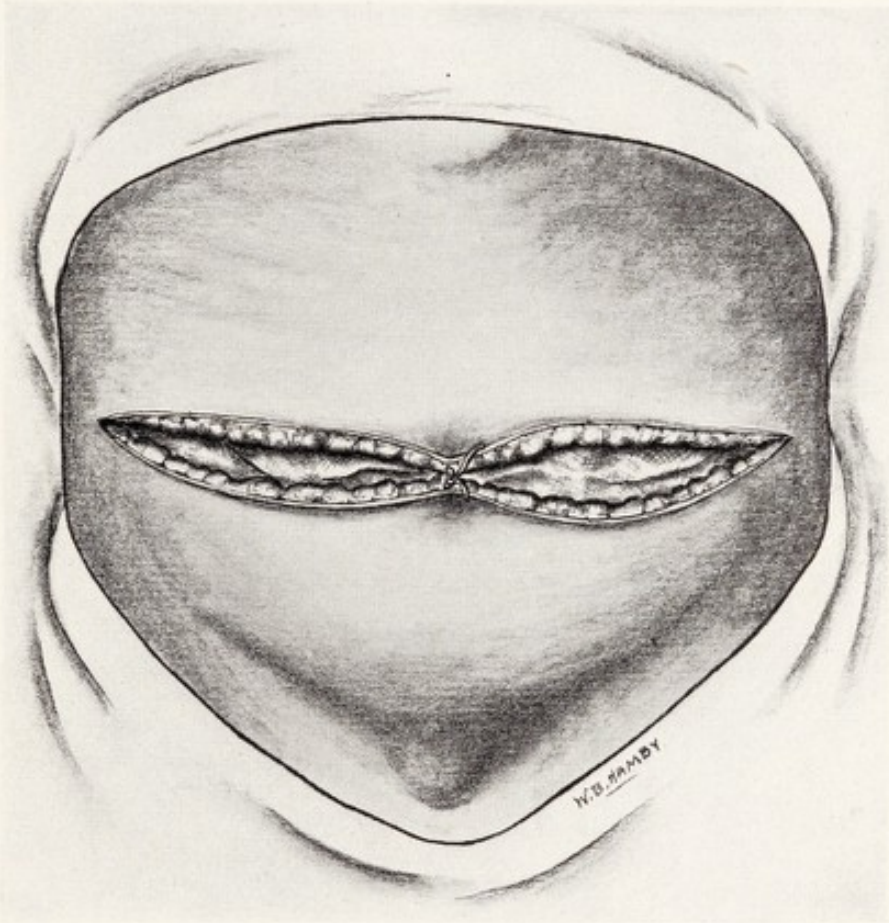
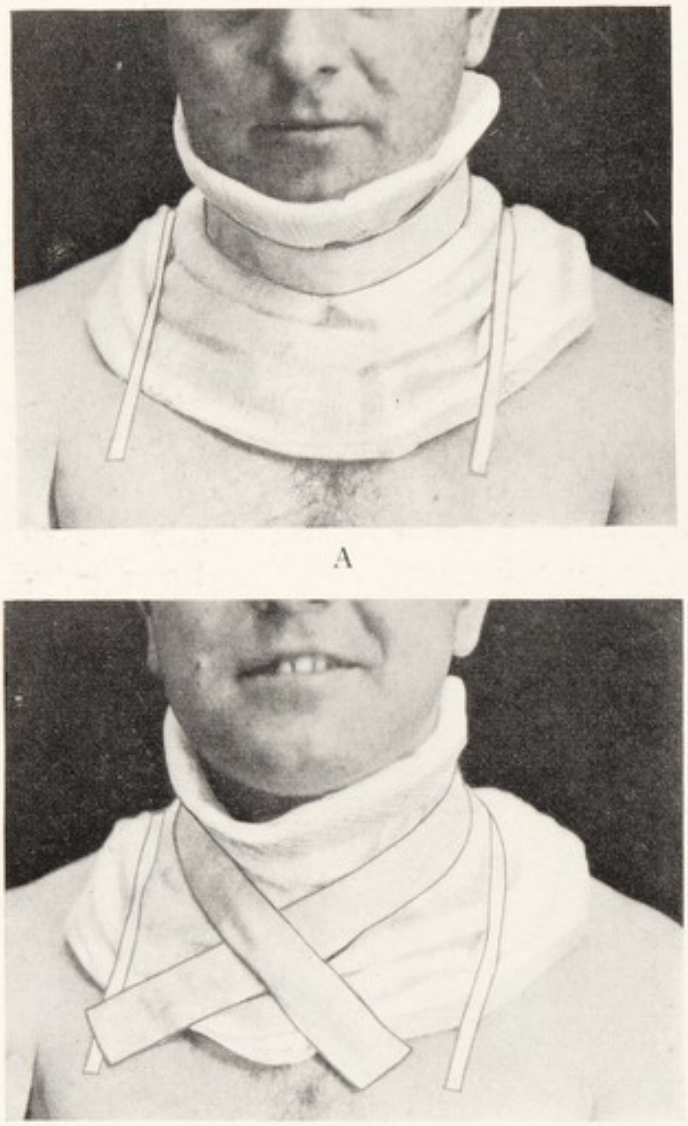


Fig. 145.—Delayed closure of wound after lobectomy.

This reciprocal relation endows the larynx with a trombone-like action and, unless care is exercised, external and internal adhesions will be made which will annoy the patient because of a pulling sensation and also because of an equally annoying puckering of the skin. The fashioning of the flap in the right plane, the maintenance of the tone of the platysma, the least possible trauma by the thyroidectomy, together with accurate reunion by light tying and few sutures, will disturb the least the physical integrity of that interestingly intricate, expressive structure—the neck.

Except when adenomata have been removed, as stated, there will be but few occasions for suturing a divided capsule.

Delayed Closure.—There can be no question that in extreme risks a delayed closure serves the patient well as it cuts short the operative



A

B

Fig. 146.—Photographs illustrating common mistakes made in applying the dressing after thyroidectomy. A, Note that dressing protrudes over chin. B, Note that broad adhesive strap is not perpendicular to axis of neck.

time, and prevents the absorption of the wound secretion, which is an important factor in the production of a postoperative reaction.

The technic of this procedure is as follows: The wound is left wide open and its interior is covered, not packed, with vaselined gauze. The gauze is made to cover the raw spaces in such a manner that at no point does raw tissue come in contact with raw tissue.

Gauze separates the rough surfaces even to the undercutting of the skin flaps; and the amount of gauze is so calculated that the flaps can be drawn over it completely and held together by one suture made through the subcutaneous tissue, but not through the skin, at the middle of the incision (Fig. 145). This maneuver prevents retraction of the flaps. The entire neck is then dressed just as if the wound had been closed.

Twenty-four hours after the operation, with the patient in bed, under analgesia and a complete local block, the vaselined dressings are removed from the recesses of the wound and the wound is closed as described above. The scar will be slightly larger than after a

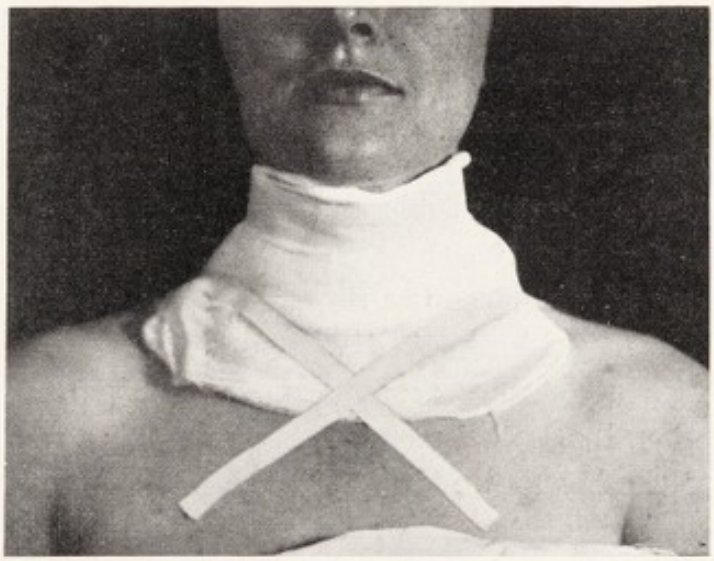


Fig. 147.—Photograph illustrating proper application of dressing after thyroidectomy. Note that dressing fits snugly under chin with main adhesive strap perpendicular to axis of neck.

primary closure but this is little enough to pay for living at all, for one might otherwise be tempted to consider the type of cases in which the wound is left open, as unsuited for operation. Such cases require short-cuts and feather-light contacts and delayed closure. One could easily reject this small group, but the almost miraculous recoveries and reconstructions which occur among these desperate cases leaves no doubt as to where duty lies.

Skin Suture.—We have tried many kinds of suture but prefer skin clips, which are removed on the third day after operation, and occasionally on the second day. The advantage of clips is that they completely control the slight oozing along the entire thickness of the skin and for a little distance back from the edges of the wound;

they make the broadest approximation in the form of an ectropion, and they are speedily introduced and as easily removed.

The Dressing.—The dressing should be so adjusted that the wound is always protected but the neck not constricted. Adhesive tapes hold the dressing in place (Figs. 146, 147).

INTRATHORACIC GOITER

Pemberton[7] and Lahey[8] have described excellently the technic for the removal of intrathoracic goiter.

This unique type of goiter not only requires unique technic, but it also presents an unique advantage. This advantage is that the recurrent nerve is much safer in a downward than in an upward displacement of the goiter.

The cases in which the removal of a large goiter is required for cosmetic reasons or because of pressure on the trachea need no comment. But there is one variant among the inactive goiters that is not accompanied by any visible deformity. I refer to the goiter that has descended into the thorax, where it compresses the greater vascular trunks and displaces the thoracic contents, even the heart.

These goiters may be removed without incident and with safety if the following simple rules are observed: The patient should not be given a general anesthetic. At the first step, the attachment of the goiter to the larynx and trachea should be completely divided and every vessel tied, leaving a clear anatomical field. The next step is to enter bloodlessly into the exact line of cleavage of the capsule of the adenoma, and the third step is to ascertain whether or not the thoracic outlet allows space enough for the exit of the goiter. If there is sufficient space, then by finesse and by the intermittent intrathoracic pressure due to the respiratory excursion, the goiter may be induced to come out without the use of force, certainly without any force from the side or from below. The finesse should be similar to that of a normal delivery by a skilful obstetrician. One point is certain, the delivery should be teasingly slow to avoid tearing of the large vascular trunks of the lower pole. Such an operation is either extraordinarily easy or it becomes suddenly difficult.

On the other hand, if during its sojourn within the thoracic cage the goiter has grown larger than the superior thoracic opening, a different mode of attack is made. The adenoma is steadied by forceps and scooped out until its size is reduced sufficiently for it to be extracted as described above. It should be emphasized that in the

removal of an intrathoracic goiter absolute control of the least drop of oozing is demanded, for if there be oozing, it may continue until the entire mediastinal space, or indeed the chest, is filled and the patient dies of asphyxia. According to Lahey in many of these cases the wound should be left open and packed with gauze for twenty-four hours.

TIME

It is a sound principle that the time consumed in any operation should be the shortest time in which it can be performed by the most highly organized team with no haste, with the utmost control of details and with a consideration of the problems presented by the individual case. In other words, the operation when completed should be as perfect both as to judgment and technic as if it had taken a longer time.

Tying Blood Vessels.—One of the time-consuming factors in the technic of an operation for hyperthyroidism is the time consumed in the securing and tying of blood vessels. As previously stated, the isolation of the trunks of the vessels involves not only too much time but too much dissection to justify it and the added time involved in the grasping and tying of tufts of thyroid, including the many blood vessels, likewise forbids the separating of the many branches, especially those coming from the trachea and the larynx. The time consumed by the operation is shortened by the method which has already been described by which tufts of thyroid tissue including the blood vessels are grasped and tied.

THE TEAM

To carry out successfully the technic described above it is clear that the operation cannot be performed by the surgeon alone, but by a team, of which the surgeon is the captain. The following make up a good working team, each member of which should be permanent, as the key positions for the performance of a thyroidectomy provide no place for the training of unskilled nurses or interns: anesthetist, scrub-up nurse, first assistant, and second assistant.

The Anesthetist.—The anesthetist is a highly important member of the team. She should be a nurse of a high order of intelligence, keenly reactive to every passing change in the condition of the patient, and a skilled psychologist, able to cajole an abnormally sensitive patient, sensitized especially to fear, and to interpret and allay each reaction. No member of the team is more essential than the anes-

thetist, and this is especially true if the operation is performed under analgesia or under local anesthesia alone.

The Scrub-up Nurse.—The scrub-up nurse must be endowed with such a clear head, such keen perception, such an accurate knowledge of the steps of the operation, that in all its vicissitudes, in every step in the technic, in every requirement of the operator and of his two assistants, she anticipates every needed thing. The position of scrub-up nurse is most important, and one who entirely fills its exacting requirements is rare.

The First and Second Assistants.—By experience and training the first assistant should himself be able to perform the operation creditably. His post is opposite the surgeon and until the thyroid is attacked his duties are those usually undertaken by a first assistant.

The second assistant should have had training in general surgery.

The successful thyroidectomy is performed not by an individual but by a team, the activity of each member of which is correlated with that of the others. Each plays an essential rôle.

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CHAPTER XXXIV

THE ADRENAL FACTOR IN HYPERTHYROIDISM AND ITS CONTROL

GEORGE CRILE

THE symptoms of hyperthyroidism are identical with the symptoms of adrenalism. Each activates the nervous system; increases heart action and blood pressure; causes dilatation of the blood vessels of the skin with resultant sweating; increases metabolism; tends to produce hyperglycemia, has a profound effect on the gastro-intestinal tract.

It is clear that the sympathetic nervous system has a definite influence upon the function of the thyroid for Cannon[1] has shown that electrical stimulation of the nerve supply to the thyroid causes an increase in the activity of the thyroid gland. Cannon[2] also showed that adrenalin exerts a stimulating effect upon the thyroid gland. There is also clear clinical evidence to the same effect, as interruption of the sympathetic stimulation of the thyroid by resection of the cervical sympathetic ganglia, as advocated by Jonnesco,[3] relieves exophthalmic goiter.

Experimental evidence also confirms the clinical observation that as the thyroid activity is increased, the effect of adrenalin on the organism is stepped up. Thus the injection of adrenalin in a patient who has hyperthyroidism produces an exaggeration of every symptom of the disease. On the other hand in myxedema the injection of adrenalin has little effect, a fact which shows that the production of adrenalin is dependent on the thyroid. Not only does adrenalin lose its power in the presence of thyroid deficiency but in the presence of adrenal deficiency as in Addison's disease hyperthyroidism cannot occur. It follows that the thyroid and the adrenal glands are equally essential for the production of hyperthyroidism.

It is also a significant fact that the exciting causes of hyperthyroidism and of thyroid crises are the same as those that produce an

increased output of adrenalin. The only factors known to me that can produce a thyroid crisis are the following:

1. Pain.
2. Emotional excitation.
3. Foreign proteins—auto-intoxication, wound secretion, focal infection, infectious disease.
4. Asphyxia.
5. Hemorrhage.
6. Inhalation anesthesia.
7. An injection of adrenalin.

With the exception of the last one, every one of these factors is capable of producing an increased output of adrenalin. Moreover, just as no other known factor can produce a thyroid crisis, so no other recognized clinical condition can cause an increased output of adrenalin.

Hyperthyroidism, then, is the result of increased adrenal activity but only in the presence of increased thyroid activity. I have seen no case in which hyperthyroidism has been associated with a normal thyroid gland and none in which the patient's condition did not improve after the removal of a sufficient portion of the thyroid gland. From the above considerations, however, we now see that partial thyroidectomy is effective because it lessens the activity of the thyroid gland and because by lessening the activity of the thyroid gland it also lessens the activity of the adrenal glands.

In view of the above considerations it would appear that lessening of the activity of the adrenal glands directly should lessen also the activity of the thyroid gland and should have both immediate and remote advantages in cases of extreme or of recurrent hyperthyroidism.

Acting upon this assumption we have performed this operation in 24 cases of recurrent or residual hyperthyroidism and in 21 cases of primary hyperthyroidism in which the condition of the patient was so acute that an operation upon the thyroid gland itself could not be contemplated for fear that the resultant crisis might overcome the already slight margin of safety.

A comparison of the immediate effects of adrenal denervation with those of thyroidectomy is significant. After thyroidectomy the patient is at first extremely nervous and difficult to quiet. After adrenal denervation the patient is usually quite calm and rests well. More sedatives are required after thyroidectomy than after adrenal

denervation. By denervation, therefore, the acute exacerbation of the hyperthyroidism, which is so dangerous in cases of extreme hyperthyroidism, is avoided.

After thyroidectomy the pulse rate is usually increased and remains so for several hours, often increasing in rate, rather than decreasing; after adrenal denervation the pulse rate gradually drops. Excessive perspiration is noted after thyroidectomy and but a moderate amount after adrenal denervation.

As for the remote results in cases of primary hyperthyroidism the permanent lessening of the activity of the adrenal glands lessens the probability of a recurrence of the disease after the removal of a portion of the hyperactive thyroid. In cases of recurrent hyperthyroidism the probability of further recurrences is lessened.

As for the technic of denervation, it requires meticulous care demanding the precision of Frazier's operation on the gasserian ganglion. A bloodless kidney incision, long enough to introduce the hand, is made and carried down along the upper border of the kidney including the upper pole, near which and deeper will be found the suprarenal buried in a special fat. On the right side the suprarenal lies among an important group of organs which include the diaphragm, the liver, the duodenum, the head of the pancreas, the vena cava and the kidney.

The suprarenal gland is soft; it cannot be subjected to traction or pressure; it has three arteries which are not easily visualized, and it has from thirty to forty nerves. The suprarenal is the spider in the sympathetic web. It is not believed that regeneration of the nerves of the suprarenal will take place, as these nerves are, I believe, efferent, not afferent. During the manipulation the blood pressure rises sharply, sometimes it is even doubled. Spinal anesthesia is exceptionally effective in denervation, and if the operation is carried out with exact technic the risk is slight.

The second denervation is performed a week or more after the first.

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CHAPTER XXXV

POSTOPERATIVE MANAGEMENT OF PATIENTS WITH HYPERTHYROIDISM

ALEXANDER T. BUNTS

FOLLOWING thyroidectomy for hyperthyroidism there is usually a period of two or three days during which a reaction is to be expected, and intelligent observation of the patient and constant watchfulness for changes in his condition during this period are usually well rewarded by a smooth recovery. It is therefore advisable, whenever conditions permit, to have a special duty nurse in charge of the patient for at least two or three days following the operation. To her the surgeon must look for the early recognition of such untoward events as "severe thyroid reaction," hemorrhage, stridor, and tetany, in order that he may be notified in time to combat these conditions effectively.

The usual uncomplicated cases present no particular problem and can be managed in a more or less routine manner. At the completion of the operation, which has been performed under analgesia, the patient is conscious and able to cooperate. After the dressing has been applied the patient is given immediately a hypodermic injection of morphine, $\frac{1}{6}$ grain, and after the skin of the abdomen has been sterilized with iodine and two small areas lateral to the umbilicus have been frozen with ethyl chloride, two needles are inserted under the skin for the administration of 2000 cc. of sterile normal saline solution to which sufficient novocaine has been added to make a 1/32 of 1 per cent solution (Bartlett's method). This is repeated if the condition of the patient demands it. The patient is then placed in a comfortable position with the head and trunk moderately elevated. An ice-bag is placed over the head, and a gauze dressing soaked in ice water and placed on the forehead has a soothing effect.

In the majority of cases a transfusion of blood is given immediately after operation and is repeated as the indications in the individual

case may demand. In one case in which there was marked myocardial damage with fluid in the chest, ascites and swelling of the ankles, five transfusions followed the primary lobectomy. The patient returned for the second lobectomy five months later in fine condition showing no signs of cardiac insufficiency.

During the first forty hours following operation the patient should be kept absolutely quiet by the administration of morphine in $\frac{1}{6}$-grain doses as often as necessary and advisable in the individual case. The temperature and pulse reactions are much less marked if the patient is free from apprehension and restlessness. As an aid in the prevention of a severe "thyroid reaction," iodine is administered in the form of Lugol's solution, 3 cc. in cream by rectum on the afternoon of the operative day, and 1 cc. in fruit juice three times a day by mouth for three succeeding days. After that period iodine therapy is discontinued.

It is of great importance to support the fluid balance of the body. The fluid intake per day should not be allowed to fall below a minimum of 3000 cc. The patient is urged to take fluids by mouth, in the form of orange juice and grape juice to which glucose has been added, and an abundance of water. If nausea should prevent a sufficiently large intake of fluid by mouth, a sufficient amount of saline solution should be given by hypodermoclysis to bring the total fluid intake to 3000 cc.

During the first two days a light diet may be given. Its consistency should permit of easy swallowing, as during the first few days after operation swallowing may be attended by considerable discomfort. Later the diet may be increased and adjusted according to the patient's individual requirements and desires. It is well to avoid the use of laxatives and enemata until the third postoperative day, because of the danger of precipitating a fatiguing diarrhea. Before expulsion of the bowel contents following an enema, the patient should be warned not to strain while on the bed-pan, because in certain cases in which the myocardium has been severely damaged there is danger of acute cardiac dilatation and death.

Following thyroidectomy for hyperthyroidism there is usually a rise in temperature of 2 or 3 degrees and a corresponding elevation of pulse rate during the first night, but the most marked reaction in temperature and pulse rate usually occurs during the second night after operation. At that time it is not uncommon to observe a temperature of 102° to 103° F. and a pulse rate of 120 to 150, and a severe

"thyroid reaction" may occasionally occur with a rapid rise in temperature to 104° or 105° F. and an extremely rapid pulse which may develop an irregular rhythm. Marked reactions are more common in hot weather. Temperatures of 102° and 104° F. are combated by the application of ice-bags (10 to 30) to the lower extremities and extending as high as to the waist. In cases where the temperature is over 103° F. it is also advisable to reopen the wound, evacuate the serum which has accumulated behind the muscles, and insert a rubber tissue drain or a gauze packing. This procedure, of course, will necessitate a secondary closure of the wound after the reaction has subsided, but its efficacy in rapidly bringing about a reduction in the alarming temperature and pulse rate cannot be questioned. In the event of a temperature of 105° F. or over, the patient should *immediately* be placed in a complete ice-pack from neck to feet.

In the control of marked tachycardia during a "thyroid reaction" morphine is the most useful drug, but tincture of digitalis by mouth in 2 or 4 cc. doses at intervals of two to four hours should also be given. In cases where medication by mouth is impossible because of nausea or lack of cooperation, digifolin should be given hypodermically in 1 ampule doses every hour for five or six doses. When a severe reaction is managed promptly and efficiently, it usually subsides in from twenty-four to forty-eight hours; otherwise it may become progressively worse and end in death.

Hemorrhage following thyroidectomy is an uncommon occurrence when meticulous care has been taken to secure good hemostasis during the operation. The nurse, however, should be instructed to be constantly watchful for symptoms and signs of hemorrhage, such as a sensation of marked tightness in the neck, dyspnea due to compression of the trachea by clots incarcerated beneath the muscles, bulging and ecchymosis of the skin flaps with escape of clots through the drain hole, pallor, rising pulse rate, and prostration. These signs should be reported to the house surgeon immediately, in order that he may see the patient and deal with the situation without delay. If the condition warrants it, the wound should be opened at once, the clots evacuated, and the bleeding vessel clamped and ligated. This should be done in the patient's room without moving him from his bed. Promptness is the keynote in the management of severe hemorrhage following thyroidectomy, because the anoxemia resulting from compression of the trachea by blood clots is poorly tolerated, particularly in patients with hyperthyroidism.

Stridor or dysphagia, or both, may occur following thyroidectomy, and they should be recognized early. They are usually indicative of impairment of function of the recurrent laryngeal nerves and of the superior laryngeal nerves. As soon as possible after the onset of stridor, a laryngeal examination should be made in order to determine whether there is an abductor paralysis of one or of both vocal cords. Tracheotomy is almost never required in the case of a unilateral paralysis, but is usually necessary in the case of a bilateral abductor paralysis. In any event tracheotomy is always indicated in the presence of marked stridor, labored respiration, and a rising pulse rate. This procedure must be carried out promptly and should be performed before the fingernails become cyanotic. If the patient is unable to swallow, and if he regurgitates fluids, it may be necessary to insert a duodenal tube into the stomach, using indirect vision with a laryngeal mirror to guide the olive tip of the tube into the upper end of the esophagus. The tube may be left in place several days for the purpose of introducing nourishment into the stomach. The function of deglutition usually returns to normal within a few days, and the tube may be removed.

Numbness and tingling of the hands and feet and tingling around the mouth, together with circumoral pallor are the earliest symptoms of tetany, and their occurrence should be reported by the nurse at once. Carpal spasm and hypertonicity of the facial muscles may occur in more marked cases. Chvostek's sign and Trousseau's sign usually are present. A tetanic spasm is almost invariably well controlled by the administration of 1 or 2 cc. of "parathormone (Lilly)" subcutaneously or intravenously, as the severity of the case may indicate. The spasm usually subsides within twenty or thirty minutes after the administration of parathormone. A blood calcium determination should be made as soon as possible, and the further use and dosage of parathormone may be regulated according to the symptoms of the patient and the blood calcium level. This treatment may be supplemented by large doses of calcium lactate by mouth, and by ultraviolet light therapy.

After operation the patient may be troubled by an accumulation of mucus in the trachea and pharynx. Codeine has been found useful in alleviating this condition, and in cases in which the mucus is extremely persistent and interferes with proper aeration, atropine is a great aid.

Bronchopneumonia is occasionally a complication, especially in

cases in which the function of the myocardium is impaired and when pulmonary congestion is present. The oxygen tent, together with codeine, atropine, and digitalis as indicated, aids greatly in the treatment of this condition. In cases of recurrent laryngeal nerve paralysis the oxygen tent is also of great value in bringing about proper oxygenation of the lungs and in preventing extreme fatigue due to the use of the accessory muscles of respiration.

It is important to keep the patient in a relaxed psychic state, free from apprehension, and to this end visitors should be restricted in number and in duration of stay for several days after operation. On the third day after thyroidectomy the clips are removed from the neck. The patient is permitted to sit up in a chair on the fourth day, if no complications have arisen. He may walk around on the fifth and sixth days and, as a rule, is allowed to leave the hospital on the seventh day. Of course, severe cardiac damage, infection of the wound, or general weakness may necessitate a somewhat longer stay in the hospital. At the time of discharge from the hospital the patient is given the following list of instructions which are to be rigidly followed for at least three months:

1. Do not follow any special diet unless ordered by your physician.
2. Do not attend social functions.
3. Reduce household cares to the minimum.
4. Spend as much time as possible in the open air.
5. Avoid excitement.
6. Walk in moderation; avoid overexertion.
7. Secure sufficient rest by the following routine:

   First month: Rise at 8.30; rest in bed from 2 to 4; retire not later than 8.30.

   Second month: Rise at 8.30; rest in bed from 2 to 4; retire not later than 9.

   Third and fourth months: Rise at 8; rest in bed from 2 to 4; retire not later than 9.30.

8. Omit the following:
   1. Stimulants of all kinds.
   2. Tobacco, alcohol.
   3. Tea, coffee, cocoa, chocolate, spices, pickles.
   4. Do not use iodized salt.
9. Continue this routine until your attending physician has

found that you have received the full benefit from the treatment.

10. Report any unusual change in your condition to your physician or the Cleveland Clinic at once; and in any event report in person or send a written report of your condition to the clinic at the end of one and of three months, and thereafter every six months for three years.

If preliminary ligations have been performed, or in cases in which only one lobe has been removed, the patient is instructed to follow these instructions for three months and then to return for further operation.

Monthly reports by mail or visits to the clinic are requested during the first three months after which reports or visits to the clinic are made at intervals of six months for three years in order that the results may be checked closely.

CHAPTER XXXVI

COMPLICATIONS WHICH MAY FOLLOW THYROIDECTOMY

ROBERT S. DINSMORE AND JAMES A. LEHMAN

HEMORRHAGE

A POSTOPERATIVE hemorrhage is a complication which occasionally confronts the surgeon. Even after the most careful hemostasis a totally unexpected hemorrhage may follow a thyroidectomy. When this occurs immediate attention and most careful management usually are required.

The bleeding may be: (1) arterial, (2) venous or (3) capillary. It may be massive, with rapid formation of a large hematoma and symptoms of suffocation, or a hematoma may form slowly. The bleeding may be anterior to the preglandular muscles, or posterior to them, the posterior location being the more common. De Quervain[1] states that bleeding from the superior thyroid artery is the most frequent cause of severe and troublesome postoperative hemorrhage but this has not been the case in our experience.

Mediastinal hemorrhage, of course, following the removal of an intrathoracic goiter usually is of two types: (1) the formation of a hematoma in the cavity left by removal of the goiter, or (2) extravasation into the anterior or posterior mediastinum. Either of these occurrences may pass unnoticed since a large hemorrhage may not produce any appreciable bulging of the neck or bleeding from the wound. Extravasation into the anterior mediastinum is more common although we have seen cases in which the extravasation passed only into the posterior mediastinum.

The prognosis in the cases with mediastinal extravasation is always grave. These cases are characterized by a very rapid and weak pulse, an increasing pallor and an enlargement of the area of mediastinal dulness. Sometimes cyanosis is present.

Subcutaneous extravasation of blood may occur. At times it is very extensive, extending from the mandible down to the umbilicus

(Fig. 148). Usually it is limited to the upper anterior chest wall. It is followed by the usual color changes as the blood undergoes hemolysis and absorption.

An extravasation into the vocal cords is a rather rare type of postoperative hemorrhage. It is characterized by a peculiar brassy quality of the voice, usually noticed about the second or third day after operation. This may lead the operator to believe that he has injured a recurrent laryngeal nerve. Laryngeal examination, however, reveals the true nature of the condition.

Since we have discontinued the routine of dividing the preglandular muscles transversely, we rarely, if ever, see a hematoma of the muscles.

The danger of a postoperative hemorrhage is not due to the loss of blood alone, but also to the fact that the patient may be suffocated by the pressure of the clot on the trachea. Moreover, hemorrhage frequently marks the onset of a long series of complications, such as nerve injury, tracheotomy and infection. Bearing these facts in mind we should proceed with a definite and orderly plan of attack. The entire operating team should be recalled. If necessary the clot may be evacuated and a gauze pack placed in the neck, until the assistants arrive.

It is best that the patient be under analgesia, produced by light inhalations of nitrous oxide. Great care should be exercised in evacuating the clot, lest the number of bleeding points be increased. It is important to remember that hemorrhage from the superior thyroid artery can often be controlled by pressing the bleeding artery forward with the fingers, holding the vessel between the thumb and index finger, and guiding a hemostat along the finger to the bleeding point.

Sometimes when a ligature has slipped off the superior thyroid artery, the artery retracts well up into the neck. In such a case it is almost impossible to see the bleeding point. Compressing the carotid artery against the vertebral column, carefully sponging until the wound is perfectly dry and then slowly releasing the pressure will enable one to see the point of hemorrhage.

If the bleeding is from a single vessel, or from several vessels which can be ligated, then the neck may again be closed. However, if there is a general oozing from the remnant of the thyroid gland, or if for any reason one is unable to secure satisfactory hemostasis, a pack should be inserted and the neck left open. This is a basic principle which is of the utmost importance in the control of hemorrhage.

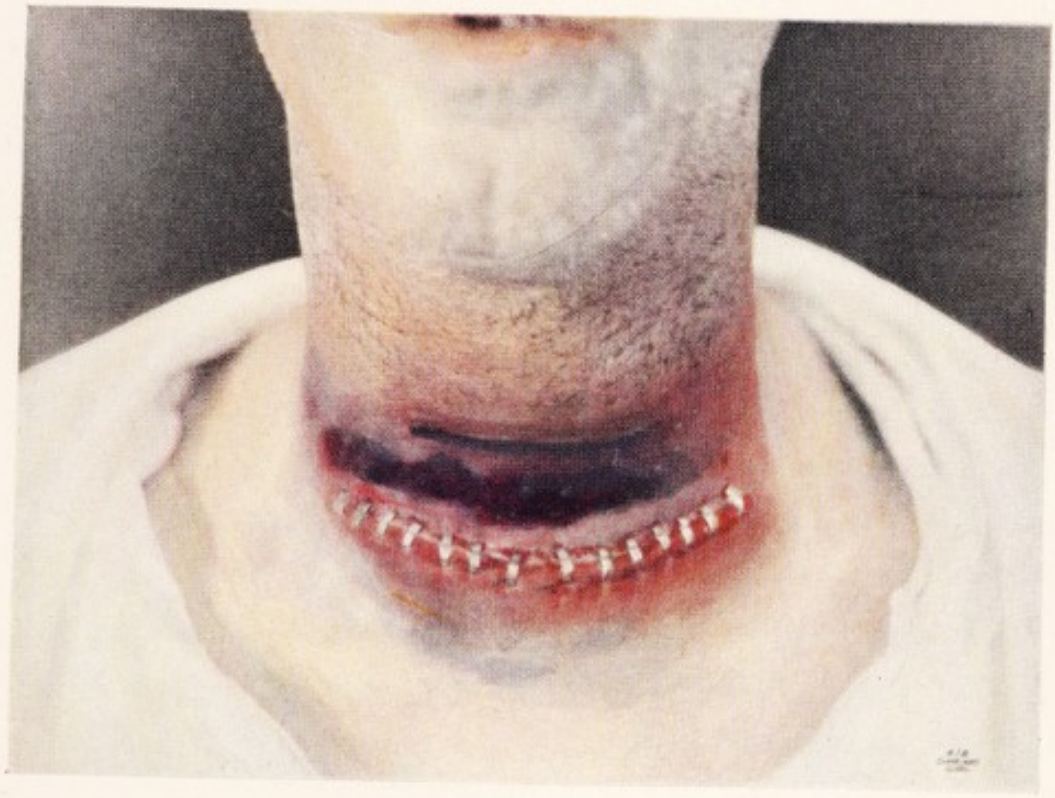

Fig. 148.—Extensive subcutaneous extravasation of blood.

Great care must be exercised in clamping bleeding points, especially along the tracheo-esophageal groove, and in the region of the inferior pole as the danger of injuring the recurrent laryngeal nerve is greatest at these points.

After the removal of an intrathoracic goiter, if the cavity is dry and is obliterated by the lungs and pleura then the neck may be closed. However, if the wound is not perfectly dry and the cavity is not obliterated, then the cavity should be packed and the wound left open. Fortunately in most of these cases, the cavities do become obliterated.

Small hematomata under the skin flaps are usually absorbed spontaneously. Unless they are very large, they are best left alone for frequent aspiration invariably leads to infection.

General measures for the treatment of hemorrhage are always instituted. Morphine is given to quiet restlessness, fluids to restore the water balance, and transfusion of whole blood to compensate for the blood loss.

POSTOPERATIVE HYPERTHYROIDISM

Postoperative hyperthyroidism or a "postoperative crisis" or the so-called "thyroid storm" was formerly a familiar picture to the thyroid surgeon. It is rarely observed today. This is due undoubtedly to the better method of preparation of the patient, to the more careful conduct of the operation, and to the anticipation and treatment of this complication before it occurs. These factors have been carefully considered in previous chapters.

Postoperative hyperthyroidism is characterized by an accentuation of all the symptoms of ordinary hyperthyroidism, that is, hyperpyrexia, tachycardia, extreme restlessness, excessive sweating, nausea and vomiting, disorientation, etc. These symptoms may become very intense, unless adequate measures for their control are instituted promptly.

The most important part of the treatment is prophylactic. The preoperative use of Lugol's solution, a long period of absolute rest in bed, the embodiment of the principles of anoci-association, avoidance of deep inhalation anesthesia and multiple stage operations have all contributed toward the prevention of this most distressing complication.

Should severe symptoms present themselves, with a rapidly rising temperature, tachycardia and restlessness, the neck should be opened immediately, the wound secretion evacuated and a light gauze pack applied. This is a point about which there is some differ-

ence of opinion. Nevertheless, in our experience, we have found that as the result of this procedure, even though a surprisingly small amount of serum is evacuated, the temperature falls promptly.

Ice should be used to control the high temperature. In this type of case, it has been our custom to put 10 ice-bags on a patient with a temperature of 102° F. Twenty ice-bags are used in the case in which the temperature is 103° F. When the temperature is 104° F. or over, the patient should be placed in a complete ice-pack which, however, should not extend above the costal margin. The patient should be carefully watched, the temperature being taken every twenty minutes and the pack removed when the temperature reaches 102° F. Ordinarily a patient should not remain in an ice-pack longer than two hours at a time.

Iodine should be administered immediately. If the patient cannot take it by mouth or if the rectum proves intolerant to the drug, then it should be given intravenously. It is well to remember that when the tincture of iodine is painted on the skin this iodine is rapidly absorbed into the blood stream. If at the time of operation it is found that the thyroid gland is incompletely involuted it is well to continue the administration of Lugol's solution for several days postoperatively.

These patients are always much more comfortable when placed in an oxygen tent. This reduces the amount of tracheal mucus, so that there is less coughing and straining. Frequently we have observed a prompt subsidence of temperature after the patient has been placed in the oxygen tent. Since the institution of oxygen therapy the number of patients requiring the application of ice for the control of a high temperature has been greatly reduced.

Morphine should be given in sufficient quantities to control the restlessness. There is little danger of overdosage with this drug, if the respiratory rate is carefully watched. Fluids should be given in large amounts, either subcutaneously or intravenously or both. A transfusion of whole blood is always helpful.

STRIDOR

The development of stridor after a thyroidectomy usually indicates that one or both recurrent laryngeal nerves have been injured. In exceptional cases, a marked edema of the larynx is sufficient to cause stridor. It should be remembered that the formation of a large hematoma may exert sufficient pressure on the trachea to cause

difficulty in breathing. We might mention at this point that edema of the glottis is more prone to develop postoperatively in individuals who have had a course of *x*-ray or radium treatment preoperatively. Edema of the glottis causes a slowly developing stridor which usually does not become troublesome in less than from eight to twelve hours.

Patients who exhibit stridor should be watched very carefully. If possible a laryngoscopic examination should be made to determine the condition of the larynx.

If the stridor does not rapidly disappear, or if the patient shows any cyanosis, a tracheotomy should be performed without delay. To delay is to court disaster. It should be remembered that if stridor is present for from six to eight hours, even in the absence of cyanosis, the patient will become so exhausted and the internal respiration so damaged that even after tracheotomy, recovery will not take place.

There is a peculiar type of nervousness and restlessness which is associated with stridor. The patient becomes very apprehensive. Sedatives seem to have no effect. After the tracheotomy, invariably the patient will fall into a deep and restful sleep and will remain asleep for some time.

There are certain essential points about the performance of tracheotomy and the postoperative care of the tracheotomy wound which should be mentioned. These have been discussed in detail by Prioleau.[2] Only a brief summary will be given here.

Only local anesthesia should be used. It is best to insert the tube through a transverse incision between the third and fourth or fourth and fifth tracheal rings. The wound should be packed lightly with gauze. Someone should be in constant attendance upon the patient for the first forty-eight to seventy-two hours after the tracheotomy is performed. Any mucus that is expelled should be promptly wiped away with gauze. Aspiration, preferably with a motor-driven aspirator, should be done as frequently as necessary. The inner tube should be removed and cleaned every hour. An extra tracheotomy tube should be at the bedside at all times. The packing and outer tube should be changed at the end of eight hours and thereafter at least twice a day.

The tube should be removed as early as possible. The early removal of the tube hastens the healing of the wound and prevents irritation of the trachea. When a tracheotomy is performed because of edema of the larynx, the evacuation of a large quantity of mucus, often bloody, is followed by a prompt subsidence of the symptoms.

In these cases it is usually possible to cover the opening in the trachea by overlapping the fascia. In cases of unilateral vocal cord paralysis it is usually possible to remove the tube in twenty-four hours. If the tube remains in longer it is impossible to suture the trachea. In that event a gauze pack should be placed over the opening in the trachea.

If the wound is kept clean, the packing changed frequently and the tube removed early, the incidence of infection will be negligible. If infection does occur, we have found the use of dichloramine-T to be very beneficial.

SHOCK

Coincident with the evolution of the present management of the patient in whom a thyroidectomy is to be performed, postoperative shock has almost completely disappeared. If the operation is performed under nitrous oxide analgesia and complete nerve blocking with novocaine together with careful dissection and meticulous control of hemorrhage then the incidence of postoperative shock should be extremely low. Despite all of our efforts to prevent it, however, we sometimes see a mild degree of shock in elderly patients after the removal of a very large goiter.

Should shock occur the well-established measures for its control should be carried out immediately. The foot of the bed should be elevated and the patient made warm, diathermia applied and abundant fluids administered by the subcutaneous route. A transfusion of whole blood, given slowly to avoid undue strain on the myocardium, is often a life-saving measure. Morphine should be given in $\frac{1}{6}$-grain doses.

COLLAPSE OF THE TRACHEA

True collapse of the trachea is mentioned only to state that it rarely, if ever, occurs. This condition is almost invariably due to injury to one or both recurrent laryngeal nerves. A very large and rapidly forming hematoma may exert sufficient pressure on the trachea to cause a true collapse. However, this is a most infrequent occurrence. The treatment of this condition has been considered in the discussion of stridor.

TRACHEITIS

Tracheitis was formerly a frequent and most distressing complication. It is largely prevented by (1) avoidance of deep inhalation anesthesia; (2) gentle sponging by the assistant; (3) preservation of the fascia covering the trachea, and (4) protection of the lateral

boundary of the trachea by a small triangular margin of thyroid tissue. The incidence of tracheitis probably bears a direct relation to the amount of trachea which is exposed at the time of operation. Irritation of the throat and coughing may be due also to stretching or other injury of the recurrent laryngeal nerve.

Codeine is a valuable drug in the treatment of tracheitis. Given in $\frac{1}{2}$-grain doses, it has proved to be very beneficial. These patients are more comfortable when placed in the oxygen tent as this seems to lessen the amount of tracheal mucus, and is a great aid in protecting the patient against bronchopneumonia.

PULMONARY COMPLICATIONS

The pulmonary complications which may follow thyroidectomy are the following: (1) pulmonary collapse, (2) bronchitis, (3) bronchopneumonia and (4) embolism. These will be considered elsewhere. A recent survey of our old postmortem records of cases in which thyroidectomy was performed, reveals a surprisingly large number of deaths due to pulmonary complications—either as the direct or as a contributing cause. With the introduction of newer methods of preoperative, operative and postoperative care the number of deaths due to this cause has been minimized.

A **massive collapse of the lung** is easily recognized. There is an abrupt onset marked by sudden dyspnea and cyanosis, a high temperature, signs of consolidation and displacement of the mediastinal structures toward the affected side. If one lobe or only part of a lobe is involved, the symptoms are less severe and the condition is more difficult to recognize. The *x*-ray is an important aid in establishing the diagnosis.

Undoubtedly a large percentage of these cases are due to bronchial obstruction from thickened, viscid secretions of the bronchus. This has been emphasized by Jackson,[3] Lee[4] and others. However, this does not explain all cases. In some cases the condition would seem to be a reflex nervous phenomenon. We have seen instances in which the collapse occurred on the same side as that of a recurrent laryngeal nerve injury.

The most important part of the treatment is prophylactic. The excessive production of mucus as a result of tracheitis can be avoided by care at the time of operation. This is true also of recurrent laryngeal nerve injury. If the condition occurs and it is thought that a mucous plug is the causative factor, then it will be relieved by a

tracheotomy with the insertion of a suction catheter. Bronchoscopical aspiration also will relieve the condition. Sometimes stimulation from coughing will dislodge the plug. The use of the oxygen tent frequently brings about a remarkable improvement of the symptoms.

Bronchitis usually occurs in elderly individuals or in those who give a history of repeated infection of the upper respiratory tract. Needless to say an operation on the thyroid gland should never be undertaken in the presence of such an infection. In those individuals who have a chronic infection of the upper respiratory tract every effort should be made to put them in the best possible condition before operation. Bronchitis is a frequent precursor of bronchopneumonia, and therein lies its chief source of danger.

Bronchopneumonia still accounts for many of the deaths which follow thyroidectomy. Despite the recent advances in the treatment of pneumonia, it is attended by a high mortality rate. In the past few years, however, the incidence of postoperative bronchopneumonia has been notably reduced.

In the year 1926, in a series of 500 consecutive thyroidectomies there were nine cases of bronchopneumonia, three of which terminated fatally. In the year 1931, in a series of 500 consecutive thyroidectomies, there were only two cases of bronchopneumonia, neither of which terminated fatally. The principal factors which have brought about this reduction in the mortality and morbidity rate are better preparation of the patient for operation, better technic and postoperative care. In particular, the use of the oxygen tent in the care of the patient who is a bad risk, has contributed a great deal to the prevention of postoperative bronchopneumonia. Since 1928 we have been using the oxygen tent in all "bad risk" cases. Of the 500 patients in 1931 referred to above, 99 were placed in the tent immediately after the operation and remained there until the postoperative reaction had subsided.

There is a small group of patients who are very much enfeebled and despite all our efforts to prevent it, have considerable mucus in the trachea and bronchi. They apparently do not have sufficient strength to cough and the mucus travels up and down the trachea with respiration, gradually traveling farther and farther into the bronchial tree. The temperature rises and cyanosis develops and a fatal bronchopneumonia seems imminent. In this type of case a tracheotomy and the frequent aspiration of the mucopurulent con-

tents of the trachea and bronchi are life-saving measures. We have seen most dramatic improvement follow in a number of such cases.

CARDIAC COMPLICATIONS

The cardiac complications which may follow thyroidectomy are the following: (1) simple tachycardia, (2) auricular fibrillation, (3) auricular flutter, (4) extrasystoles and (5) acute dilatation of the heart. Obviously these complications occur most frequently in elderly patients and in patients in whom the hyperthyroidism has been of long duration. In children, however, simple tachycardia invariably occurs. A pulse rate which in an adult would occasion some alarm is of no significance in a child.

Simple tachycardia is a constant accompaniment of thyroidectomy. The pulse rate increases at the time of operation and remains elevated for from forty-eight to seventy-two hours. At the end of that time the tachycardia usually subsides promptly. If a severe tachycardia persists for any length of time postoperatively, auricular fibrillation will occur in many cases. The use of digitalis preoperatively reduces the incidence of postoperative auricular fibrillation. Should the pulse rate become alarmingly high, digitalis may be given hypodermically, by rectum, or by mouth. It should be remembered that morphine will exert a definite quieting effect upon the circulation.

Auricular fibrillation when it occurs either is a continuance of a previously existing fibrillation or is a new manifestation in patients whose rhythm has previously been normal. It is seen most frequently in the elderly individual, with an adenomatous goiter and hyperthyroidism of long standing. The return of the heart rhythm to normal, after thyroidectomy alone, depends chiefly upon the following factors: (1) the duration of the irregularity previous to the operation, (2) the degree of arteriosclerosis and myocardial degeneration, (3) the age of the patient and (4) the presence of complications such as focal infection.

Anderson[5] has recently published the results of his studies of auricular fibrillation with special reference to quinidine therapy. He found, in a study of a series of 75 cases, that thyroidectomy alone restored normal rhythm in only 32 per cent of the cases. In a later study of a series of 75 cases, he found that thyroidectomy alone restored normal rhythm in 60 per cent of the cases. However, if quinidine is administered in all cases in which auricular fibrillation is present, on the third day after operation, then 96 per cent will revert

to normal rhythm at the time of discharge from the hospital. Because of these findings, it has been our practice to administer quinidine on the third postoperative day to all patients who at that time have auricular fibrillation.

A test dose is first given. If no ill effects are noted then 5 grains of quinidine sulphate are given every four hours day and night for twenty-four hours. The pulse should be counted before the administration of each dose, the medication being discontinued if the pulse is found to be regular. If no improvement is noted at the end of twenty-four hours' treatment 5 grains of quinidine sulphate are given every three hours for twenty-four hours and then every two hours for twenty-four hours and occasionally for forty-eight hours. In the majority of cases a normal rhythm will be restored after a few doses, but occasionally the treatment must be continued for two or three days. We rarely encounter a patient who is sensitive to quinidine.

Auricular flutter is of very rare occurrence. In three of our cases the patients were treated with quinidine, a normal heart rhythm being restored in two of them. In the third case the auricular flutter persisted despite intensive quinidine therapy.

Extrasystoles occur more frequently before than after operation. The increased heart rate due to the operation usually causes them to disappear. Extrasystoles should not be regarded lightly, even though they may be temporary. It is wiser to regard them as having some pathologic significance. This is especially true in the case of a patient over fifty years of age. In the young patient extrasystoles are usually of no importance. The condition is easily recognized by the irregularity, inequality and intermission of the pulse. However, in some instances an electrocardiographic tracing may be necessary to differentiate it from auricular fibrillation. The condition itself does not require digitalis.

Acute dilatation of the heart may occur. The added strain of operation upon the already failing myocardium may be sufficient to cause an acute dilatation. The most important part of the treatment is, of course, prophylactic. Every effort should be made to put the patient in the best possible condition before operation is attempted. Often the first symptoms are the final ones and a rapidly fatal outcome ensues. The treatment is the same as for acute myocardial failure.

EMBOLISM

One of the most striking points pertaining to thyroid surgery is the relative infrequency of postoperative embolism. Despite the cutting of large vascular channels, the ligation of big veins and unavoidable trauma necessitated by frequent sponging, embolism is seldom encountered.

Emboli may arise in either the venous or the arterial system. Those arising in the venous system usually originate at the site of operation. A not uncommon source is the auricular appendix. A large hematoma is always a possible source of embolus formation, as is the rough handling of tissues at operation. Cerebral emboli occur most frequently in elderly arteriosclerotic patients.

The symptoms of embolism depend upon the organ involved and the size of the embolus. If the embolus lodges in the lung, a chill or chilly sensation usually follows with marked dyspnea and cyanosis, rapid pulse, fever and pain in the chest. Undoubtedly, many small emboli lodge in the lung and pass unnoticed. However, the presence of a large embolus in the lung is easily diagnosed and the mortality rate associated with such emboli is high. Cerebral embolism is readily recognized.

The treatment of embolism is expectant. The use of the oxygen tent in cases of pulmonary embolism has proved beneficial.

COMPLICATIONS IN THE ALIMENTARY TRACT

Difficulty in swallowing is occasionally experienced after the operation. This is probably due, in most cases, to stretching of the recurrent laryngeal nerve, one fiber of which enters the esophagus at a point opposite the larynx. The patient should be advised that the condition will remedy itself in a short time. When this condition occurs it is well to have the patient take fluids in very small amounts for a short period of time.

Nausea and vomiting are largely prevented by the use of local anesthesia and analgesia. Sometimes a patient may become nauseated from the use of morphine. When nausea and vomiting do occur, it is best to restrict the ingestion of food or fluids by mouth for from twenty-four to forty-eight hours. Saline solution should be administered subcutaneously.

When diarrhea follows thyroidectomy it is only an expression of active hyperthyroidism, being due to hyperperistalsis of the entire gastro-intestinal tract. For this, and for the abdominal cramps which

may be associated with hyperthyroidism, we have found the use of paregoric and belladonna very beneficial. Two drachms of paregoric and 10 minims of tincture of belladonna should be given every four hours until the condition is relieved.

INFECTION

An infection in a thyroidectomy wound is always to be regarded with alarm. It should receive prompt and radical treatment, because of the danger of injury to the parathyroid bodies and recurrent laryngeal nerves as the result of their involvement in the inflammatory process or in late scar tissue formation. Infection may also be the indirect cause of hemorrhage resulting from the sloughing of ligatures or tissue.

The treatment of infection depends upon its severity and its location. Should a severe infection develop beneath the muscles, the wound should be opened widely and should be irrigated and packed with gauze. Iodoform gauze or gauze soaked in 1 : 5000 acriflavine is satisfactory. If the infection is limited to the space beneath the skin flaps, it is well to remove several skin clips and to irrigate gently with warm saline solution. Large hot fomentations frequently exert a beneficial effect, but they should not be continued for too long a time. It is essential that the wound be kept scrupulously clean by frequent change of dressings. Sometimes an unsightly scar results following an infection. The skin may become attached to the trachea and cause dimpling and retraction when the patient swallows so that a plastic operation becomes necessary. If this occurs it is best to wait about six months before attempting any such procedure.

COLLECTION OF SERUM

The formation of serum in a thyroidectomy wound may be due to several causes: (1) the large area of raw surface exposed, (2) extravasation of blood beneath the flaps, and (3) the large amount of catgut used to secure hemostasis after the removal of a large goiter.

It is true that in a certain percentage of cases absorption will occur, but as a general rule, it is best to evacuate any appreciable amount of serum which collects. This can best be done by aspiration with a syringe and needle, or by the insertion of a probe through the line of incision and gentle expression of the serum. The former method is the one to be preferred. It should be borne in mind that

repeated probing or aspiration will frequently be followed by a low-grade infection despite all efforts to prevent it.

ACUTE HYPOTHYROIDISM

Acute hypothyroidism is a transient condition which manifests itself about the second or third day following thyroidectomy. In 1883 Kocher[6] reported that 30 of his first 100 thyroidectomies were followed by a very characteristic picture, to which he gave the name "cachexia strumipriva." About this same time the Reverdins[7] noted the relationship of this condition to myxedema. As early as 1859 Schiff had noted that the removal of the thyroid gland of the dog was followed by certain symptoms.

Postoperative hypothyroidism occurs more frequently in elderly individuals who have had hyperthyroidism for a long time. It is not so common now as it was before the institution of the use of Lugol's solution in the preparation of the patient for operation. Formerly it was necessary to remove almost every vestige of the thyroid gland, in order to prevent recurrent hyperthyroidism. A more generous portion of the gland can now be left, with a reasonable assurance that there will be no recurrence.

It is probable that several factors contribute to the production of this condition. Obviously the removal of a large part of the thyroid gland will be followed by a prompt fall in metabolism. Likewise it is reasonable to assume that there is a temporary suppression of the function of the remaining portion of the gland, due to the following factors: (1) Trauma from manipulation during operation and (2) disturbance in the blood supply due to edema. A like suppression of function following thyroidectomy was shown by McCullagh to occur in the parathyroids. He found that in 76 per cent of his cases thyroidectomy was followed by a prompt fall in the level of the serum calcium, the normal level being resumed in from seven to ten days.

The acute form of hypothyroidism is characterized by drowsiness and a peculiar pallor and glistening of the skin. Sometimes nervousness and mental confusion develop. Not uncommonly complete disorientation occurs. Frequently these patients complain of numbness and tingling of the extremities, unassociated with any evidence of tetany. There is a repugnance to food, either liquid or solid.

This condition rapidly disappears after the administration of thyroid extract. It is well to give one large dose, amounting to from

5 to 10 grains, as soon as the condition is recognized. This should be followed by the administration of 2 to 3 grains daily for several days.

Chronic postoperative hypothyroidism is, of course, another problem which has been considered in a separate chapter.

HYPERTHYROID PSYCHOSIS

The psychosis which is associated with and caused by hyperthyroidism partakes of the nature of a toxic psychosis. Various other mental states have been described as being associated with hyperthyroidism such as manic-depressive psychosis, schizophrenia, paranoia, etc. Undoubtedly in these cases the hyperthyroidism is coincident and bears no etiologic relationship to the psychosis. It must be remembered, however, that hyperthyroidism may aggravate an existing psychosis and that a psychosis may aggravate hyperthyroidism.

It is important to make a clear distinction between cases in which a true thyrogenic psychosis is present and those in which the hyperthyroidism occurs coincidentally with a major psychosis. This is necessary before we can institute treatment or offer a prognosis. Careful inquiry into the family history and the past history of the patient is of the utmost importance. Then an analysis of the symptoms and of the mental state should be made. Finally it may be necessary to await the subsequent course before a definite opinion can be expressed.

It is beyond the scope of this volume to enter into any discussion relating to the pathogenesis of this condition. However, a few generalizations may be made. We have noted that the psychosis is not limited to any type of individual, and that children are not more susceptible than adults. Likewise, psychotic manifestations are usually but not invariably associated with a severe degree of hyperthyroidism. Sometimes, however, the mental symptoms are very severe and the hyperthyroidism rather mild. This is witnessed most frequently in elderly arteriosclerotic patients.

Karnosh, who has seen many of these patients with us, prefers to classify them according to the severity of their symptoms as follows: (1) neurotic, (2) paranoid, (3) schizomanic, and (4) toxic delirious. This is an arbitrary classification, but one that we have found serviceable. The symptoms vary from a mild apprehension of the neurotic type to a wildly excited, toxic, delirious state.

In a psychosis of the neurotic type the patient is irritable, sensitive, and apprehensive. He finds fault with everything and frequently

misinterprets certain phases of the preoperative regimen. The nurse is often more aware of this than the doctor.

A patient of the paranoid type shows fleeting periods of confusion, sensory deprivation and some blurring of perception. He is given to violent outbursts. Extreme restlessness and apprehension are present leading to expressions of ideas of persecution.

In a patient of the schizomanic type one sees an excitement confusion, flight of ideas and great motor activity. His talk is rambling, generally of past experiences, and not of things about him. Frequently he has hallucinations, usually visual. The tremor involves the lips, tongue and extremities.

The toxic delirious patient is a familiar picture to everyone. He is greatly emaciated, and has fever and rapid pulse and marked precordial activity. Restraint in bed is necessary. There is a marked acrotremor and constant fumbling movements. This condition rapidly terminates in complete physical exhaustion, which is followed by stupor and death.

The prognosis in the case of a delirious patient is always grave. It has been our experience that if a toxic delirium lasts for more than seventy-two hours, the outcome is fatal in about 50 per cent of the cases. In the cases with less severe manifestations, the outlook is as a rule favorable. The delirium rapidly clears up when the hyperthyroidism is controlled.

The treatment of any of these psychoses is essentially that of acute hyperthyroidism. Rest in bed, sedatives, large quantities of fluids, iodine and blood transfusion. If hyperpyrexia is present, ice-packs should be employed. If possible the patient should be in an oxygen tent.

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CHAPTER XXXVII

THE MECHANISM OF POSTOPERATIVE PNEUMONIA

GEORGE CRILE

Mucus, Collapse of Lung, Bronchopneumonia.—One of the causes of death following thyroidectomy is collapse of the lung followed by bronchopneumonia. This complication is met especially in the patient whose recurrent laryngeal nerves have been injured, and in the patient subjected to a certain technical error, that is, to exposure and irritation of the sensory nerves of the trachea and larynx. This irritation of the sensory nerves on the outer surface of the trachea and larynx is interpreted by the reflex centers as being the same as irritation of internal sensory nerves caused by the presence of foreign bodies. The surgeon is the foreign body outside. As much mucus is produced by irritation of the sensory nerves on the outer surface of the trachea and larynx as by irritation of the internal sensory nerves. When both recurrent nerves are injured so that tracheotomy is required there is always much mucus.

Once mucus has formed, there is the possibility that a part of the bronchial tree will be plugged, a condition which usually leads to pneumonia. The sequence of events is the production of mucus, mucous plugs, collapse, pneumonia and death. Mucus also predisposes to pneumonia in another way, for free mucus may become infected. There are then two ways in which mucus may inaugurate bronchopneumonia; one, by plugging a bronchus, with resultant infection; the other, by infection of the free mucus in the tracheobronchial system.

These are not the sole causes of pneumonia, but they certainly are the most common.

If, in addition to the presence of mucus, paralysis of the vocal cords interferes with effective coughing, there is a still greater probability that bronchopneumonia will develop. If the operation is so conducted that the sensory nerves on the larynx and trachea as well as the recurrent nerves are not disturbed or exposed, the incidence

of postoperative pneumonia will be reduced to a minimum. In the Cleveland Clinic since the technic of thyroidectomy has been so planned as to leave the covering of the larynx and trachea undisturbed, the recurrent nerves have not been exposed nor subjected to traction, and we have experienced a marked fall in the incidence of bronchopneumonia. If in the postoperative course, the patient neither coughs nor has an impaired voice, pneumonia rarely develops.

In a series of 500 consecutive thyroidectomies performed in 1926, selected at random the incidence of bronchitis or bronchopneumonia was found to have been 1.8 per cent. In 500 consecutive thyroidectomies performed in 1931 the incidence was 0.6 per cent.

Low Vitality and Bronchopneumonia.—When a normal vigorous individual whose every organ is free from infection is suddenly killed, his entire body is quickly overrun and destroyed by bacteria. In the state of low defense just before death from any cause, pneumonia is so common that it is designated terminal pneumonia.

The vigor of living tissue is marked by its defense against infection. The vigor of the tissue of the lungs is its principal defense against pneumonia. If this is true, then if the factors that impair the defense are avoided, if through the course of the operation, vitality and defense of the tissue is protected, pneumonia should rarely occur. Let us then analyze the factors in the operation that may cause a depression in the defense.

Of prime importance is inhalation anesthesia. All inhalation anesthetics depress the vitality of plants and animals alike, during the period of their effect, hence inhalation anesthesia *per se* predisposes to pneumonia. The defense is lowered also by hemorrhage, shock, suboxidation and asphyxiation. Against these factors we inaugurate a program of prevention. Since the highest incidence of pneumonia occurs in enfeebled patients, in such cases we maintain the defense throughout and follow the operation by building up the water-electrolyte-nutritional balance before operation, by increasing the volume of good blood by blood transfusion before and immediately after operation, by protecting the patient against shock by blocking the nerve, and by maintaining the normal temperature of the body.

Treatment of Bronchopneumonia.—The treatment of postoperative pneumonia has been completely changed as the result of an understanding of the rôle of mucus, that is, that mucus is infectible and that it may plug up bronchioles, and hence lower the resistance of areas of the lungs.

Chevalier Jackson[1] in particular has shown that in bronchoscopic practice the extraction of mucus is followed by prompt relief. In the Cleveland Clinic for some years we have treated bronchopneumonia by making a high transverse incision between the rings of the trachea and passing an ordinary tracheotomy cannula into this opening. Through the cannula we pass a No. 16 F. rubber catheter as far down the bronchial tree as it will go. An electric sucker apparatus is attached to the catheter through which we can do repeatedly, even continuously, what Dr. Jackson with his unparalleled skill does once with the bronchoscope, which nature does ineffectually by coughing.

Results.—The clinical results of this treatment in some cases are as striking as the phenomena of the crisis of lobar pneumonia. A temperature as high as 104° or 105° F. may abruptly fall to 101° or 102° F., and the pulse from 150 to 110 or 120. When the trachea is opened mucopus in some cases literally floods the field immediately. The local appearance of infected material, and the quick change in the clinical picture shows clearly that the problem is the same as that presented by the absorption of pus anywhere else. The bronchial tree is sucked out at frequent intervals and a surprisingly large amount of pus is evacuated. This does what coughing cannot do, namely, empties the bronchial tree quite completely. If no other complication intervenes death very rarely occurs. In bronchopneumonia the indication for tracheotomy is not asphyxia at all, it is the diagnosis of bronchopneumonia, or of collapse of the lungs. It is a question whether this may not be a useful method of treatment for bronchopneumonia in nonsurgical as well as in surgical cases.

In addition to the complete drainage of the bronchial tree we sustain the patient by a high caloric diet; by putting him in an oxygen tent; by blood transfusion.

SUMMARY

Technical care in the prevention of injury or irritation of the larynx and trachea and of their nerve supply, the maintenance of a high resistance before, during, and after the operation, the prompt drainage of the bronchial tree at the inception of bronchopneumonia have all but eliminated death from postoperative pneumonia.

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CHAPTER XXXVIII

THE DIAGNOSIS AND TREATMENT OF PARATHYROID TETANY

E. PERRY MCCULLAGH

Introduction.—Parathyroprival tetany is the expression of hyperirritability of the nerve cells due to a decrease in available calcium. It is characterized clinically by a decrease in total serum calcium, an increase of inorganic phosphates in the blood, paresthesias, intermittent, bilateral tonic muscular spasms especially of the hands, and in chronic cases by trophic changes; the motor, sensory and sympathetic nerves and the higher centers are all involved. The disease is due to injury to or removal of a major portion of the parathyroid glands. If the parathyroid glands are in abnormal positions the condition may follow the standard operative procedure for the removal of the thyroid gland. It is more common after operations for recurrent or residual hyperthyroidism.

Incidence.—The disease is comparatively uncommon. Among 11,508 cases seen at the Cleveland Clinic in which thyroidectomy was performed, tetany has occurred in only 1.3 per cent. The ratio of female to male patients on whom thyroidectomy has been performed here is about 4 to 1. However, in this entire series tetany has been seen in men only 6 times. In five of these six cases it followed thyroidectomy, in two of the five it has become chronic. In one it was present for three days following parathyroidectomy for hyperparathyroidism.

The frequency with which tetany is diagnosed postoperatively is in a large measure directly proportional to the acuteness of observation and the frequency with which serum calcium determinations are made. Unless serum calcium estimations are made routinely after thyroidectomy, some cases will be undiagnosed.

History.—The history of the development of our present knowledge of tetany is extremely interesting. Some of the important high-lights include the first description of tetany in children made

in England in 1815 by Clarke[1] in a paper in which he called attention to spasms of the glottis and the extremities.

The disease was named by Corvisart[2] in 1852. In 1874 Erb[3] made careful studies of the electrical excitability of the motor nerves to which attention had been called previously. In 1875 Trousseau[4] called attention to the sign which bears his name. In 1878 Chvostek, Sr.,[5] and in 1888 Hoffman[6] described the signs which bear their names.

The parathyroid glands were described by Virchow[7] but at that time their significance was not appreciated. In 1880 Ivar Sandström[8] described the parathyroid glands and the credit for their discovery is rightly due to him. In the same year the first description of post-operative tetany was published by Weiss[9] in Vienna.

In 1890 Gley[10] showed that removal of the parathyroids caused tetany; at this time the work of Sandström was almost forgotten. Vassale and Generali[11] in 1897 applied this knowledge to the human, although neither of these great advances were taken seriously for many years by those interested in the disease.

Between 1900 and 1920 a great deal of work relating to the physiology of tetany was in progress. In 1900 Gregor[12] suggested a relationship between diet and tetany. In 1901 Sabbatini[13] showed that the excitability of the motor cortex could be diminished by an isotonic solution of calcium chloride. From the year 1908 on, the names of W. G. MacCallum and K. M. Vogel[14] figure very largely in the development of the calcium theory of tetany. These workers showed that improvement in the symptoms of tetany followed the administration of calcium and in 1913 they stated their belief that tetany is closely dependent upon a disturbance of the calcium content of the blood.

Many theories arose as to the function of the parathyroid glands and the mechanism of parathyroprival tetany. It is not appropriate to discuss these here. Suffice it to say that all except the calcium theory have fallen very largely into disrepute.

The achievement which crowned all previous efforts in this field was the production of an active parathyroid extract.

In December, 1924, A. M. Hanson[15] reported an active parathyroid extract which was beneficial in the treatment of tetany and at about the same time Collip[16] announced the extraction of a parathyroid hormone which would regulate the level of blood calcium and prevent or control parathyroprival tetany. Thus the treatment of this condition was placed on a new and sounder scientific basis.

ACUTE TETANY

The Clinical Picture

In the majority of cases acute tetany makes its appearance within from a few hours to a few days after thyroidectomy, but occasionally it may appear for the first time as late as several weeks after operation. Sometimes the diagnosis can be made before any symptoms are complained of by the patient. In such cases within the first few days after the operation the patient who is often in a semireclining position

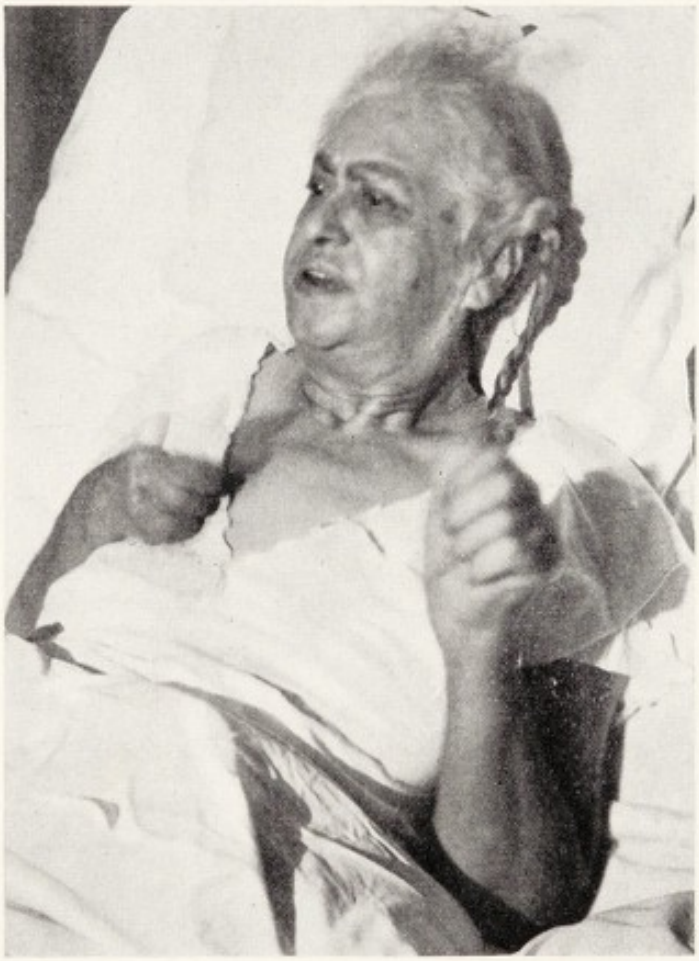

Fig. 149.—Characteristic facies in acute parathyroid tetany.

will be seen holding the arms and hands in a position suggestive of tetany, the arms being flexed at the elbows and the hands flexed at the wrists. At this time the patient can move the arms and hands at will and no spasticity can be noted on passive manipulation, but if the patient's hands are dropped at the sides, they will soon assume the characteristic position again, apparently for greater comfort. The patient may not voluntarily complain of paresthesia but if questioned she will almost invariably state that for some hours

there has been a tingling numbness in the hands and perhaps also in the feet and lips. This is a very constant and important early symptom, being practically always the first manifestation of the disease. If the disease is suspected early, further confirmation is necessary and an attempt is made to elicit Chvostek's sign, which is usually but not always present at this state, in fact some patients may have a severe tetanic convulsion and not show Chvostek's sign. Trousseau's sign, however, has been invariably present in our cases if the pressure is applied long enough. When the disease is suspected blood is aiways taken for serum calcium and phosphate estimations before any treatment is given.

If the attack progresses the order of events is about as follows: The fingers become stiffer and fine fibrillary twitching may be seen about the hands and mouth. The features become drawn, the patient becomes restless and the facial expression suggests fear. The patient may complain of blurred vision. If the onset occurs soon after operation the redness of the face is in striking contrast to the circumoral pallor. Lacrimation may occur. The hands become more tightly drawn, the arms more forcibly flexed at the elbows, the toes are flexed and adducted, the ankles are plantar flexed and inverted, and the legs are extended. Speech is difficult and usually is not attempted but the patient groans, grunts, or cries because of the pain. The respirations become fast, jerky, and incomplete. There is often an inspiratory stridor, especially if the recurrent laryngeal nerves have been injured. In some cases the thorax becomes rigid, the abdominal muscles contracted, the head drawn back and the whole trunk hyperextended. Severe abdominal pain may occur. The spasms become alternately worse and better. The whole attack may last for only a few minutes or for some hours and occasionally death may occur during an attack, or peculiarly enough an attack may subside completely without treatment. After a severe attack the muscles may be stiff and sore for several days.

Symptomatology

1. **Muscles.**—The most characteristic muscle spasm in tetany is the contraction of the hand. Usually the hand is flexed at the wrist, the fingers and thumb flexed at the metacarpophalangeal joints and extended at the interphalangeal joints. The digits are adducted forming the typical "obstetric hand" (Fig. 150).

At times the fingers are flexed at the metacarpophalangeal joints and extended at the interphalangeal joints but abducted (Fig. 151). It has been observed that some patients show the obstetric hand when

Fig. 150.—Characteristic contraction of hand in acute parathyroid tetany.

Trousseau's sign is elicited and the "main en presse papier" when Pool's sign is elicited. Sometimes the fingers and thumb are all flexed so that a fistlike position is assumed sometimes with the thumb

Fig. 151.—Contraction of hand sometimes seen in acute parathyroid tetany.

in the palm (Fig. 152). Occasionally a clawlike position may be seen. The forearm is usually midway between pronation and supination but may be forcibly pronated.

The feet are less frequently affected but when they are, the toes are flexed, the foot inverted and the plantar flexure occurs at the ankle; sometimes eversion is seen (Fig. 153). Sometimes the great toe is extended.

The leg usually is extended at the knee and the thigh extended on the abdomen. The contractions of the abdominal, thoracic, and trunk muscles have been mentioned. The extra-ocular muscles are not usually affected. The contractions of the muscles of the face

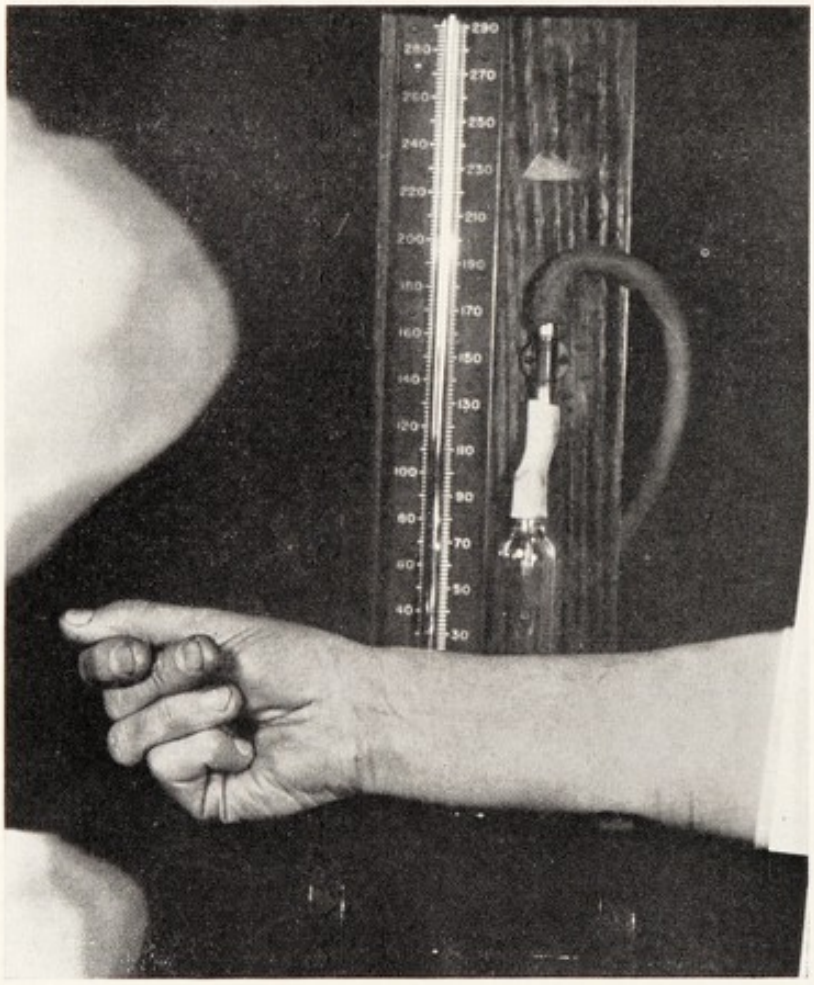

Fig. 152.—Contraction of hand sometimes seen in acute parathyroid tetany.

are very interesting. An anxious or frightened expression often appears before obvious or definite contraction of special muscles can be identified. In patients who are observed over a period of time the degree of tetany present may be accurately estimated by the facial expression. When the contractions are more severe the lips become pressed together and pushed forward ("carp mouth"). The nose appears pinched and the muscles of the forehead and eyebrows

are drawn together in a frown. Sometimes a masklike expression is seen.

Spasms of the tongue and pharynx are not uncommon and laryngeal spasm frequently occurs in those cases in which the laryngeal nerve has been injured.

The abdominal pain is presumably due to spasm of the muscles of the stomach or intestines. In one of our cases abdominal pain led to the diagnosis of cholecystitis which was thought to be aggravating the chronic tetany which was known to exist. The abdominal pain,

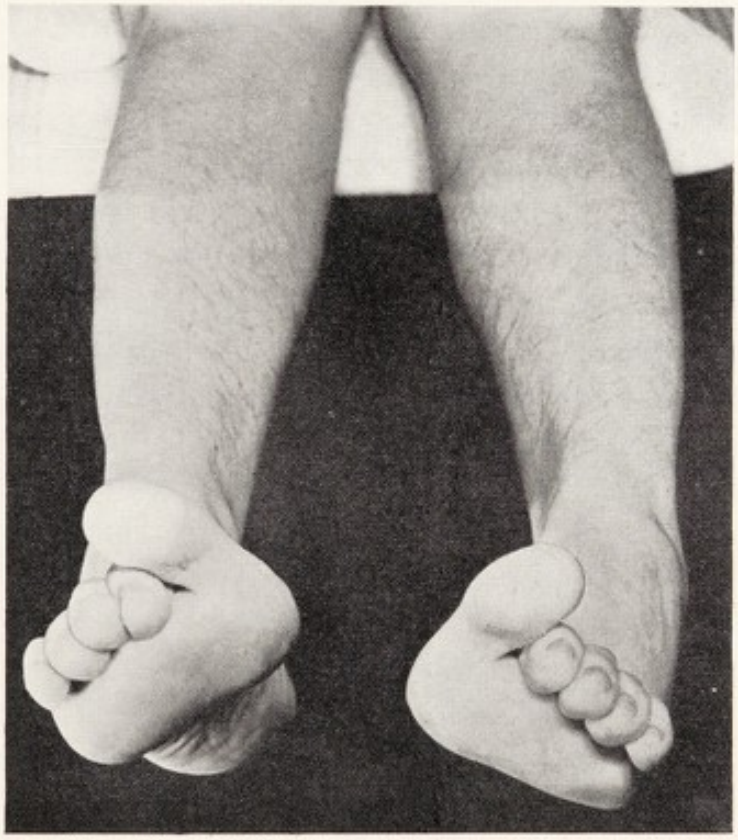

Fig. 153.—Contracton of feet sometimes seen in acute parathyroid tetany.

however, disappeared completely before the intravenous injection of 2 cc. of a 10 per cent solution of calcium chloride was completed.

The fibrillary twitchings have been mentioned. In one of our cases we observed a coarse digital tremor similar to that seen in paralysis agitans. This disappeared entirely when the tetany was completely controlled.

2. **Motor Nerves.**—*Mechanical Excitability.*—Trousseau's sign, described in 1864, is one of the most useful in the diagnosis of postoperative tetany since it can nearly always be elicited. It is the production of typical carpal spasm by compression of the arm. It

may be elicited in some cases by digital pressure in the bicipital groove or by the application of a simple tourniquet to the upper arm. We prefer to use the method described by Barker, which consists in the application of the cuff of a sphygmomanometer and the elevation of the pressure to 200 mm. of mercury. The pressure should be kept at this level for five minutes if the sign does not appear more promptly. Usually it appears within three minutes if it is going to appear at all. By using a constant pressure in this way a quantitative element is brought into use, at least in so far as an individual case is concerned, so that one may get some idea of the severity of the condition at any given time.

Cases have been reported in which tetany existed and the sign was not present, but in this series it has always been present unless the condition has been under complete control. When the test is positive one may see first a fine fibrillary twitching and as the fingers gradually become stiff the hand may assume any of the four positions described above. Such a spasm may cause considerable pain. The contraction disappears rapidly after the pressure is released. Occasionally one may see a carpal spasm in the opposite hand while the test is being applied. In one case it was observed to precipitate a severe acute attack. The test occasionally gives positive results in the absence of tetany.

The mechanism of the response to this test has been the subject of considerable controversy but it appears to be most closely associated with the mechanical excitability of the motor nerves.

Chvostek's sign, described in 1878, is a demonstration of increased mechanical excitability of the facial nerve, produced by tapping, which causes a sudden contraction of the muscles of the face. Chvostek described 3 grades of severity. In the most severe (Chvostek I) tapping the facial nerve in front of the lobe of the ear causes a contraction of the muscles of the forehead, eyelids, cheek, nose, and upper and lower lips. In the second grade (Chvostek II) tapping of the nerve causes contractions at the side of the nose and the angle of the mouth. In the third grade (Chvostek III) the angle of the mouth alone responds. The last grade may sometimes be seen in apparently normal individuals. On the other hand, the sign may not be elicited in tetany. In a very severe case of chronic tetany, observed for more than six years, Chvostek's sign has never been obtained even during a severe attack.

Pool's sign, described in 1907,[17] but mentioned in 1904 by

Ferenczi,[18] is the production of carpal spasm by stretching the nerves of the brachial plexus on elevating the arm above the head with the forearm extended.

Schlesinger's sign, described in 1910,[19] is the production of spasm of the muscles of the legs and feet by marked flexion of the thighs at the hip joints with the knees extended.

Schultze's sign, described in 1882,[20] is the appearance of a dimple in the tongue at the site of light percussion.

Electrical Excitability, Erb's Phenomenon.—Hyperexcitability of the motor nerves as the result of a galvanic stimulation is perhaps the most constant sign in tetany. Its use is not often necessary in the diagnosis of parathyroid tetany, however, since the signs of mechanical excitability plus blood calcium and phosphorus studies are usually sufficient. Cases are occasionally seen in which severe attacks of tetany occur while the serum calcium is above 9 mg. per 100 cc. In such cases even though Trousseau's and Chvostek's signs are present some doubt may arise as to the origin of the tetany when one reflects that Trousseau's sign may be hysterical in origin and that Chvostek's sign is seen occasionally in a normal individual. It happens also that tetany-like convulsions with hyperpnea may occur in cases in which thyroidectomy has been performed. Such cases have been seen in which the hyperpnea has appeared to have been of hysterical origin, the tetany being due to alkalosis from the hyperpnea. It is in the diagnosis of such cases that we have found Erb's phenomenon to be of value. It is true that in such cases Trousseau's and Chvostek's signs are usually absent between attacks and that the serum calcium and blood phosphate contents are normal, but one is usually grateful for any good confirmatory evidence and this is supplied by a test of the electrical excitability.

Stimulation of the median nerve alone is sufficient as slight contractions in the muscles of the hand are plainly seen.

Only three of the important changes in electrical excitability which are present in tetany will be mentioned here; namely, increased excitability as evidenced by (1) cathodal opening contraction, (2) cathodal closing contraction, and (3) anodal reversal.

The most important and conclusive finding is that in all cases of tetany which are not completely controlled by treatment, a cathodal opening contraction (C.O.C.) appears on the application of less than 5 ma. of current. In most cases considerably less than this current is required.

A cathodal closing contraction (C.C.C.) becomes an important diagnostic aid if this reaction occurs on the application of less than about 0.7 ma. of current. With currents of greater intensity the production of this reaction is not of definite value.

In more marked cases anodal reversal may take place, that is, anodal opening contraction (A.O.C.) may require less current for its production than anodal closing contraction (A.C.C.) or a current of equal intensity may produce either of these reactions whereas a normal anodal opening contraction requires considerably more current than does the normal closing contraction. Actually in practice the C.O.C. may be shown to be definitely abnormal and both anodal contractions may require considerably more than 5 ma. of current so that even though a moderate degree of tetany may exist enough discomfort may follow the use of anodal currents to make definite measurements impossible. Definite changes in electrical excitability may be demonstrable together with a shift in the level of the blood phosphates while the total calcium level may remain normal.

3. **Sensory Nerves.**—Paresthesia as mentioned above is a constant and important early symptom. It occurs usually first in the hands, appearing later in the feet and finally in the face. Sometimes paresthesia may appear first in the feet. In chronic cases paresthesia may be the only symptom present for long periods, the so-called "sensory tetany."

Tetany produces increased electrical excitability of the sensory nerves, a reaction which is known as *Hoffman's phenomenon.* It is undoubtedly because of this that patients with tetany often complain bitterly of the discomfort associated with measurements of electrical excitability while the same stimulation applied to a normal individual produces only slightly disagreeable sensations.

4. **Sympathetic Nervous System.**—*Muscle Spasms.—The Eye:* Intermittent spasm of the ciliary muscle occurs commonly in cases of tetany and explains the blurring of vision which not infrequently accompanies an acute attack. Spasm of the dilator pupillae has been described.

The Gastro-intestinal Tract.—As we have already stated, abdominal pain, presumably the result of gastric or intestinal spasm is not uncommon in severe attacks of tetany. In one of our cases as mentioned above the pain was supposed to be due to cholecystitis as the other manifestations of tetany were not marked.

Diarrhea is seen occasionally after massive doses of calcium but in our series it has always seemed to be the direct result of the calcium rather than of the tetany itself. A similar bladder irritability has been observed in two cases.

Vasomotor System.—The circumoral pallor sometimes seen in acute cases is striking. Falta and Kahn[21] reported the occurrence of marked anemia of the phalanges of the third, fourth and fifth fingers after the application of the bandage for the elicitation of Trousseau's sign. Dermographia occurs frequently in cases of tetany.

In this connection it is interesting to cite a case of chronic tetany which has been observed over a period of six years. During this period the patient has had a rather marked arterial hypertension, the systolic pressure having at times been as high as 220 mm. of mercury with a diastolic pressure of 140 mm. It has been observed repeatedly that the pressure is always somewhere in the neighborhood of the above values even for several weeks at a time when the tetany is more severe but that when the tetany is controlled the pressure falls to a systolic level of about 180 mm. with a diastolic pressure of 100 to 110 mm. In considering this case it has always been interesting to speculate whether this change in the blood pressure is a direct effect of vasospasm from the tetany alone or whether a hypersensitivity to epinephrine which is well recognized in tetany may be playing a prominent part in the production of this phenomenon.

Other phenomena pointing to involvement of the sympathetic nervous system may be mentioned. Falta and Kahn reported one case of tetany in which *lacrimation* was present and I have seen one case in which marked lacrimation is a constant accompaniment of an acute attack, but in my case no increase in salivation has ever been noted as it was in theirs. *Tachypnea* and *dyspnea* are frequently seen in cases of acute tetany and have been related by some observers to a possible bronchial spasm. In the cases we have observed the tightness in the chest of which the patient complains and the jerky character of the breathing suggest strongly that spasm of the intercostal muscles and diaphragm may be playing a major part in the production of these phenomena. In our series *hyperhidrosis* has only been noted in those cases in which the tetany has occurred during the febrile postoperative period and it is doubtful whether it could be ascribed to tetany in any of them. *Tachycardia* frequently occurs in an acute attack of tetany and may perhaps be ascribed in part to the tetany itself but it is obvious that in most instances excitement or pain are

important factors. A *rise in temperature* during an attack has been described as occurring in man and in animals. *Hypersensitivity to adrenalin* and *to pilocarpine* are present in tetany.

Central Nervous System.—In our series of cases of acute tetany, epileptiform seizures and psychoses have not occurred in any case. The excitement, apprehension and peculiar expression of fright have already been mentioned.

The Reflexes.—The tendon reflexes are normal in tetany.

CHRONIC TETANY

If the symptoms do not disappear and the serum calcium and blood phosphates return to normal levels in a few days the disease usually becomes chronic and treatment is required for an indefinite period. This indefinite protraction of the disease does not always occur, however, for in some cases the disease seems to disappear permanently after active treatment has been necessary for months. This has occurred in at least two cases in our series. In one of these cases, that of a girl, nine years of age, with severe hyperthyroidism, very active tetany began on the day following operation. The patient required large doses of calcium daily and some parathyroid extract (Collip) almost daily for three months. At the end of this time the serum calcium reached normal limits and the patient has remained completely symptom-free for two years without treatment. In the other case, that of a woman, forty years of age, the patient presented herself six months after operation; her teeth were quite loose, she had the typical symptoms and signs of chronic tetany and the serum calcium was 8 mg. per 100 cc. The patient tolerated calcium lactate poorly but the symptoms were completely controlled by a high calcium diet and large doses of calcium carbonate. This treatment was followed for ten months during the later part of which period the serum calcium was always found to amount to about 10 mg. per 100 cc. The treatment was abandoned gradually and for a year the patient has received no treatment. During this time the serum calcium has been found repeatedly to amount to about 10 mg. per 100 cc. and the patient has remained symptom-free.

If the disease is mild the patient may go on for a long time with no symptoms except paresthesias in the hands and transient stiffness in the fingers. The importance of such mild symptoms may be overlooked by the patient and a severe generalized convulsion with

unconsciousness may suddenly occur. This happens more frequently in young patients.

In many cases if treatment is not given or if it is insufficient, mild symptoms may be present and occasionally in the presence of some exciting cause a typical acute attack may occur. This is more likely to occur in younger women in whom the exciting cause is frequently the menstrual period or it may be an acute intercurrent infection, fatigue, or excitement or the acute attack may be due to diarrhea or the inadvertent use of phosphates in some form. Focal infection is frequently an aggravating factor.

In older patients who have not had sufficient treatment the spasticity may increase gradually and become very marked until the patient finds great difficulty in getting about at all and may walk with a typical spastic gait. Coarse tremors may appear. Aching pains may be present in the muscles and the joints.

Some patients do not seek treatment until marked trophic changes have taken place such as a cataract, trophic changes of the nails, hair or teeth, or edema, effusions or albuminuria.

It happens not infrequently that improvement in the symptoms may be ascribed to a true improvement in the disease itself when it is due only to an increasing tolerance to a low serum calcium. In such cases an attempt should always be made to avert trophic disturbances, especially cataract, by appropriate treatment.

Symptomatology

Certain aspects of the symptomatology of chronic tetany have not been mentioned in the discussion of the acute form of the disease.

Psychoses.—Depression of the mental faculties or unconsciousness is uncommon in cases of acute tetany. On the other hand slowing of mental processes and a poor memory occur with relative frequency in cases of chronic postoperative tetany even though unassociated with hypothyroidism.

The question of psychoses in tetany has been discussed by Arndt,[22] Franckl-Hochwart[23] and by Barrett[24] who believes there is no specific psychosis of tetany. Fünfgeld[25] reported 12 cases in which a psychosis was associated with tetany and Findley[26] cited an interesting case of postoperative tetany with psychosis.

Psychoses have been present in four cases in our series. In two it has been so severe as to necessitate institutional care. In one case the

psychosis is mild and exhibits itself only as a fear of which the patient cannot rid herself. She fears that she will kill her sister's child by enclosing her in a small space. She is unwilling to bathe in a tub for fear that the water may cover the child, she will not close drawers or doors because the baby may be suffocated and takes extreme care in dressing lest the child be under the clothing. In all three of the above cases, however, a careful history reveals that there were occasional signs of psychosis preceding the onset of tetany.

In the fourth case, however, this is not true. The patient, a woman fifty years of age, had had tetany which was sometimes severe, for nine years. Through carelessness, treatment was stopped and on a certain day the husband returned home to find that his wife did not recognize him. She was completely disoriented as to time and place and was very depressed. She complained of upper abdominal pain. She was brought to the hospital immediately and showed no carpal or pedal spasm and no Chvostek's sign, which she has never shown at any time. Trousseau's sign was elicited. The nature of the condition was recognized, however, and an intravenous infusion of 10 cc. of a 10 per cent solution of calcium chloride was given immediately at about 10 o'clock in the evening. On the following morning the patient was quite normal mentally. Just preceding the infusion of the calcium solution the serum calcium had been 7.2 mg. and the phosphates 6.4 mg. per 100 cc. This incident occurred more than a year ago and no other signs of psychosis have been noted since that time. The patient has never been able to recall the incidents described above. It seems probable that in this case the psychosis was the direct result of the tetany.

Tetany and Epilepsy.—Redlich[27] cited 72 cases in which tetany and epileptiform seizures occurred together. Twenty-one of these were cases of postoperative parathyroid tetany in which no epileptiform seizures had been present before the onset of the tetany.

Sudden generalized convulsive seizures with unconsciousness have occurred four times in our own series. All four of these patients were women. In no case had any convulsion occurred previous to the onset of the tetany and in none has a generalized convulsion occurred since the tetany has been treated. In no case was there an aura and in none could a definite history of clonus or of involuntary micturition or defecation be elicited. It does not seem necessary to postulate the presence of any lesion in the central nervous system except what may be incident to the tetany in such cases as these.

In the above-cited cases at least, it appears probable that the convulsions are a form of tetany.

THE ENDOCRINE SYSTEM

The Thyroid.—A great deal has been said in the past regarding the relationship between the thyroid and the parathyroids and in the text-books the subject is dealt with at some length. A great deal of experimental evidence may be found in support of the idea that the thyroid and parathyroids have antagonistic actions. This is not in keeping with the views of many observers, including Biedl[28] and Kocher,[29] that thyroid administration is beneficial in the treatment of postoperative tetany. The observations of Biedl and Kocher, in turn, seem to be at some variance with those of Falta and Kahn[21] who stated that signs of mild hyperthyroidism not infrequently appear after an attack of tetany.

Rabinowitch[30] has reported a series of blood calcium studies following thyroidectomy in cases in which no tetany existed and could not show that the activity of the parathyroids had varied except as much as could be accounted for on a basis of parathyroid trauma.

In 1928 I made 550 serum calcium estimations in cases of thyroid disease in which no tetany existed and found no changes in serum calcium levels which could not be accounted for on a basis of parathyroid trauma. No relation between the level of serum calcium and the basal metabolic rate could be shown.

From our own observations I can say that in those cases in which hypothyroidism has coexisted with tetany the administration of thyroid extract is necessary to control the skin changes and the edema due to the hypothyroidism and to raise the metabolism. After these signs disappear, however, the tetany remains as severe as before. In some cases of tetany in which edema, paresthesia and a pasty pallor are present, the basal metabolism may be normal. In such cases the edema and other signs disappear when the serum calcium reaches a nearly normal level, and the basal metabolism is not changed. In our experience it has not been necessary to administer thyroid extract in order to control the skin changes if they are unassociated with a low basal metabolism.

There may be some interrelationship between the parathyroid and thyroid glands but repeated clinical observations have failed to convince me that such a relationship exists.

Pituitary Gland.—There is little evidence that suggests that parathyroid deficiency produces any effect on the pituitary gland. Ott and Scott[31] have shown that injections of pituitary extract were beneficial in the treatment of tetany and it is known that polyuria is frequently associated with tetany. Hunter[32] mentions that polyuria may occur also in hyperparathyroidism.

Adrenals.—That hypersensitiveness to epinephrine is present in tetany has been pointed out by Falta and Rudinger[33] and is well recognized. This will not be discussed here.

Pancreas.—There is but little evidence of any association between the function of the pancreas and of the parathyroids although temporary glycosuria of the alimentary type has been reported in cases of idiopathic tetany in humans. There is, however, a definite and important relationship between carbohydrate and phosphate metabolism which has a distinct bearing on the metabolism in tetany. This relationship will be discussed later.

The Gonads.—The occurrence of tetany during the periods of pregnancy and lactation has been thoroughly studied in the past but the tetany which is usually associated with these conditions is not of the parathyroprival type, although it has been shown that partial parathyroidectomy may cause a sufficient lessening of parathyroid reserve in rats to induce the onset of tetany during pregnancy. It is a remarkable fact, however, that experimental evidence does not coincide with that secured by clinical observations in parathyroprival tetany. In our series three patients with chronic tetany have passed through the periods of pregnancy and lactation without presenting any manifestations of tetany although in each of these cases there had been intermittent attacks preceding the beginning of pregnancy. A fourth patient who has had a definite parathyroid deficiency for four years has been pregnant for about six months. She was receiving calcium lactate in doses of 240 grains per day before the beginning of pregnancy. The same treatment has been continued up to the present time and there have been no manifestations of tetany. Unfortunately in these cases no serum calcium estimations have been made during pregnancy. The same observation has been made by others as is indicated in reports of such cases as that of Findley which has been mentioned above. In his case a woman with moderately severe tetany was apparently able to pass through pregnancy repeatedly with little difficulty.

In contradistinction to the above observations it should be noted that in cases of chronic tetany in women acute attacks of tetany are likely to occur at or during the menstrual period. It has been shown by some that the menstrual fluid has a high calcium content. This finding I believe does not adequately explain this coexistence because I have observed repeatedly that the symptoms of tetany begin to increase some time before the establishment of the menstrual flow.

One patient has been observed who has had tetany for two years. The uterus had been removed several years before we saw her but the time of the menses could always be recognized by soreness in the breasts and a sense of weight in the pelvis. At this part of the menstrual cycle the symptoms of tetany were usually aggravated although of course no blood was lost.

In some patients paresthesia and stiffness of the fingers increase from one to two days before the flow commences. It appears to us therefore that the relationship is in the nature of a hormonal balance. The mechanism of such a balance is obscure but will no doubt be clarified with the further development of our knowledge of the function of the pituitary and ovarian sex hormones. No interrelationship between function of the parathyroids and of the testes is known.

The Bones and Joints.—The early writers on tetany frequently mentioned pain in the joints as a symptom of tetany. We have seen patients treated by physiotherapy, special orthopedic shoes, strapping of the feet and various similar measures because of discomfort which later was shown to be due entirely to parathyroid deficiency.

It is interesting to note that some patients who have had parathyroid tetany for years show marked clinical and radiological evidence of hypertrophic arthritis. According to the contentions of LeRiche[34] and Ballin[35] arthritis of this type is frequently caused by hyperparathyroidism. These authors apparently do not believe that hyperparathyroidism is the cause of hypertrophic arthritis in all cases, but it is interesting to note that cases have been observed in which hypertrophic arthritis has advanced to the presence of tetany.

Tenosynovitis may be caused by the metabolic disturbances associated with chronic tetany. I have not seen it described elsewhere. In one of the cases in this series, that of a woman, thirty-six years of age, moderately severe chronic tetany had existed since 1921 and constant treatment was required. The patient was in the habit of taking daily from 8 to 12 drachms (32 to 40 Gm.) of calcium

lactate powder. In 1930 the administration of the calcium was discontinued for experimental reasons and treatment with parathyroid extract alone was instituted. The tetany became very severe in spite of the administration of as much as 13 cc. (260 units) of the extract in one day. During this time pain and stiffness occurred in the left thumb together with extreme tenderness along the course of the dorsal tendons. The tetany was quickly controlled by the addition of sufficient calcium but the tenderness of the tendons persisted for several months. Later when the tetany suddenly became severe the same condition was observed in the right thumb. This time it disappeared immediately after the intravenous injection of calcium chloride. Recently coincidentally with an acute cold the symptoms of tetany recurred and the tenosynovitis developed again. The tetany was quickly relieved by the administration of parathyroid extract together with large doses of calcium by mouth.

Radiological examination reveals remarkably little change in the calcification of the bones in untreated cases of chronic tetany. Recently a woman presented herself who had had parathyroprival tetany more than ten years but had received no treatment. She showed many trophic changes. Her hands were *x*-rayed on the same film with the hands of a normal woman of her own age. Slight decalcification could be detected in the bones of the patient with tetany but it was thought that they were not more than could be accounted for on a basis of disuse.

TROPHIC CHANGES

In chronic tetany trophic changes may affect many structures. The most important of these to the patient are the **eye changes** which produce cataract. According to Ruedemann[36] the cataract associated with tetany differs from that form which is designated "senile cataract." In tetany the early changes in the lens are of a diffuse character affecting chiefly the posterior corticocapsular area, whereas in the senile type the nuclear area is affected early and spicular radiations of opacified tissue are present. There are no dependable figures as to the frequency of lens changes in this series since many of these patients have not been seen for years, some of them not since the immediate postoperative period. Changes in the lens do not clear up on treatment of the tetany. In such cases if the condition of the lens is mistaken for senile cataract and an operation is performed before the tetany is under complete control an acute attack may be

precipitated and vomiting may occur with resultant prolapsus of the iris.

In many chronic cases which have been untreated for long periods **nail changes** occur. The nails become dull in color, have roughened surfaces and may be thrown into transverse folds. The surfaces of the nails may be scaly. The fingernails alone may be affected. We have seen one case in which the fingernails became a dull chalky white in color and were shed completely but the nails of the thumbs and of the toes showed no apparent changes, except that their color became somewhat dull. Sometimes such nail changes are incorrectly diagnosed as due to a tenial infection. When proper treatment is instituted the growing nail is normal and soon replaces the trophic structure. In postoperative parathyroid tetany the **teeth** are seldom as severely affected as they are in infantile tetany. However, untreated cases have been seen in which the teeth have become loose but have become tight again within a few days following the institution of treatment.

In our series we have not seen any cases in which the **hair** has been affected grossly but cases have been reported in which there has been a general defluvium.

Edema may occur in tetany when the condition is unassociated with hypothyroidism, cardiac decompensation, nephritis or abnormalities in the blood proteins.

A case was seen recently in which untreated tetany had been present for many years. The patient had bilateral cataracts, marked nail changes, mild ascites and edema which was marked in the legs and extended as high as the waist, and effusions filled both pleural spaces to the level of the midscapula. At the outset the serum calcium was 5.7 mg. and the phosphates 6.5 mg. per 100 cc. The patient had been on a very low protein diet for months and purposely this diet was not changed for a month. The urine contained albumin, 4 plus, and a few hyaline casts. The total blood proteins, the albumin, globulin and the albumin-globulin ratio were normal. The treatment administered in this case consisted of 2 drachms (7.8 Gm.) of calcium lactate powder six times daily and 1 to 2 cc. of Collip's parathyroid extract daily. On three occasions within the first few days of treatment large quantities of fluid were withdrawn from both pleural spaces.

Within two weeks the edema, ascites, effusions and albuminuria had disappeared. A month later the patient looked and felt normal;

she had presented no symptoms of tetany and showed no signs of it except in the lenses and the nails, the fasting serum calcium being 10.2 mg. and the phosphates 5.3 mg. per 100 cc.

THE DIFFERENTIAL DIAGNOSIS

In our series, in certain cases the tetany has been mistaken for grand mal, or for Parkinson's disease, and in one case the tetany was overlooked because the symptoms of the accompanying psychosis masked it. Trophic changes of the lens have been mistaken for senile cataract, trophic disturbances of the nails have been considered due to a tenial infection.

In some cases the paresthesias and the poor color of the skin has led to the diagnosis of hypothyroidism.

Occasionally gastric tetany or tetanic convulsions associated with hysterical hyperpnea cause a temporary difficulty in diagnosis.

In general medical practice idiopathic tetany of adults cannot be said to be of rare occurrence. If blood is taken during an attack and shows both calcium and phosphorus levels to be normal; if the intravenous administration of large doses of calcium does not give immediate relief; and if parathyroid extract does not lessen the severity of a seizure; then even though Chvostek's, Trousseau's and Erb's signs are present the parathyroid glands can surely not be implicated.

METABOLISM IN TETANY

Since this chapter is devoted chiefly to diagnosis and treatment any remarks on metabolism will be necessarily very limited and the only points which will be mentioned are those relating to calcium and phosphates and their relationship to carbohydrates and vitamin D.

Calcium.—The most important and constant single criterion of the severity of parathyroid tetany is the degree of depression of the level of total serum calcium. Calcium is present in the blood in several forms—as calcium ions, un-ionized organic calcium combinations and in un-ionized inorganic combinations. There is no satisfactory physical or chemical method by which these various fractions can be distinguished. The diffusible calcium is probably chiefly ionic and inorganic. The most satisfactory method of determining the diffusible fraction is that which was used by Cameron and Moorehouse,[37] namely, the measurement of calcium in the spinal fluid. The symptoms of tetany are probably more directly due to changes in the ionic calcium content than to changes in the total calcium content.

The symptoms of tetany which follow alterations in the level of blood calcium appear to be due to changes in the nervous system and not to changes in the contractile mechanism. We believe that this is true because (1) calcium is known to affect cortical excitability; (2) curare which has no direct effect on muscle abolishes tetanic spasms in parathyroprival tetany; and (3) the central as well as the motor, sensory and sympathetic nerves are all affected in this disease.

Phosphates.—Retention of phosphates is one of the two outstanding metabolic features in parathyroprival tetany. It seems surprising that more attention has not been focused upon the measurement of the serum phosphate content in applying this physiologic principle clinically. In parathyroid insufficiency the blood phosphates are increased and the urinary phosphates are decreased.

The importance of phosphates in tetany lies in the fact that their increase in the blood stream aggravates the symptoms and may precipitate an attack while their decrease in the blood alleviates the symptoms. The level of blood phosphates in tetany is dependent chiefly on two factors: (1) the amount of phosphate thrown out of the blood stream during carbohydrate assimilation and (2) the rate of excretion of phosphates by the kidneys.

It appears that one of the important functions of the parathyroid hormone is to increase the excretion of phosphates and the beneficial effect of this may be due to the fact that a decrease in blood phosphates increases calcium ionization.

THE RELATION OF CARBOHYDRATES TO PHOSPHATE METABOLISM

Harrop and Benedict[38] showed that in cases in which normal glucose tolerance curves were secured the level of the blood phosphates fell, the lowest point in the phosphate curve being subsequent to the highest point in the glucose curve.

They believed that phosphates are utilized temporarily during the transference of glucose from the blood. It has been known that this principle is applicable in the treatment of parathyroprival tetany in dogs and in humans.[39]

It has also been shown that in tetany lactose is more effective than other carbohydrates in lowering the level of blood phosphates. The mechanism of this action is obscure.

Vitamin D.—A great deal has been said in recent years about the effect of various forms of vitamin D on the serum calcium and there

are some who believe that the actions of the parathyroids and of vitamin D have so much in common as to make them almost identical. It is unfortunate perhaps that a single criterion (serum calcium) has been used in many cases for the measurement of the activity of both factors. There are many factors which may raise the temperature, the basal metabolism and the blood sugar, but because their effects are the same these factors are not considered identical. It has been clearly shown that irradiated ergosterol may cause hypercalcemia in either normal or parathyroidectomized dogs.

Recently a case has been reported in which hypercalcemia was caused by the injection of viosterol intravenously into a patient with tetany. In this case 0.5 cc. per day of a preparation standardized as 8000 D. was used for five days. The blood changes were extremely interesting. It should be noted that the author (Reed[40]) stated that the patient was taking parathormone two or three times a week and this probably accounted for the fact that the blood phosphate content was no higher than 3.9 mg. per 100 cc. when viosterol injections were begun. During the period of the injections the serum calcium rose from 6.3 to 12.2 mg. per 100 cc. but the phosphates also rose from 3.9 to 6.5 mg. per 100 cc. which is an observation we have never made in cases in which parathormone was used. Thus if phosphate changes were used as a criterion the effect of viosterol in this case would be said to be quite different from what would be expected from parathyroid extract.

Jones, Rapopport, and Hodes[41] have recently called attention to several important differences between the action of viosterol and the parathyroid hormone. They point out that in parathyroidectomized dogs with tetany an extreme hypercalcemia may be produced within a few days by the administration of viosterol. It is unlikely that hyperplasia of an hypothetical amount of parathyroid tissue could take place to this extent in such a short time.

Also ergosterol may cause a greater hypercalcemia than is caused by parathyroid extract because dogs die of parathyroid hypercalcemia when the serum calcium is about 15 mg. per 100 cc. and may be relatively well with a hypercalcemia of 19 or 20 mg. per 100 cc. when this is caused by viosterol. Parathyroid hypercalcemia is associated with an increased viscosity of the blood and this association is not found in viosterol hypercalcemia. Viosterol shows no constant effect on the concentration of inorganic phosphorus. It is well known that such an effect is produced by parathyroid hormone which lowers

the level of inorganic phosphates in the blood. Also it should not be forgotten that an excess of vitamin D (Harris[42]) causes pathologic calcifications while hyperparathyroidism causes pathologic decalcification.

TREATMENT

Acute Stage.—The treatment of tetany can almost be summarized in the one word *calcium*. Calcium in some form must be given in large amounts and the doses must be repeated at frequent intervals. All other forms of treatment are relatively unimportant as compared with this.

In acute tetany as soon as the diagnosis is made serum calcium and phosphorus studies are made before any treatment is begun.

If the attack is mild, calcium lactate in water or milk is given every two hours by mouth in doses of two heaping teaspoonfuls (about 240 grains—16 Gm.) until relief is obtained. If it is not possible for this to be given orally the rectal route may be used.

Parathyroid extract (Hanson's or Collip's) is seldom necessary, and should never be depended upon for quick results unless calcium is given also. The actual cause of the symptoms is lack of available calcium. If the attack is sudden and severe and immediate relief is required calcium should be given intravenously. In my own experience the most effective calcium compound for intravenous use has been calcium chloride, of which I usually give 10 cc. of a 10 per cent solution. Great care must be taken not to allow the tissues to become soiled as a slough may result. Usually this intravenous infusion is given by gravity, saline being allowed to run in before and after the calcium, but in the presence of a severe convulsion it may be necessary to use a syringe. If a 10 per cent solution of calcium gluconate is used, 10 to 20 cc. may be given. The effect of the latter is not usually so strikingly prompt and complete as that produced by calcium chloride.

If an acute attack occurs where calcium treatment is not immediately available the course of the attack may be shortened and its severity lessened by the administration of morphine or any other sedative in sufficient dosage. Ten to 20 cc. of 25 per cent solution of magnesium sulphate may be given intramuscularly or any other anesthetic may be employed. Carbon dioxide may be administered or rebreathing may help and large doses of glucose given by mouth or the intravenous administration of glucose or saline have a distinctly beneficial effect though it is not prompt or marked.

It should be borne in mind that in tetany the level of serum calcium is much more readily changed than in the normal individual and in this condition hypercalcemia may be caused by the oral administration of calcium. Therefore, frequent blood calcium and phosphorus estimations are a necessary part of the intelligent treatment of tetany.

Chronic Stage.—If the symptoms of tetany do not disappear within from one or two days to one or two weeks the case may be considered chronic and in such cases treatment is usually required for an indefinite period. In our hands the administration of calcium lactate powder has proved to be the most efficacious method of treatment. In the milder cases a teaspoonful taken from one to three times a day is sufficient. In the more severe cases as much as two heaping teaspoonfuls may be taken as often as six times a day without any resultant disturbance. The dose is best taken before or between meals. Occasionally calcium lactate causes diarrhea and in such cases its efficiency is lost. For the same reason laxatives in any form are to be avoided as they may precipitate an attack of tetany. In the few cases in which calcium lactate is not well borne similar doses of calcium carbonate powder may be used, but usually this is not quite so effective. Large doses of calcium will occasionally cause bladder irritability and in one of our cases the patient always experiences a desire to urinate shortly after taking a large dose of calcium.

The use of phosphates in any form is to be strictly avoided as they are usually readily absorbed and will precipitate an attack. Some of the commercial preparations of calcium contain phosphates and these are distinctly harmful in cases of tetany. Sometimes attacks of tetany are observed during which the serum calcium is at the same level as when the patient is free from symptoms. In such cases the attacks are usually caused by a temporary increase in the blood phosphates. For this reason, there are some cases in which the symptoms cannot be completely controlled by the use of calcium alone and in which the administration of lactose will cause complete relief. We believe that this benefit is due to the fact that lactose has the power of reducing the blood phosphate content. Lactose may be given in powder form in doses of one to six teaspoonfuls per day. This also may cause diarrhea if given in too large doses and when it does its use is disadvantageous. It has come to my attention several times within the past year that in patients whose serum calcium and blood phosphorus levels have been kept relatively normal for many

months by the use of calcium and lactose, diffuse aching pains have developed in the muscles which have disappeared promptly after the injection of parathyroid extract. The accompanying chart indicates the chemical changes in the blood which may follow the use of lactose in tetany (Fig. 154). Some of the experimental work which has led us to these conclusions has been published elsewhere.[39]

In the chart, the upper line indicates serum calcium levels. The point at the left end of this line which is circled is the average of nine serum calcium determinations at monthly intervals preceding the beginning of the period covered by the chart. During that time

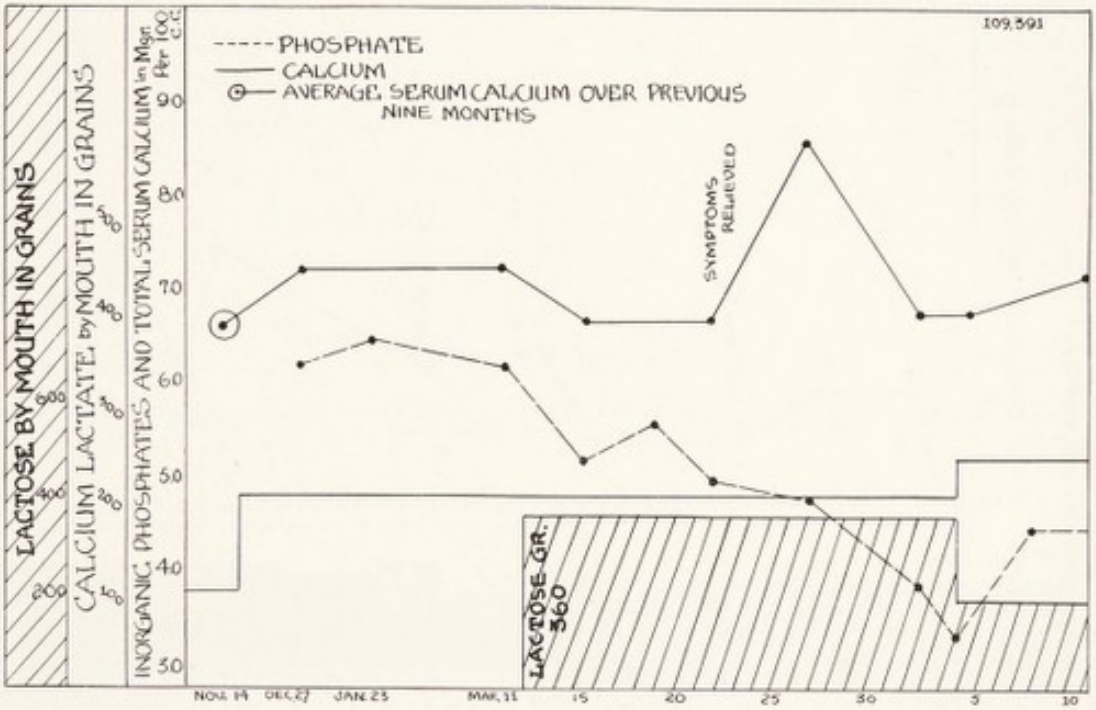

Fig. 154.—Chart showing chemical changes in the blood following the administration of lactose in parathyroid tetany.

the patient had received 100 grains of calcium lactate per day and had mild symptoms daily. This is represented by the lower line at the left. On November 14th, the dosage of calcium was increased to 200 grains a day. The serum calcium rose and the symptoms were lessened but did not disappear. The blood phosphates are indicated by the interrupted line.

On March 12th, lactose powder in three daily doses amounting to 360 grains was added to the treatment. The marked fall in blood phosphates which followed is apparent. When the phosphate level fell to below 2 mg. per 100 cc. the patient's symptoms were markedly alleviated. On April 4th, the phosphate level was lower than was

considered necessary and the lactose intake was therefore reduced to 180 grains a day and the blood phosphate level rose but only to the upper normal level. The serum calcium during this time showed no constant change. The rise on April 27th is unexplained.

Following these observations larger doses of calcium have been given and the tetany has remained well controlled for eighteen months.

The following charts (Figs. 155–160) give some indication of the relative values of the administration of calcium, parathormone and of parathyroid transplantation in the treatment of tetany. These charts are copies of clinical charts made during the course of a single

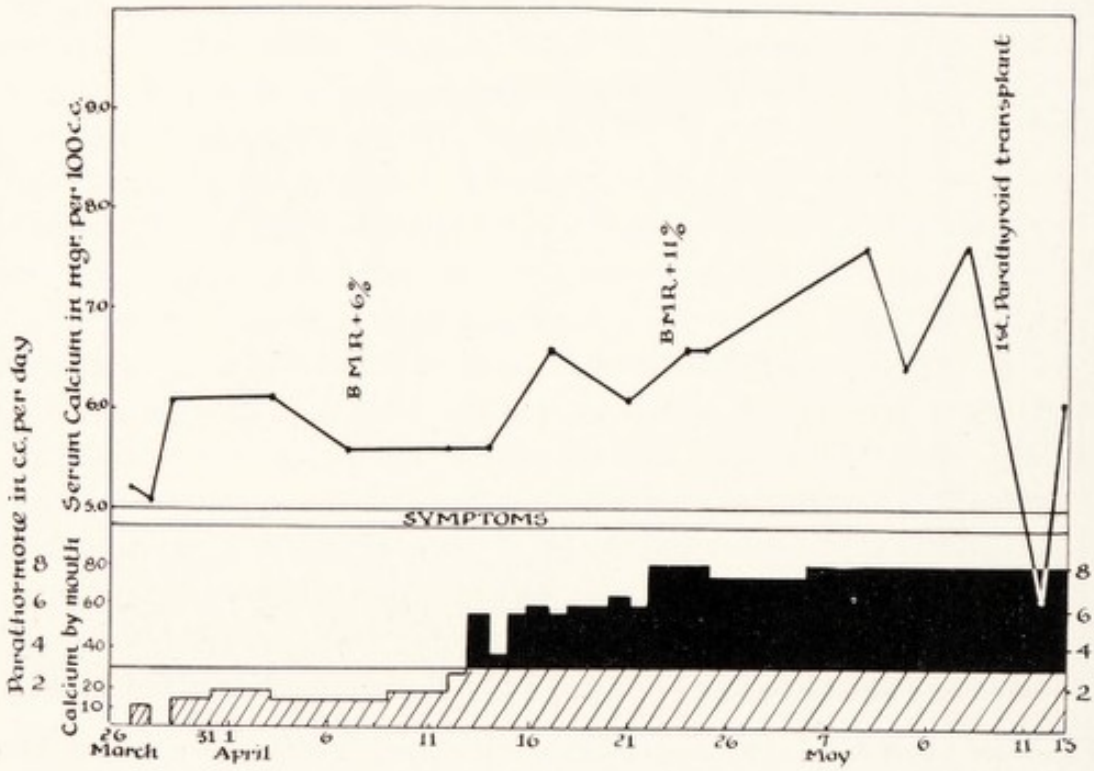

Fig. 155.—Chart indicating the progress of a patient with parathyroid tetany who was treated with calcium and parathormone and by parathyroid transplantation I.

case which was under observation several years ago. To some extent they demonstrate the evolution of our present ideas regarding the clinical management of this condition.

In this case, that of a woman twenty-six years of age, severe tetany developed following a thyroidectomy for recurrent hyperthyroidism. Preceding the beginning of the record (Fig. 155) while the patient was taking 30 grains of calcium lactate per day, the serum calcium varied by about 5 mg. per 100 cc. The patient presented symptoms daily and had frequent severe attacks.

In the first chart (Fig. 155) the upper black line represents the serum calcium level. The straight black lines below this indicate the presence of symptoms. The amount of parathyroid extract given is shown below (in cubic centimeters of parathormone) by the black area and the amount of calcium lactate given daily by mouth is represented by the white area. Any overlapping of the calcium intake by the parathormone dosage is represented by the areas of cross hatching.

During the forty-eight days represented here the patient was taking 30 grains of calcium lactate per day. While she was taking

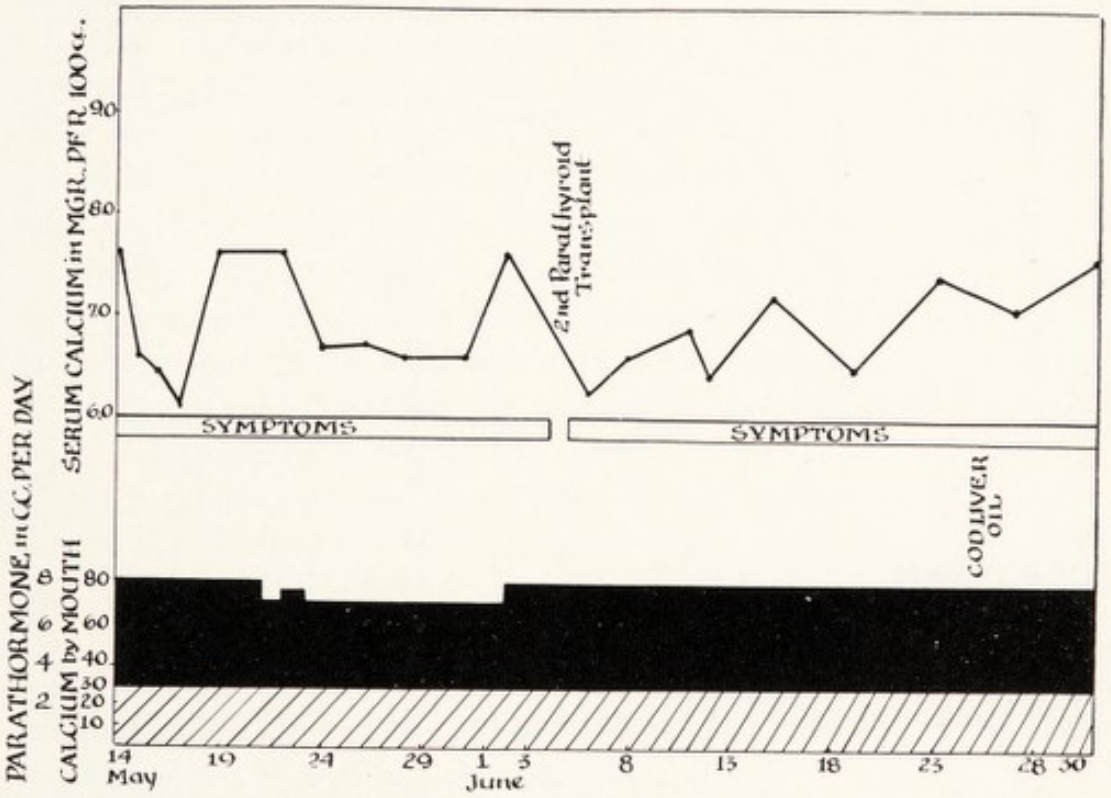

Fig. 156.—Chart indicating the progress of a patient with parathyroid tetany who was treated with calcium and parathormone and by parathyroid transplantation II.

1.5 cc. (30 units) of parathormone (Collip) in addition the serum calcium averaged about 5.5 mg. per 100 cc.

When the parathormone dosage was increased to 8 cc. per day the serum calcium rose to about 7 mg. per 100 cc. Near the end of this chart is shown the effect of an attempted parathyroid transplant on the serum calcium content. It produced no rise in serum calcium above an average of about 7 mg. per 100 cc. and did not alleviate the symptoms.

Figure 156 shows the effects on the same case of the daily administration of 30 Gm. of calcium lactate with 140 to 160 units of parathyroid extract and the next chart (Fig. 157) shows a gradual reduction of the dose which averaged about 5 cc. of parathormone (Collip) —100 units—per day. This was continued until the first part of December.

In Figure 156 the serum calcium averaged about 7 mg. per 100 cc. during the forty-eight days depicted and, as shown, symptoms were present almost daily.

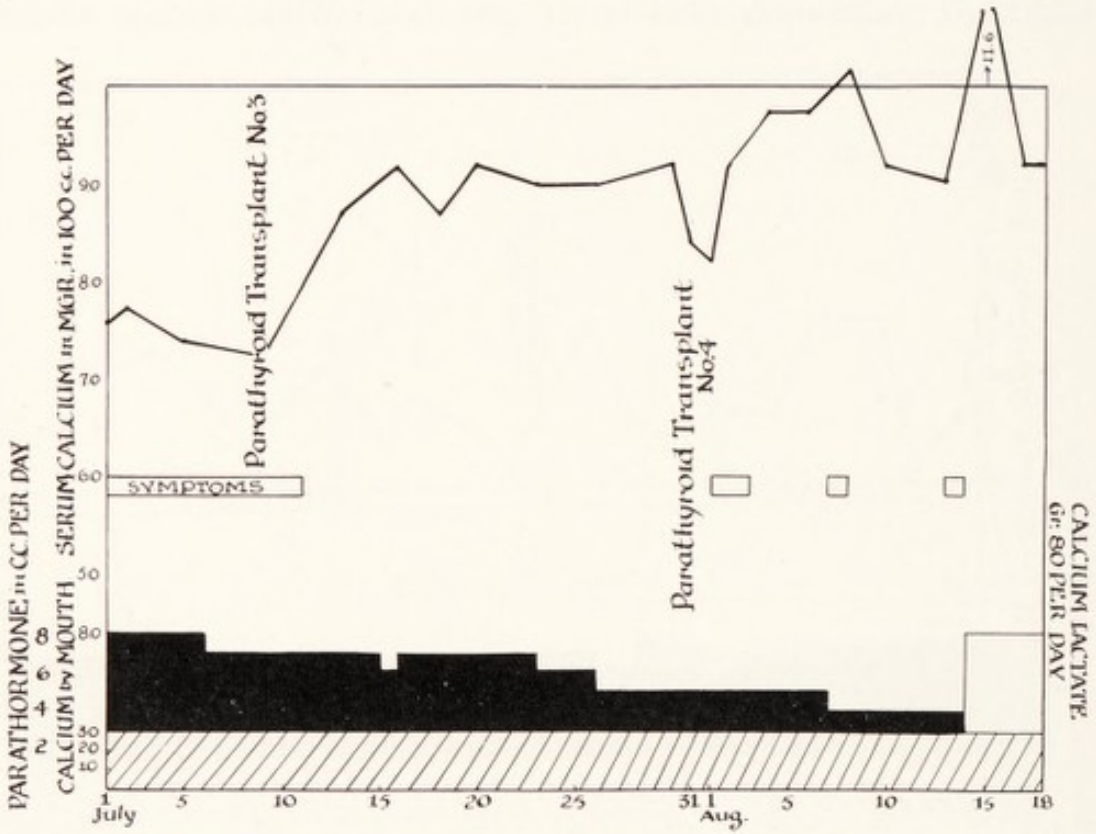

Fig. 157.—Chart indicating the progress of a patient with parathyroid tetany who was treated with calcium and parathormone and by parathyroid transplantation III.

This chart suggests the question as to the dosage of parathyroid extract. A Collip unit of parathyroid extract is 1/100 of the amount which will raise the serum calcium of a 20 kilo dog, 5 mg. per 100 cc. during a period of fifteen hours. Thus 1 cc. of material containing 20 units would raise the serum calcium of such an animal 1 mg. If we calculate the dosage in a human on a weight basis we find that such a patient as the one shown here who weighed about 165 pounds is very nearly four times the weight of the standard dog. We might suppose then that four times the amount of parathormone would be

necessary for the production of the same response in our patient as would produce a similar response in the test animal, that is, 4 cc. or 100 units might be expected to raise the serum calcium 1 mg. per 100 cc.

The average of five serum calcium determinations made while the patient was taking 30 units of parathormone per day is 5.6 mg. per 100 cc. The average of nine determinations shown in Figure 156 while the patient was using 160 units per day is 6.8 mg. per 100 cc. The difference in dosage between these two periods is 130 units per day which in a 20 kilo dog would raise the serum calcium 6.5 mg. In a human four times that weight it might be expected to raise the calcium 1.6 mg. The actual rise here was 1.2 mg. The close parallelism is apparent. Such results as these have been shown in other patients. However, the amount of available calcium is a factor and if patients are given large amounts of parathyroid extract the serum calcium may continue to fall and the phosphates to rise as in the case cited previously. On the other hand an occasional case of severe chronic tetany is seen in which even very large doses of calcium alone gradually lose their effect unless small amounts of parathyroid extract are used. In such instances as these the parathyroid extract appears to have a somewhat greater activity than usual.

Such findings as the above bring up the question as to whether or not the reactions to parathormone may not in large measure be due to a lack of available calcium. In the case reported by Lisser and Shepardson[43] such appears to be a definite possibility as the patient died in spite of large doses of parathormone while only small amounts of calcium were given. Allardyce[44] noted no increase in the activity of parathormone in dogs on addition of calcium to the diet, but he does not state the quantities of calcium added. The question as to what constitutes an overdose of parathyroid extract also comes to mind. In the case we have described large doses were given daily for nine months with no apparent ill effect, 160 units per day being given for the greater part of two months. It is difficult to correlate this observation with the reports of cases in which an overdosage of parathormone has been diagnosed. In a case recently reported parathormone overdosage was diagnosed after the use of only 50 to 100 units of parathormone per day for two to three days, the calcium intake during that same period having been reduced.[45] The patient presented symptoms and signs of tetany and had a low serum calcium content. Obviously the symptoms were not due to hyperparathy-

roidism and it seems probable to us that they were due to calcium deficiency.

In Figure 158 the further course of the patient described above is shown. A rise in the serum calcium content followed the third and fourth parathyroid transplants in spite of the fact that the dose of parathormone was steadily lessened. The improvement in symptoms during this period is striking. Near the end of the period covered by this chart the calcium dosage was raised to 80 grains per day and the marked effect of the administration of calcium by mouth together with the parathormone may be noted.

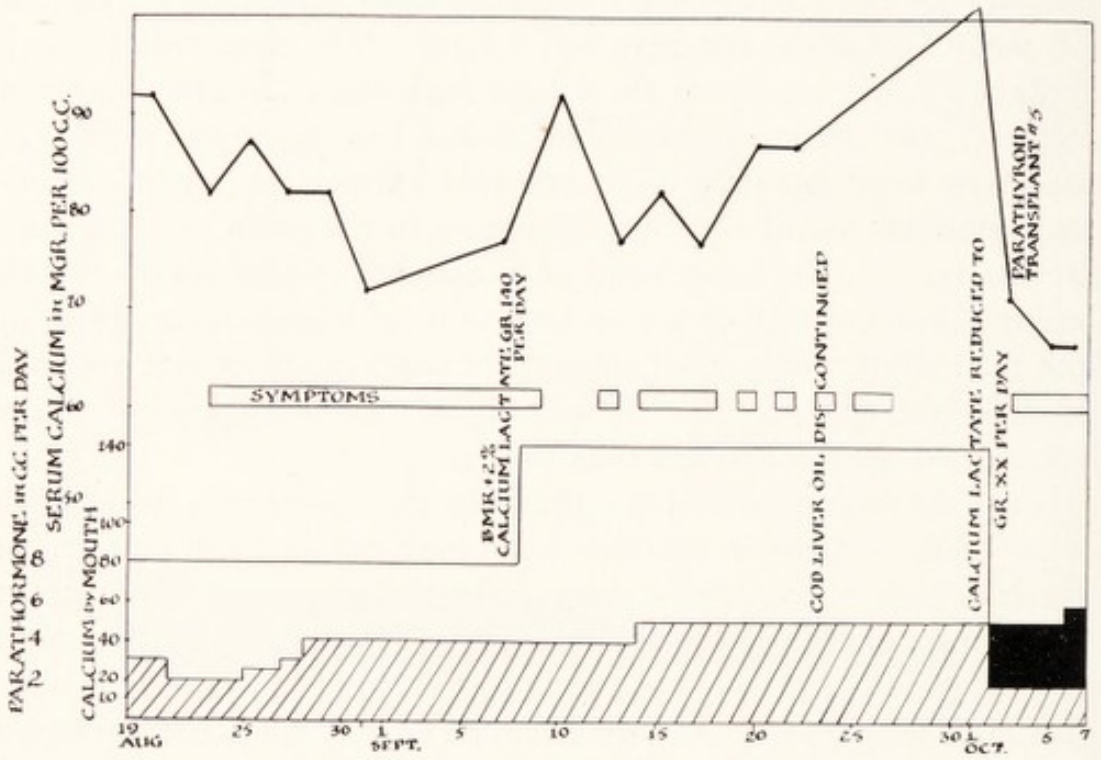

Fig. 158.—Chart indicating the progress of a patient with parathyroid tetany who was treated with calcium and parathormone and by parathyroid transplantation IV.

Figure 158 shows a gradual fall in the serum calcium level after the parathyroid transplants so that in spite of the administration of larger doses of calcium the serum calcium level was again at 7.2 mg. per 100 cc. one month after the last transplant. On September 8th, the intake of calcium was raised to 140 grains per day and the steady increase of the serum calcium is apparent. The fact that this increase was not due alone to parathormone is evidenced by the fact that there was a sharp decrease of serum calcium when the calcium intake was reduced to 20 Gm. per day at the time of the fifth parathyroid transplant.

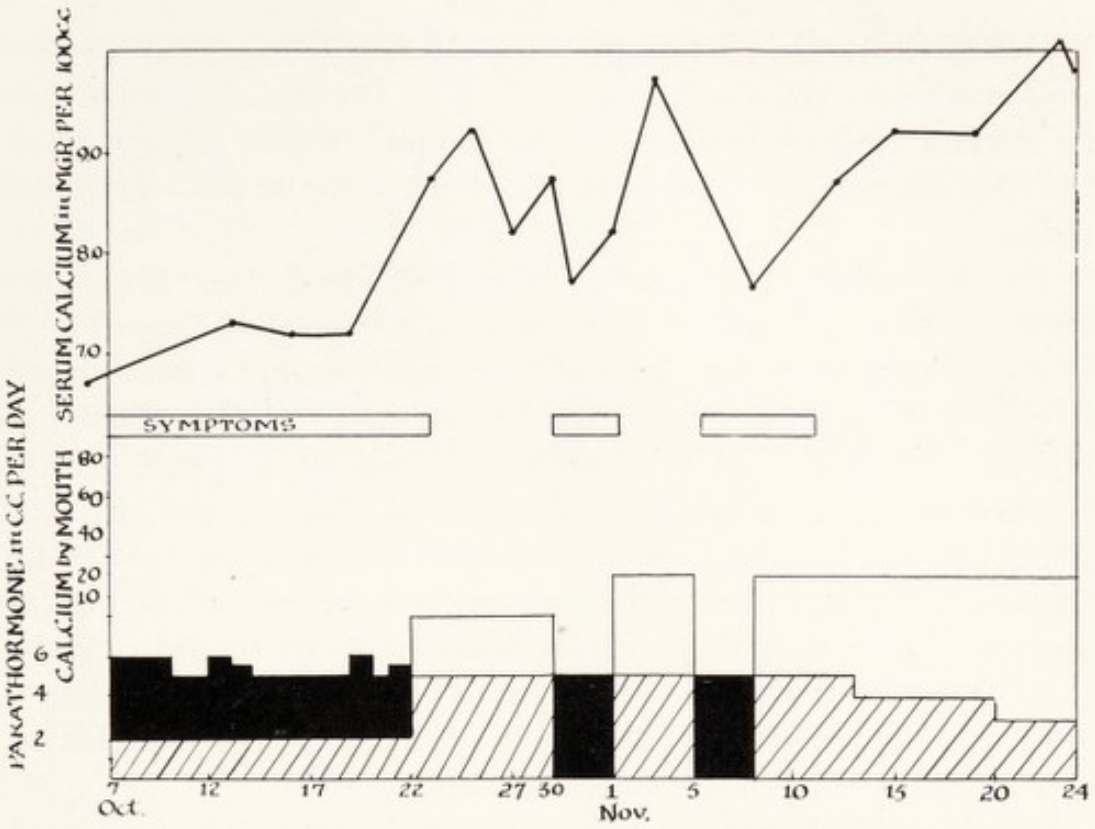

Fig. 159.—Chart indicating the progress of a patient with parathyroid tetany who was treated with calcium and parathormone and by parathyroid transplantation V.

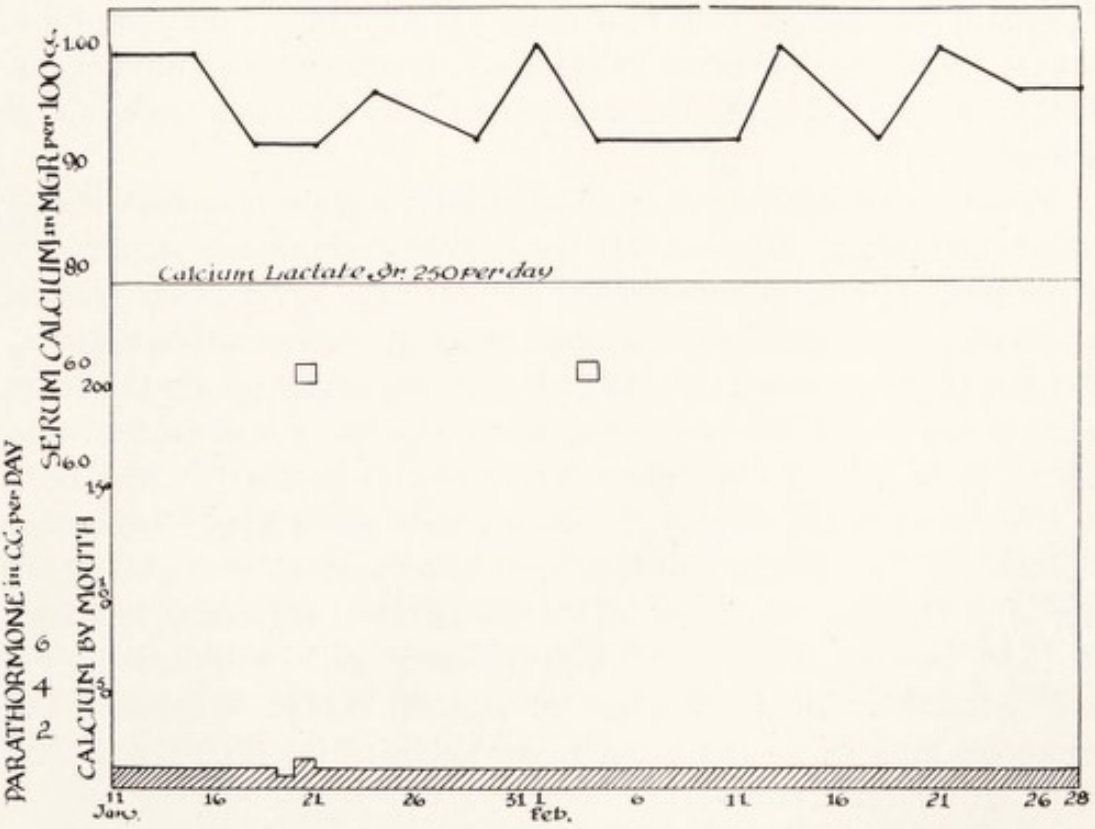

Fig. 160.—Chart indicating the progress of a patient with parathyroid tetany who was treated with calcium and parathormone and by parathyroid transplantation VI.

During the period covered by Figure 159 the amounts of parathormone used were relatively constant. It is obvious that each time the calcium intake was increased the symptoms were improved and that this improvement was associated with an increase of serum calcium.

The last chart in this series (Fig. 160) shows that the serum calcium could be brought to normal and kept there by the use of large doses of calcium by mouth and only 1 cc. (20 units) of parathormone per day. During this period the patient had mild symptoms on only two occasions. In 1929 she lost her life by accident, not as the result of tetany. It is more than probable that if this girl were alive today her condition could be controlled completely by the use of even larger doses of calcium alone or with lactose, without parathormone. Such large doses of parathormone as are indicated above are never used in tetany now and in fact it is rarely that it is necessary to use parathyroid extract at all and when required in addition to other measures only small amounts are usually given.

Parathyroid Transplant.—Parathyroid transplants have been tried ten times in this series. Usually the clinical result has been about as indicated in the case described above. The activity of the transplant was indicated in four cases by lessening of the symptoms and by an increase of serum calcium. It certainly was temporary in three cases, the effect not being apparent after the sixth week in any of these.

In one case it was necessary to administer intravenous infusions of calcium gluconate (10 cc. of a 10 per cent solution) every second day in addition to the administration of 180 Gm. of calcium lactate by mouth before parathyroid transplantation. After the transplantation the phosphates fell to a level below that observed on the large doses of calcium which were being given and the serum calcium was higher when calcium was given by mouth alone than it had been previously when the calcium injections were given also. A gradual decrease of the serum calcium one month after transplantation indicated that the condition of the patient was regressing although for three months longer the symptoms were well controlled by the daily administration of 240 Gm. of calcium orally. Gradually the symptoms grew worse and about a year following the graft the patient again had severe tetany.

Vitamin D.—That vitamin D has an influence on the blood calcium content in parathyroprival tetany is undeniable. However, its

employment as a major factor in the treatment of this disease is quite another matter.

The use of ultraviolet light in the treatment of tetany causes a slight measurable increase of serum calcium and a mild symptomatic benefit. The same is true of viosterol.

The accompanying chart (Fig. 161) is that of a woman with chronic parathyroid tetany who had received no treatment before the administration of viosterol was started. She was given 100 minims of viosterol (250 D.) for seventeen days with no resultant measurable increase of serum calcium, no decrease of blood phosphates and no

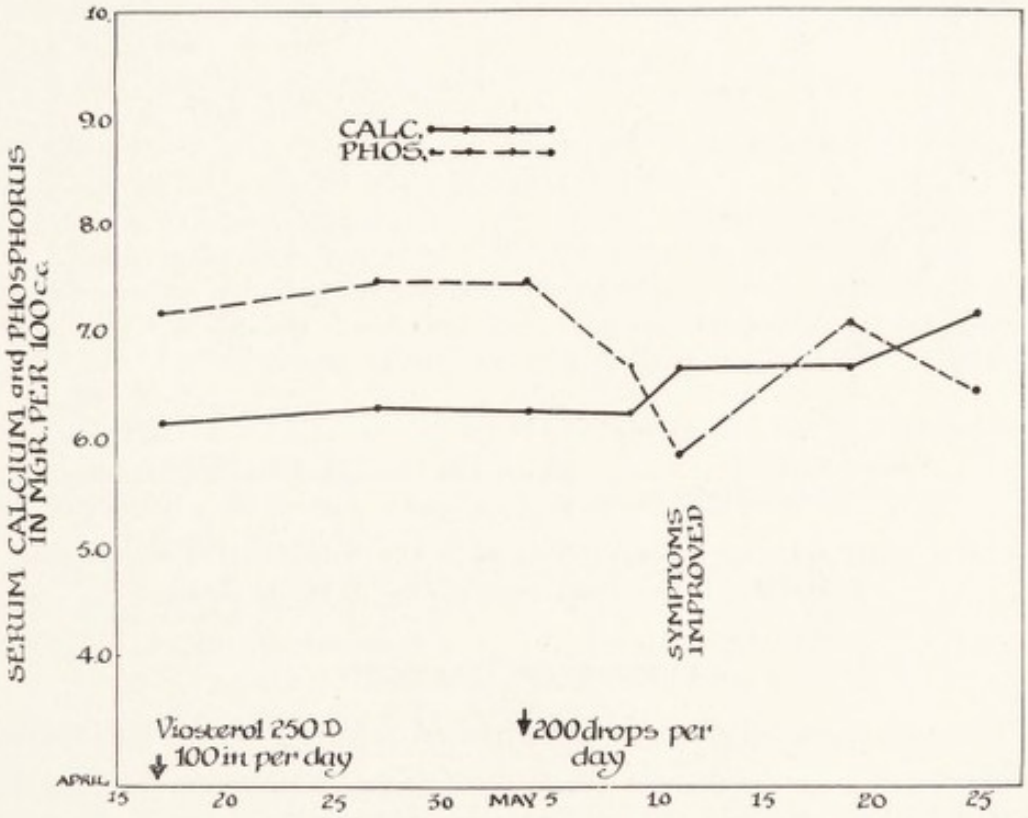

Fig. 161.—Chart showing chemical changes in the blood after the administration of viosterol.

improvement in symptoms. The dose was then raised to 200 minims per day with a resultant slight rise of the calcium level and fall of the phosphate level. After twenty-one days of this increased dosage there was only questionable symptomatic benefit. The inadequacy of the administration of small doses of cod liver oil for relief of symptoms is obvious.

Figure 162 demonstrates the rapid rise of the serum calcium level and definite fall in the phosphate level of the same patient, two and one-half months after the discontinuance of viosterol. At the time

this chart was made the patient was receiving calcium lactate by mouth in doses of a teaspoonful three times a day. The symptoms were completely relieved.

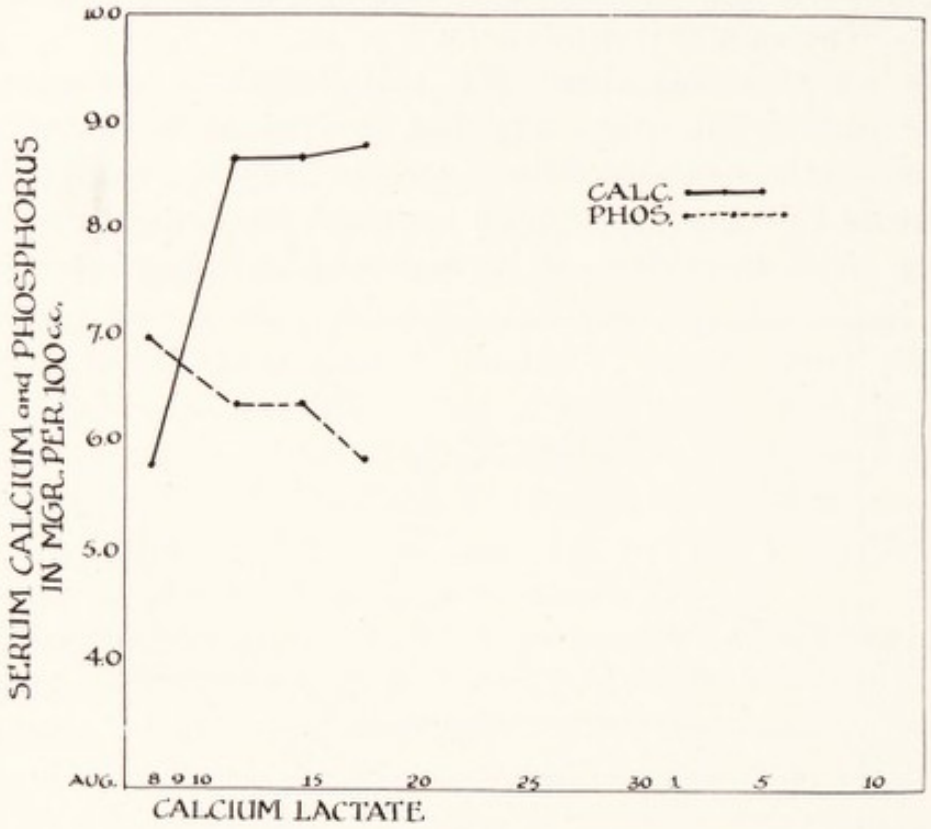

Fig. 162.—Chart showing chemical changes in the blood after discontinuance of viosterol. (Chart from same patient as in Fig. 161.)

Summary of Treatment

The treatment of chronic parathyroid tetany may be summarized as follows:

1. In acute attacks give calcium intravenously.
2. In cases not in acute tetany give calcium lactate powder by mouth in doses varying from one level teaspoonful to eight heaping teaspoonfuls per day. If this is poorly borne calcium carbonate may be substituted.
3. If large doses of calcium alone are insufficient the addition of lactose powder in doses of one to six teaspoonfuls per day may bring relief.
4. Small doses of parathyroid extract may be necessary in rare cases.
5. The permanent value of parathyroid transplants is doubtful.
6. Vitamin D as a therapeutic agent has very limited value.

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CHAPTER XXXIX

END-RESULTS OF OPERATIONS FOR HYPERTHYROIDISM

GEORGE CRILE

UNFAVORABLE END-RESULTS

THE total number of operations on the thyroid gland performed by my associates and myself has been 22,441. Of these 5533 have been ligations and 16,908 have been thyroidectomies, of which 12,747 have been performed for hyperthyroidism. Formerly the operative mortality was high but with improving methods of management the mortality has steadily decreased. For the last 5000 consecutive thyroidectomies the mortality rate has been 0.84 per cent. In two series now in progress (July 6, 1932) we have performed 1402 thyroidectomies and lobectomies on patients under forty-five years of age and 175 on patients forty-five years of age and over without a death in either series. For a number of years our statistical department has followed the patients upon whom these operations have been performed and has tabulated the data concerning them. In the majority of cases, this "follow-up" has been based on personal interviews and examinations. Our ideas have often been changed as the result of our accumulating experience and information. We are well aware that final and absolute truth is not attainable, but *working* truth is attainable, and as no truth is more valuable than failure, let us consider the cases in which operation has failed to relieve the symptoms completely or even partially.

Cases in Which the Symptoms Have Simulated Those of Hyperthyroidism.—This group includes cases in which neurocirculatory asthenia, effort syndrome, psychoses, etc., have been associated with a goiter, and in which symptoms of hyperthyroidism have been present. In many instances there has been a moderate increase in the basal metabolic rate, ranging from plus 15 to plus 25. In most of these cases the course of the disease has continued unchanged and the operation has been useless. The underlying condition has not been made worse by the operation, but the patients in this group have

been justly dissatisfied. However, as experience accumulates, we are able to make the differential diagnosis with increasing accuracy.

Cases in Which Delirium Has Been Present.—Operations for acute hyperthyroidism have been unsuccessful in cases of hyperthyroidism with delirium, in which prolonged hospitalization and treatment have failed to bring the patient to a conscious state, and in which it has seemed obvious that death was approaching. Either the end was accelerated or the patient recovered physically from the operation, while the mentality remained permanently submerged. Happily, there has been only a small group of such cases in our total series, for since we became aware of this sequence we have not operated upon persistently delirious patients. Although operation is not advised in the presence of persistent delirium, in cases of temporary, slight delirium in younger persons, patients have been cured by a cautious approach through ligation of one lobe, then later, of the other lobe, followed by a period of rest at home for three months, and a return to the hospital for the thyroidectomy. Surprisingly good results have followed carefully graded operative procedures in selected cases of intermittent delirium.

Hyperthyroidism in Senile Patients.—Occasionally we see senile patients in whom, although they are mentally clear most of the day, transient delirium may occur at night and occasionally in the daytime. In our earlier experience we submitted such patients to thyroidectomy. Our end-results soon showed that these patients are too near the borderline for such a hazard, so that now we hold strictly to the rule that unless a senile patient is rational all the time, thyroidectomy is unsafe.

Cases in Which Technical Errors Have Been Made.—To the unfavorable results due to the causes listed above must be added those fortunately rare cases which result from technical errors, among which is bilateral abductor paralysis. In cases in which this unfortunate sequel has occurred, a special tube adapted by Dr. J. M. Waugh, having a valve which permits the intake, but shuts off the egress of air through the tube, thus allowing free breathing, but giving the patient a useful voice, has done much to remedy the condition. Dr. W. V. Mullin has pursued a painstaking research to discover the possibilities of repair of the nerves, but as yet with indifferent success.

Persistent paralysis, mostly unilateral, has occurred in 1.08 per cent of our total series.

The occurrence of **postoperative tetany** is another consequence of a technical error. Happily, this occurrence, too, is rare, for the parathyroid bodies can either be preserved or, if they have been removed, they can be found by a search of the thyroid immediately after its excision, and can be replaced according to the technique described in Chapter XXXIII. Temporary or persistent hypoparathyroidism occurred in 0.97 per cent of our total series.

Postoperative Hypothyroidism.—Extending experience and a continuous "follow-up" on the part on the surgeon are the only means whereby errors as to the amount of thyroid tissue that should be left can be corrected, and there will even be some surprises. For example, as first observed by the elder Kocher, it occasionally happens in the case of a patient with a large nodular goiter that after the removal of the greater part of the thyroid gland, the subnormal basal metabolic rate, instead of being lowered still further, may rise to normal. The mechanism of this unexpected result is not clear.

Whether hypothyroidism occurs spontaneously or results from the removal of too much of the thyroid gland, it presents many clinical surprises. There are two points worth mentioning in regard to its treatment: First, by feeding thyroid extract in a dosage which is constantly checked by estimations of the basal metabolism, the sluggish, inactive thyroid can be made to grow through what seems to be a process of excitation. Thyroid extract, however, must be administered only under careful supervision, or hyperthyroidism may be produced. The second point is that in hypothyroidism there is low gastric motility and low acidity or anacidity, so that coincident with the administration of thyroid extract dilute hydrochloric acid should be given. Hypothyroidism persisted in 2.7 per cent of our cases in which this postoperative sequel occurred.

Recurrent Hyperthyroidism.—There has been a recurrence of hyperthyroidism in 3.03 per cent of our total series, 0.89 per cent occurring within the first year after operation, and 1.5 per cent within two years. When there is a recurrence of hyperthyroidism, we have found that the one and only way to overcome it is to reoperate, unless the surgeon is certain that he has removed enough of the gland in the first instance (Fig. 163). If this is the case then it is evident that the recurrence is caused by focal infection somewhere in the body, or that the patient is being subjected to social maladjustments, worry, overwork, or some other strain not disclosed by the clinical investigations. In a small group of cases recurrence of the hyper-

thyroidism may develop even after reoperation and after all adverse influences have been removed. These cases, however, have certain characteristics, among which are the maintenance of weight, an increased metabolism, ranging from plus 15 to plus 25, tachycardia, nervousness, tremor, fatigue, sweating, etc. It is as if they had a peculiar but unknown susceptibility to the disease. In 21 of these

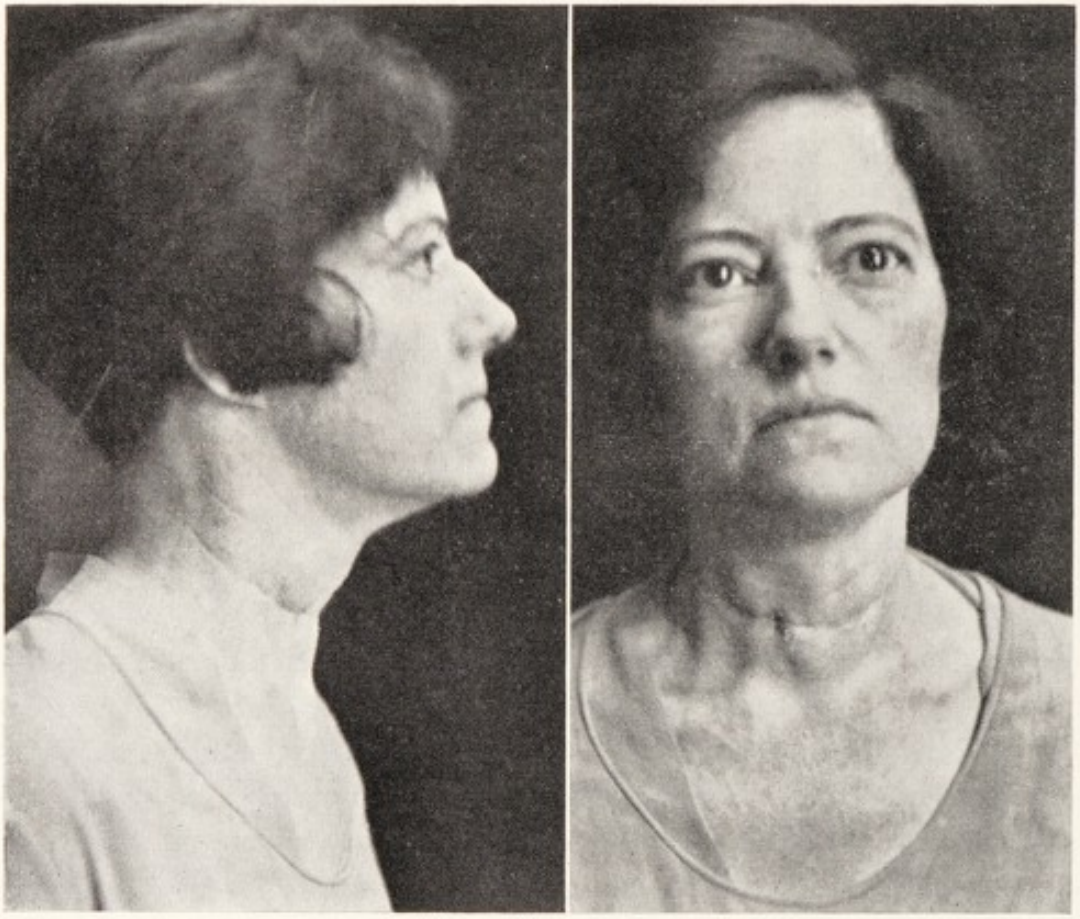

Fig. 163.—Recurrent hyperthyroidism. In this case, that of a woman forty-two years of age, a thyroidectomy had been performed five years before. The basal metabolic rate was plus 52 per cent. The patient had lost 23 pounds in the preceding eight months. She presented all the typical symptoms of hyperthyroidism. At operation a nubbin of thyroid tissue of about the size of an English walnut was found. This was bound down by dense adhesions. Pathologic diagnosis: Diffuse hyperplastic goiter with moderate hyperplasia.

cases of residual hyperthyroidism we have attacked the adrenal gland. In 8 cases unilateral adrenalectomy was performed; in the others, bilateral denervation of both adrenals was done in two seances. The patients on whom these procedures were performed were improved or cured. In several of these cases, active hyperthyroidism was present at the time of operation. As soon as the adrenal was excised

or the nerves of the adrenal divided, the tachycardia diminished, and the pulse pressure, hyperhidrosis, and nervousness abated. It is now four years since the first of these denervations was performed, and the patient is still quiescent.

In our series, among the stated causes of recurrences were the taking of excessive thyroid extract, pregnancy, focal infections, and the administration of iodine and iodized salt.

FAVORABLE END-RESULTS

Of our series of 12,690 cases of hyperthyroidism subjected to and recovering from operation, 97 per cent are in good or fair condition one year or more after operation. There was a gain in weight in 80.7

A B C

Fig. 164.—Patient before and after operation for hyperthyroidism. A, Before operation. B, Two weeks after operation. C, One year after operation.

per cent, and a resumption of normal occupation in less than a year in 86.3 per cent.

Relation of Basal Metabolism to End-results.—It is a well-founded generalization that improvement following operations bears a direct relation to the metabolic rate and that the higher the rate and the more profoundly the patient is affected, the greater the benefit, both objectively, when considered in relation to the relief of symptoms, and subjectively, when considered in relation to the opinion of the patient. On the other hand, we have had some excellent results in cases in which the operation was performed on patients whose basal rate was normal, although they exhibited the usual symptoms of hyperthyroidism. We are beginning to hold the belief that in these exceptional cases the adrenalin sensitization test usually gives a positive result.

Blood Pressure.—In the great majority of cases of hyperthyroidism there is a decrease in the pulse pressure following operation. In cases of adenomata with hyperthyroidism there is on the average some fall in the blood pressure, although occasionally there is an actual rise.

Sensitiveness to Temperature.—In all of the cases that are cured, a normal heat tolerance is established.

Hair.—In cases of hyperthyroidism the hair usually grows more abundantly following thyroidectomy.

Headaches.—Among the many patients with hyperthyroidism who complain of headaches prior to operation, about 50 per cent are relieved by thyroidectomy.

Mental and Emotional States.—In cases of severe hyperthyroidism exaggerated emotionalism and a depression mentality are present. The intense emotionalism overwhelms the intellect and the memory. Ideas become confused and mental effort quickly fatigues the patient. After thyroidectomy, the emotionalism is diminished, the mental confusion gives way to normal and orderly mental processes, and mentality gains its usual supremacy over the emotions. In consequence of this restoration, the individual exhibits normal behavior, the student's work is again carried normally; the housewife regains her lost position in family cooperation and control; the business man again rationalizes his work. Nothing in the domain of medicine is more gratifying than the mental, emotional and social restoration of these patients.

Carbohydrate Metabolism.—The carbohydrate metabolism is profoundly disturbed in hyperthyroidism but thyroidectomy restores this to the normal as completely as it does the mental and emotional states. Among these results, as shown by Dr. H. J. John (see Chapter XVII) is the cure of cases of diabetes by a thyroidectomy.

Gastro-intestinal.—In the midst of the fury of hyperthyroidism, there are numerous disturbances in the gastro-intestinal tract, such as gas, increased motility, diarrhea, peptic ulcer, etc. Routinely the hyperperistalsis of the stomach and intestine returns to normal after thyroidectomy, and of special importance is the fact that the peptic ulcer will often heal and the disturbance in the digestive tract disappear. Although we have seen 20 cases in which peptic ulcer associated with hyperthyroidism disappeared after thyroidectomy, it does not follow that thyroidectomy in the absence of hyperthyroidism will have any effect on peptic ulcer. In our cases it was

interesting, however, to note that when peptic ulcer and hyperthyroidism were associated and no operation was performed on the thyroid gland but bilateral denervation of the adrenal glands was done, the peptic ulcer disappeared with the hyperthyroidism.

The Heart.—Dr. Anderson (see Chapter XII) has shown that among the outstanding benefits of thyroidectomy is the restoration of the heart to its normal state. Cardiac hypertrophy, dilatation, arhythmia, tachycardia, decompensation with swollen extremities, ascites, pleural effusion—all of these symptoms diminish or disappear.

Hyperthyroidism and Pregnancy.—In our early experience, in obstetrical consultations we advised termination of the pregnancy, but later we allowed the pregnancy to go on through labor before operating on the thyroid. This procedure, however, was soon abandoned in favor of immediate thyroidectomy. Pregnancy offers no great interference with safe surgery, provided two features are avoided, namely, mental shock and direct injury of the gravid uterus.

In our series the most commonly performed operation in the presence of pregnancy with associated hyperthyroidism has been thyroidectomy. Among these cases we have seen no miscarriage regardless of the stage of pregnancy, and in some cases the children born of these thyroidectomized mothers have now matured and their development has been normal. Successful pregnancies followed operation in women in the child-bearing period in 11.03 per cent of our cases.

Malignancy is present in from 1 to 2 per cent of all goiters that are removed, and Dr. Allen Graham who has made extensive studies on the pathology of the thyroid, places the incidence of carcinoma in adenomata at from 2 to 4 per cent. Ninety-five per cent of all cancers of the thyroid occur in discrete, well-defined adenomata.

On the basis of potential malignancy, therefore, and because of the ease and safety of operation, the removal of this type of adenoma is indicated.

There is an added reason, however, for the removal of these adenomata; namely, that a certain percentage of them affect the heart, causing the so-called "goiter heart," with the development of a low grade of hyperthyroidism. The clinical results of the excision of such adenomata are excellent.

Hyperthyroidism in Children.—We have seen children in whom thyroidectomy has been performed, grow up, marry and beget normal children.

Ocular Symptoms.—According to Dr. Ruedemann (see Chapter

XVI), exophthalmos has disappeared in 75 per cent of 400 cases in which the symptom was present before operation but a group remains in which exophthalmos persists. There is also a small group in which, paradoxically, the exophthalmos increases after operation, even in the absence of every other symptom of the disease.

The weakness and paralysis of the ocular muscles which are often present in cases of hyperthyroidism, disappear slowly after operation, but so long as this symptom is present, nervousness and headache may persist. The widening of the palpebral fissure, which is more common than exophthalmos, disappears more rapidly than exophthalmos and rarely persists.

CERTAIN CONDITIONS ASSOCIATED WITH HYPERTHYROIDISM

Tuberculosis.—We have had 85 cases of pulmonary tuberculosis associated with hyperthyroidism with no immediate mortality, and in many of the cases the tuberculosis disappeared completely (see Chapter XIII). In these cases the patient burdened with two diseases, when relieved of one, was able to overcome the other.

Arthritis.—According to Dr. Duncan, in 65 cases associated with hyperthyroidism, especially those in which the spine and the shoulders were involved, the arthritis disappeared after thyroidectomy (see Chapter XVIII).

Diabetes.—In a study of 620 cases in which hyperglycemia either with or without glycosuria was present, Dr. John found that in 420 the condition cleared up completely after thyroidectomy. In the remaining 220 cases a frankly diabetic condition was present. Of these, thyroidectomy was followed by improvement in 55 per cent, in 15 per cent the condition remained stationary, and in 30 per cent it became more severe. Of the whole group, only 35.7 per cent are still taking insulin. (See Chapter XVII.)

Extreme Nervousness.—In advanced cases, especially those of long standing in which extreme nervousness is manifested, the nerve balance may not be completely restored after operation. In such cases the patient has a diminished reserve upon which to draw when compelled to meet trying situations.

SUMMARY

When properly performed, thyroidectomy improves or cures every patient with hyperthyroidism. It is our opinion that a patient who shows a normal metabolism and no symptoms of hyperthyroidism

two years after a thyroidectomy for hyperthyroidism should be considered favorably for life insurance.

Since the thyroid gland is the sole governor of the basic rate of oxidation, and when overactive the sole cause of an increased metabolic rate, thyroidectomy, theoretically and as a fact established by experience, controls the symptoms.

We now know that the thyroid gland does not in itself originate hyperthyroidism—hyperactivity is imposed on the thyroid—but the fact remains that the thyroid gland is the key to the cause and the control of the disease.

There is a physiologic dilemma that surgery has solved. If the surgeon leaves a normal amount of thyroid tissue, and the brain-adrenal-sympathetic system is still surcharged with energy, the remaining part of the thyroid may be stepped up rapidly and the disease may be reproduced, for the thyroid has a great facility for the production of hyperplasia. The surgeon, through trial and error, has found it necessary to overcure his patient, thus reducing the brain-adrenal-sympathetic system to a state of underactivity, by taking out such an added amount of thyroid tissue that for a time the patient will be temporarily in a state of hypothyroidism while the remaining hyperplastic thyroid reverts to the normal or colloidal state. It is during this cycle of hypo-activity—a period usually lasting about six months—that the patient finds herself transformed from a hyperactive state to a state of serenity and tranquillity, in which a gain in weight is made; in which mental poise and quiet reign; in which social adjustments are easy; in which repose replaces excitement.

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