spects of

THYROID DISEASE

CRILE

L. E. Coffin M.D.
March 10. 1949

Practical Aspects of

THYROID DISEASE

By

GEORGE CRILE, Jr., M.D., F.A.C.S.

Department of Surgery, Cleveland Clinic

ILLUSTRATED

Philadelphia & London · 1949

W. B. SAUNDERS COMPANY

MADE IN U S A.

PRESS OF
W B SAUNDERS COMPANY
PHILADELPHIA

Dedicated to

JANE HALLE CRILE

PREFACE

This volume is designed to present the picture of diseases of the thyroid gland in such a way that medically trained readers may emerge with a better understanding of the aims of the surgeon, and surgically trained readers may better understand what the internist and radiologist are able to accomplish.

The surgical conquest of hyperthyroidism, initiated at the turn of the century and established in safety by the preoperative use of iodine, had become so well accepted that, until the introduction of thiouracil, few chose to consider hyperthyroidism as other than a surgical problem. Today, as a result of the discovery of powerful and effective antithyroid drugs, the controversial issue of whether or not hyperthyroidism is better treated by conservative (medical) management has again arisen. In the not-too-distant future it is quite possible that the radiologist, using radioactive iodine, will be called upon to play an ever-increasing part in the treatment of diseases of the thyroid gland.

The greater number of thyroid disorders that are now being treated by the internist increases his responsibility with regard to the problems formerly decided by the surgeon. Therefore, the internist today must learn to evaluate the significance of adenomas in respect to potential malignancy. He must learn to recognize symptoms of pressure and to distinguish them from the choking sensations that occur under nervous tension. And finally, he must have a clear idea of what constitutes a good thyroidectomy. No internist has fulfilled his obligations if he refers a patient with a discrete adenoma suspected of being cancer to a surgeon who will not perform an operation which cleanly removes the entire adenoma. Nor has he fulfilled his duties if he is unaware that there are types of thyroiditis that are better treated by roentgen therapy than by thyroidectomy and refers his patient to a surgeon who does not recognize this fact.

The surgeon who has built up a practice in surgery of the thyroid gland will find himself confronted with new problems in the management of hyperthyroidism. If he wishes to avoid unnecessary deaths he must now prepare his patients with the newer antithyroid drugs. Therefore, he must understand the basic physiology of the thyroid and its response to the derivatives of thiourea. Certain patients he will unquestionably elect to treat with these drugs alone rather than to advise operation. But, unless he be content to serve merely as a technician to remove the thyroid when the internist tells him that the patient is adequately prepared, he must be thoroughly cognizant of the pitfalls and problems of the medical treatment of hyperthyroidism.

Most diseases of the thyroid gland no longer fall into the domain of the surgeon alone but belong in the broad field of general medicine. Both physicians and surgeons must be familiar with the recent developments in the diagnosis and treatment of thyroid disease and must work together cooperatively, not competitively, to give the patient the benefit of the type of treatment best adapted to his case.

In this volume no attempt has been made to summarize the extensive and often controversial literature dealing with the physiology and pathology of the thyroid gland. Only the salient features of our increasing knowledge of the function of the thyroid and as much as practicable of the literature dealing with clinical aspects of thyroid disease have been included.

In the main, the conclusions in this book have been drawn from my own experience in the surgical treatment of approximately 1000 patients with diseases of the thyroid gland and from observations made on several hundred patients with hyperthyroidism treated with the antithyroid drugs in the Section on Endocrinology under the direction of Dr. E. Perry McCullagh.

Although impressive statistics could be accumulated by a survey of the more than 25,000 records of thyroidectomies performed by Dr. George Crile, Sr., and Dr. R. S. Dinsmore, I have chosen to study my own patients, all of whom I have examined, operated upon, and observed after operation. In certain of the more rare conditions in which the smaller group is too small to be of statistical value, the figures quoted refer to the larger series.

I express my appreciation to the other members of the Cleveland Clinic Staff whose material is, in part, included in these studies, and pay respect to the memory of Dr. George Crile, Sr., whose keen imagination, vast experience, and dominant interest in diseases of the thyroid gland made him one of the outstanding teachers, surgeons, and physiologists of his time.

GEORGE CRILE, JR.

Cleveland, Ohio
January, 1949

CONTENTS

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 9

Chapter 10

Chapter 11

Chapter 12

Chapter 13

Chapter 14

Chapter 17

Chapter 18

Chapter 19

Chapter 20

Chapter 21

Chapter 22

Chapter 23

Chapter 24

Chapter 25

Chapter 1

PHYSIOLOGY OF THE THYROID

Normal Function

The thyroid gland secretes and stores an iodine-containing hormone which influences the metabolic processes of the body. In the absence of this hormone, profound metabolic changes affecting practically every system in the body take place. Although life is not usually threatened, severe symptoms of thyroid deficiency soon develop.

Hormones secreted by the thyroid gland are complex amino acids and proteins in which iodine has been incorporated. Thyroxin* is the most important of these hormones. Its administration to a patient suffering from thyroid deficiency will specifically correct all symptoms and signs resulting from this deficiency. In addition, diiodotyrosine and possibly other iodine-containing compounds appear to be present in the thyroid secretion but are probably of lesser importance in regulating the metabolic processes of the body.

The thyroid may not be the only organ capable of making thyroxin. As early as ninety-six hours after the injection of radioactive iodine into thyroidectomized rats, 30 per cent of the radioactive iodine contained in the liver and in the small intestine was organically bound, 20 per cent as diiodotyrosine, and as much as 8 per cent as thyroxin. It must be concluded, therefore, that tissues other than the thyroid can produce thyroid hormone.

The mode of action of these hormones is not known, but it has been shown that oxidation in the tissues is retarded in the presence of a thyroid deficiency and is increased in the presence of excessive amounts of the thyroid hormone.

---

* Isolated by Kendall.

Hypertrophy and Hyperplasia of the Thyroid

Relationship of the Thyroid Gland to Iodine. Since iodine is an essential ingredient of the thyroid hormone, it is clear that the thyroid requires a certain constant minimal supply of iodine if it is to maintain its output of active hormones. If this supply is deficient, as in regions of endemic goiter, striking changes in the thyroid take place.

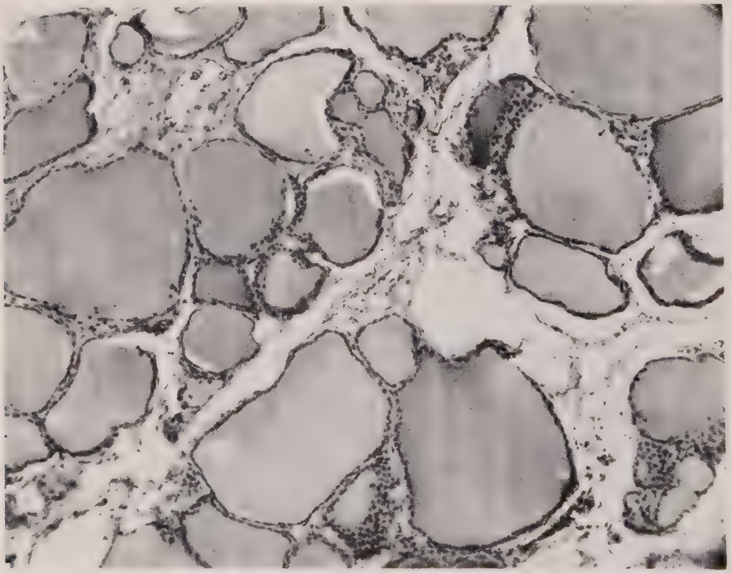


Fig. 1. Normal thyroid.

The first of these changes is a hypertrophy and hyperplasia of the entire gland (Figs. 1, 2, and 3). The stores of colloid are quickly exhausted and the low cuboidal cells lining the follicles become columnar and increase in size and number. The entire gland becomes hyperplastic and enlarges, the colloid vanishes, and the iodine content of the gland is diminished. This is known as the hyperplasia of iodine deficiency and represents a normal compensatory mechanism by which the thyroid attempts to maintain its output of active hormone in the presence of a deficiency of raw materials (Marine).

Physiologic Hypertrophy and Hyperplasia. Similar hypertrophy and hyperplasia of the thyroid gland occur when four-

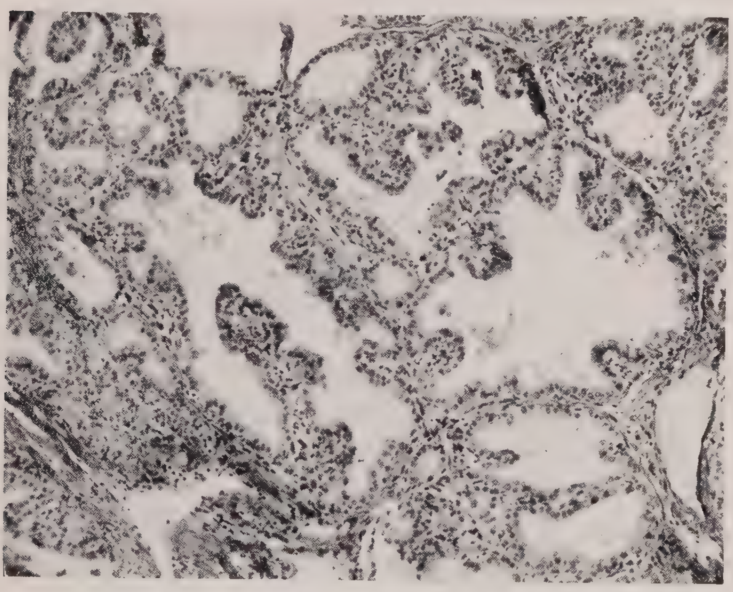


Fig. 2. Hyperplasia of thyroid.

fifths or more of the normal dog's thyroid tissue is removed. The remnants of the gland enlarge and become hyperplastic in an attempt to maintain the output of active hormone. Hyperplasia of these remnants can be prevented by administration of small doses of iodine (Marine).

There is, in addition to the conditions mentioned, a definite tendency for the thyroid gland to undergo hypertrophy and hyperplasia in response to increased demands for its hormone, such as may occur with pregnancy, at puberty, and during the winter. This tendency is most definite in regions of endemic goiter when a relative iodine deficiency may occur at times of increased metabolic activity. The administration of small doses of iodine will prevent this type of hyperplasia.

Mechanism of Hyperplasia. The stimulus producing hypertrophy and hyperplasia of the thyroid gland is always the same, namely, a demand for more thyroid hormone than the gland can produce. This may be the result of the inability of a normal gland to produce sufficient hormone, as in the presence of an iodine deficiency; it may be the result of the destruction or removal of so much of the thyroid gland that the remainder

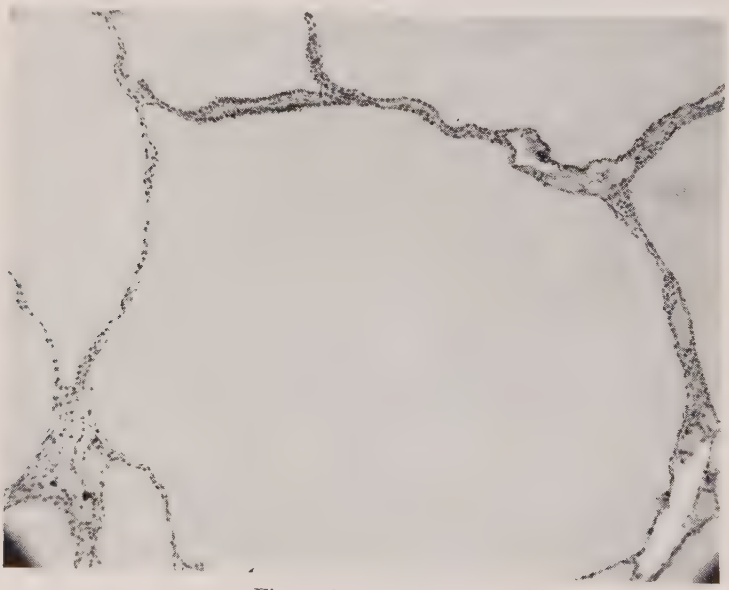


Fig. 3. Colloid goiter.

cannot maintain an adequate output of hormone; or the deficiency in hormone may be a relative one caused by increased demands rather than by a diminished supply. In any case, a deficiency of active thyroid hormone results in a compensatory hypertrophy and hyperplasia of the thyroid, and this compensatory hyperplasia can be prevented by the administration of adequate amounts of iodine.

Compensatory hyperplasia of the thyroid does not appear to be initiated in the thyroid gland itself but seems to be imposed on the thyroid by the pituitary gland. Thus, compensatory hyperplasia of the thyroid cannot be accomplished when the pituitary gland has been removed, and, conversely, the administration of the thyrotropic hormone of the pituitary causes hyperplasia of the thyroid (P. E. Smith and I. P. Smith). The relationship of the pituitary hormone to the hypertrophy and hyperplasia of the thyroid in Graves' disease has been suspected but not proved.

Goitrogens

The foregoing discussion summarizes the status of our knowledge of the physiology of the thyroid gland in 1942, when Astwood in this country and Purves and Hercus in New Zealand independently and almost simultaneously reported the goitrogenic effect of the thiourea derivatives. Prior to this Mackenzie, Mackenzie, and McCollum had found that rape seed diets induced goiters in rats, and Richter and Clisby had found phenylthiourea to be goitrogenic in rats. It had long been known that goiter could be produced in rabbits by the administration of a cabbage diet, but small amounts of iodine abolished this effect as they did the goitrogenic effect of the thiocyanates. Therefore, prior to 1942 it was not known whether the thiocyanates and cabbage directly affected the thyroid gland or whether they acted indirectly by interfering with the absorption of iodine.

Many years ago McCarrison concluded from studies made in India that some factor other than iodine, possibly bacteria, played a part in the development of endemic goiter. More recently Greenwald has reviewed the entire question of endemic goiter in its relation to iodine and concluded that although large amounts of iodine may prevent goiter, iodine deficiency *per se* is not its primary cause. He argued that if iodine deficiency were the primary cause of goiter,

1. Goitrous individuals should have low metabolic rates. (They do not.)
2. Goiters should contain less iodine than do normal glands, not only per gram of tissue but per entire gland. (They do not.)

3. It should be possible
   a. to produce goiter in animals by placing them on iodine-free diets. (It is possible only on certain diets.)
   b. to prevent goiter by the addition to such diets of such small amounts of iodine as are found in ordinary foods. (It is not possible to prevent the development of goiter on certain diets unless much more iodine is added than is present in an ordinary nongoitrogenic diet.

The evidence that there is a deficiency in the iodine intake in goitrous regions is not clear, as there is much variation in the iodine content of vegetables from the same soil at the same time. Greenwald concludes that the beneficial effects of iodine, such as they are, appear to be the result not of making good a deficiency but of a pharmacodynamic action of iodides.

In all probability there is much truth in these assertions that endemic goiter is not due entirely to a deficiency of iodine. We know that certain of the sulfonamides, methyl cyanate, thiocyanates, and the thiourea derivatives, as well as cabbage and rape seed diets, will produce goiter. In most cases iodine given in large amounts will diminish or abolish the goitrogenic effect of these agents. It is therefore reasonable to suppose that there are goitrogenic agents whose effect can be neutralized when sufficient iodine is given but which cause the development of goiter when the intake of iodine is low.

It has not as yet been established with certainty whether the mode of action of all of the known goitrogens is the same. For example, the goitrogenic effect of cabbage can be abolished by the addition of relatively minute doses of iodine. Similarly, the thiocyanate goiter in rats has been shown by Rawson *et al.* to take up 87 per cent of a tracer dose of radioactive iodine, whereas only 10 per cent is taken up by the thiouracil goiter. Some believe that these differences indicate that the mode of action of the drugs is different. It is possible, however, as suggested by Astwood, that the apparent difference may be one only of degree, the goitrogens that require an iodine deficiency being qualitatively similar but quantitatively low in inherent potency. Thus, added iodine would abolish the goitrogenic effect of minimal doses of thiouracil just as it does the goitrogenic effect of cabbage.

Astwood has given an admirable summary of recent developments in our knowledge of thyroid physiology. He states that the mode of action of the goitrogens or antithyroid drugs is inhibition of the formation of thyroid hormone. This, Astwood proved by observing that: (1) animals became hypothyroid

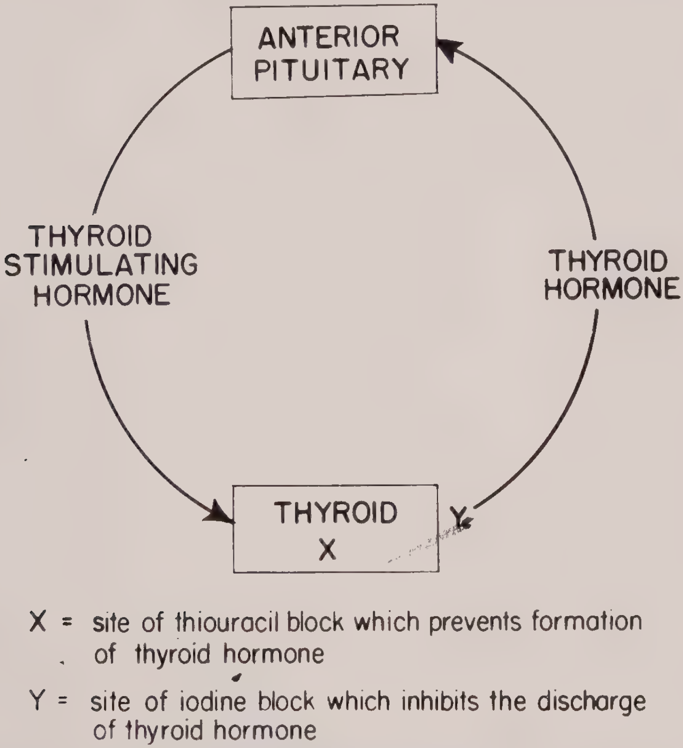


Fig. 4. The relationships of the pituitary and thyroid (modified from Means). A deficiency of circulating thyroid hormone stimulates the pituitary to increase its output of thyroid-stimulating hoermone.

during treatment; (2) thyroid feeding abolished the goitrogenic effect; (3) hypophysectomy abolished the effect of the goitrogen; and (4) the drugs did not modify the calorigenic effect of thyroid hormone.

Subsequent studies indicate that as soon as treatment with adequate doses of one of the thiourea derivatives is started no new thyroid hormone is produced. The hypertrophy and hyperplasia of the thyroid are compensatory in nature and are imposed on the thyroid not directly by the antithyroid drug but indirectly by stimulation of the pituitary. Thus it is a deficiency of circulating thyroid hormone which stimulates the pituitary, which in turn imposes on the thyroid its compensatory hyperplasia (Fig. 4).

When iodine is given to an animal under treatment with thiourea there is only a slight inhibition of the compensatory enlargement of the thyroid, but the concentration of iodine in the thyroid may rise sharply in a matter of a few minutes. For example, a single dose of potassium iodide after ten days of thiouracil feeding caused a return of the iodine content of the thyroid to one-half of normal. But the iodine which is accumulated in a thiouracil-treated gland must enter little, if any, into the synthesis of the thyroid hormone and appears to remain unattached to protein, as it is 96.7 per cent water soluble. This accumulation of iodine by fully inhibited glands without appreciable influence on the synthesis of the thyroid hormone implies that there is a mechanism distinct from the iodination of protein that permits the accumulation and storage of iodine. It is this function that appears to be paralyzed by the administration of potassium cyanate (Astwood).

Astwood, in speculating on the chemistry involved in the formation of thyroxin, assumes that iodide and tyrosine enter into its formation. Iodide must be oxidized before it can unite with tyrosine to form diiodotyrosine, which must then be subjected to a second oxidation, in order that two diiodotyrosine molecules may couple through an ether linkage to form thyroxin.

Free tyrosine is not involved in these reactions but rather tyrosine residues of a protein. When these are converted to thyroxin residues, thyroglobulin results. Thiouracil does not interfere with the mechanism which permits the thyroid gland to accumulate iodine but blocks the formation of active thyroid hormone (Astwood).

In vitro experiments with thyroid slices indicate that neither the sulfonamides nor the thiourea derivatives inhibit the uptake and concentration of iodine by thyroid tissue, although these compounds inhibit the incorporation of the iodine into diiodotyrosine or thyroxin. *In vitro*, radio-iodine exchanges rapidly with the normal iodine in diiodotyrosine. This may explain some of the clinical observations made with radio-iodine which are inconsistent with other laboratory findings. Further inconsistencies may be explained on the basis of the formation of thyroxin in tissues other than the thyroid (Morton).

Thiouracil acts by preventing the completion of physiologically active hormones and does not affect preformed hormone in the thyroid gland or in the blood and tissues. Rawson *et al.* believe that when thiouracil is given to a patient who has not had iodine and has little stored hormone, the curve of response is the "decay curve" of thyroxin and represents the consumption of the hormone which was in the thyroid gland and in circulation when administration of the drug was begun. The normal thyroid gland contains enough hormone to maintain a normal rate of secretion for thirty-three to fifty days, provided no more hormone is being made. In hyperplastic glands the amount of stored hormone is less and in large colloid goiters it may be considerably more. When the synthesis of thyroid hormone is blocked the stored hormone in the thyroid gland continues to be delivered until all of it has been utilized. After the gland has been emptied of its active thyroglobulin the basal metabolic rate of oxygen consumption by the peripheral cells falls. Either the low metabolism *per se* or the loss of the inhibiting effect of the thyroid hormone upon the pituitary results in an increased elaboration of the thyroid-stimulating hormone of the pituitary, which in turn causes thyroid hyperplasia.

Astwood states that several factors may explain the infrequency of gross thyroid enlargement in patients with Graves' disease who have been treated with thiouracil. First, the dose used clinically is much lower on a basis of body weight than that required to induce myxedema or cretinism in animals and is considerably lower than that required to induce a maximal enlargement of the thyroid gland. It is possible that the clinical dosage, especially the maintenance dose, corresponds more closely to the low dosage required to induce a partial failure of thyroid hormone synthesis than to the dosage levels needed for total inhibition and the production of the more striking compensatory enlargements of the thyroid gland.

The second possible explanation is that the thyroid gland in Graves' disease may be already under the influence of nearly maximal pituitary stimulation and hence cannot respond further to the added stimulus of inhibition of the production of thyroid hormone.

Bibliography

1. Astwood, E. B.: Chemotherapy of hyperthyroidism. Harvey Lect. (1944–1945) *40:* 195–235, 1945.
2. Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: Action of certain sulfonamides and of thiourea upon function of thyroid gland of rat. Endocrinology *32:* 210–225 (Feb.) 1943.
3. Astwood, E. B.: Thiouracil treatment in hyperthyroidism. J. Clin. Endocrinol. *4:* 229–248 (June) 1944.
4. Idem.: Treatment of hyperthyroidism with thiourea and thiouracil. J.A.M.A. *122:* 78–81 (May 8) 1943.
5. Greenwald, I.: Is endemic goiter due to lack of iodine? J. Clin. Endocrinol. *6:* 708–741 (Nov.) 1946.
6. Hercus, G. E., and Purves, H. D.: Use of thiourea and its derivatives in treatment of thyrotoxicosis. New Zealand M. J. *43:* 213–217 (Oct.) 1944.
7. Livingston, E. M., and Pack, G. T.: End-Results in the Treatment of Gastric Cancer: An Analytical Study and Statistical Survey of Six Years of Surgical Treatment. With a Foreword by Bowman C. Crowell. New York: Paul B. Hoeber, 1939.
8. McCarrison, R.: Etiology of Endemic Goitre. London: J. Bale & Sons & Danielsson Ltd., 1913.
9. Mackenzie, J. B., Mackenzie, C. G., and McCollum, E. V.: Effect of sulfanilylguanidine on thyroid of rat. Science *94:* 518–519 (Nov. 28) 1941.
10. Marine, D.: Etiology and prevention of simple goiter. Medicine *3:* 453–479 (Nov.) 1924.
11. Marine, D.: Influence of thyroid gland on increased heat production occurring during pregnancy and lactation. Tr. A. Am. Physicians *39:* 180, 1924.

12. Morton, M. E., Chaikoff, I. L., Reinhardt, W. O., and Anderson, E.: Radioactive iodine as indicator of metabolism of iodine; formation of thyroxine and diiodotyrosine by completely thyroidectomized animal. J. Biol. Chem. *147:* 757–769 (March) 1943.
13. Rawson, R. W., *et al.:* Action of thiouracil upon thyroid gland in Graves' disease. J. Clin. Endocrinol. *4:* 1–11 (Jan.) 1944.
14. Richter, C. P., and Clisby, K. H.: Toxic effects of bitter-tasting phenylthiocarbamide. Arch. Path. *33:* 46–57 (Jan.) 1942.
15. Salter, W. T., Bassett, A.M., and Sappington, T. S.: Protein-bound iodine in blood; its relation to thyroid function in 100 clinical cases. Am. J. M. Sc. *202:* 527–542 (Oct.) 1941.
16. Smith, P. E., and Smith, I. P.: Repair and activation of thyroid in hypophysectomized tadpole by parenteral administration of fresh anterior lobe of bovine hypophysis. J. M. Research *43:* 267–283 (June-July) 1922.

Chapter 2

PATHOLOGY OF ENDEMIC GOITER

Classification

The classification of the common pathologic conditions of the thyroid gland adopted by the American Society for the Study of Goiter is as follows:

Diffuse goiter	with hyperthyroidism
	without hyperthyroidism
Nodular goiter	with hyperthyroidism
	without hyperthyroidism

In this classification diffuse goiter with hyperthyroidism and nodular goiter with hyperthyroidism correspond respectively to Graves' disease and toxic adenoma. Diffuse goiter without hyperthyroidism and nodular goiter without hyperthyroidism represent different manifestations of endemic goiter.

This classification is simple but is not entirely satisfactory. Too much emphasis is placed on the presence or absence of nodules in the thyroid, a question that often cannot be decided by clinical examination of the patient (see Chapter 5). Moreover, the presence or absence of nodules in the thyroid does not determine whether the disease from which the patient suffers is Graves' disease or whether the hyperthyroidism is secondary to adenomas in the thyroid.

Lahey has attempted to solve this difficulty by dividing patients with hyperthyroidism into two categories. The first he calls "primary hyperthyroidism," and in this category he places all patients who have Graves' disease, regardless of whether or not nodules are present in the thyroid. The second group he calls "secondary hyperthyroidism" because the hyperthyroidism is secondary to adenomatous change in an old endemic goiter.

This classification is valuable because it distinguishes clinically between the patients who are thought to have Graves' disease and those whose hyperthyroidism is the result of autonomous activity of an adenoma or adenomas occurring in an endemic goiter. But the terminology is unsatisfactory because secondary hyperthyroidism is likely to be confused with recurrent hyperthyroidism. In addition to this, the terminology has not been accepted widely and hence requires explanation.

Another term for Graves' disease is exophthalmic goiter. A patient may have typical Graves' disease with a diffuse hyperplasia of the thyroid and all the classic symptoms except exophthalmos. Are we justified in calling this disease exophthalmic goiter when there is no exophthalmos? Although it is not desirable to base terminology on the name of the individual who first described the disease, it seems that in the case of Graves' disease this is the lesser of two evils. If a patient has hyperthyroidism with a diffuse goiter which contains one small adenoma, even if she has exophthalmos and a diffuse enlargement and hyperplasia of the entire parenchyma of the thyroid, the presence of the adenoma makes it difficult to call this a diffuse goiter. Yet we would like to classify this disease where it belongs under the clinical heading of diffuse goiter or Graves' disease.

Because of these difficulties in terminology I am forced to fall back upon the term Graves' disease to describe the type of hyperthyroidism which bears no relationship to endemic goiter and in which the entire parenchyma of the thyroid is involved in the overproduction of thyroid hormone.

The nomenclature that will be used to describe the common disorders of the thyroid is:

Diffuse goiter without hyperthyroidism
Nodular goiter without hyperthyroidism
Graves' disease
Nodular goiter with hyperthyroidism

In addition, the term "discrete adenoma" will be used to describe a clinical, not a pathologic, entity, in which there is an adenoma which appears to be more than a simple involutionary nodule and which, from the clinical standpoint, appears to have qualities of neoplasia which establish it as a possible tumor of the thyroid rather than as an involutionary nodule.

The term "multinodular goiter with or without hyperthyroidism" will be applied to goiters which have two or more nodules and which in general are the end results of involutionary changes initiated by the stimulus which produces endemic goiter.

The Growth and Development of Endemic Goiters

The periods of the greatest physiologic demands on the thyroid are during adolescence and during pregnancy. At these

Fig. 5. Children of one family all having diffuse enlargements of the thyroid.

times endemic goiters frequently appear or enlarge. In their earliest stages these goiters may be hyperplastic, but as hypertrophy proceeds, as adequate iodine intake is restored, or as physiologic demands are lessened, the gland is able once more to satisfy the body's requirements for thyroid hormone, and involution of the hyperplastic gland takes place. The follicles again become filled with pink-staining colloid, and the iodine content of the thyroid rises. But, although compensation is restored, the gland is no longer normal in size or in histologic structure. Instead it is diffusely enlarged, the follicles have increased in size, and their cells tend to be flattened. This is the diffuse goiter without hyperthyroidism so commonly seen in adolescent children in regions of endemic goiter (Fig. 5).

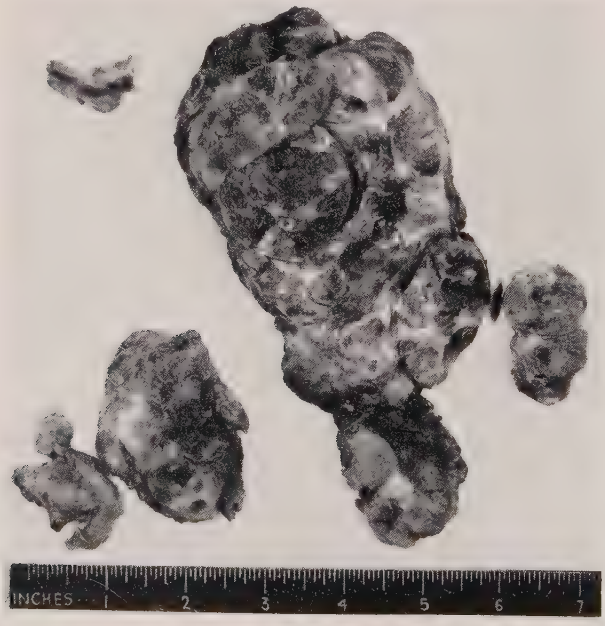


Fig. 6. Multinodular goiter, the result of longstanding endemic goiter. Note the multiple adenomas in different stages of differentiation.

Although the thyroid gland is capable of undergoing repeated cycles of hyperplasia and involution in response to repeated episodes of iodine deficiency, each cycle produces further changes in the microscopic appearance of the thyroid, and with each cycle the gland tends to undergo a further change.

Large diffuse goiters rarely are seen because, with repeated cycles of hyperplasia and involution, the gland begins to react irregularly and develops involutionary nodules. Reinhoff's studies (1929) have shown that this is the result of degeneration of certain areas, with regeneration taking place simultaneously in neighboring parts of the gland. Inadequacy of blood supply may play a part in the formation of these degenerative islands of tissue, but no matter what the etiology is, as time passes, large diffuse goiters become nodular, and circumscribed adenomas may develop (Fig. 6).

Wegelin's necropsy studies (1926), conducted in a region of endemic goiter (Switzerland), show this transition from diffuse to nodular goiter as age advances. Nearly all the thyroids examined in this series were goitrous. In the younger age groups, 100 per cent of the goitrous glands were of the diffuse type. As age advanced, the incidence of nodules rose steadily until in the oldest age groups 100 per cent of the glands were nodular (Fig. 7).

It is thus clear that the so-called multinodular goiter is the result of a physiologic compensatory process initiated by a goitrogen or by iodine deficiency. The same type of involutionary process often occurs in longstanding Graves' disease and results in the transformation of the original diffuse goiter to the nodular type. The neoplastic tendencies associated with advancing age may play a part in the development of nodules or adenomas, but, unlike adenomas elsewhere, adenomas of the thyroid are more physiologic than neoplastic, and their tendency to become carcinomatous is accordingly much less.

The Discrete Adenoma

There is another type of adenoma that may appear in the thyroid which has more highly developed neoplastic qualities than the involutionary nodules of a multinodular goiter. This type of tumor has been described as a fetal adenoma, and it has been implied that it originates as a fetal rest. The name "fetal adenoma" is a histologic term implying an extremely hyperplastic type of cellular arrangement similar to that seen in the thyroid of a fetus. This term is unsatisfactory, because from the clinical standpoint a solitary or discrete adenoma may show well-differentiated, colloid-filled follicles or any intermediate stage of differentiation down to the true fetal type. A more satisfactory and descriptive term for this type of tumor is "discrete adenoma" (Lahey).

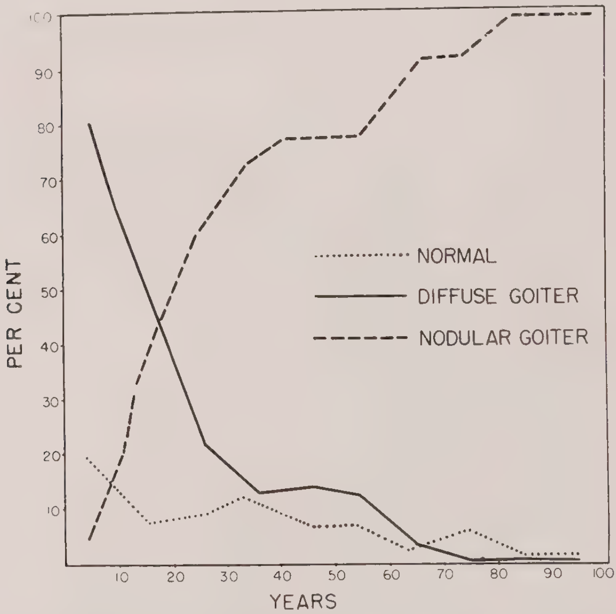


Fig. 7. Chart shows the incidence of various types of goiter found in autopsies in Switzerland. Note increasing incidence of nodular goiter in the older age groups. Adapted from Wegelin by A. Graham. (Courtesy of Ohio State Medical Journal.)

The discrete adenoma is a well-differentiated and sometimes a solitary tumor of a different consistency from the rest of the thyroid. Histologically, it may be hyperplastic or in colloid phase. On gross pathologic examination it may be the only adenoma in an otherwise normal thyroid (rare), it may be a solitary tumor in a colloid goiter, or it may be the only well-differentiated adenoma in a multiple adenomatous goiter. The discrete adenoma is a clinical, not a pathologic, entity. It implies merely that there is a discrete tumor well circumscribed from the remainder of the gland, thus suggesting a neoplastic

Fig. 8. Solitary, discrete adenoma of the thyroid indistinguishable clinically from an early carcinoma. (Nelson Loose-Leaf Surgery, Vol. 2. Courtesy of Thomas Nelson and Sons.)

origin rather than a purely physiologic origin. The chief importance of this type of adenoma is that from the clinical standpoint it cannot be differentiated with certainty from an early carcinoma (Fig. 8).

Bibliography

1. Lahey, F. H.: Apathetic thyroidism. Ann. Surg. *93:* 1026–1030 (May) 1931.
2. Reinhoff, W. F., Jr.: Diseases of Thyroid Gland. In Lewis' Practice of Surgery. Vol. VI, Chap. 1. Hagerstown, Md.: W. F. Prior Co., 1929.
3. Wegelin, C.: In Handbuch der speziellen pathologischen Anatomie und Histologie. (Henke, F., and Lubarsch, O., editors.) Achter Band—Drüsen mit innerer Sekretion. Berlin: Julius Springer, 1926.

Chapter 3

THE PREVENTION AND TREATMENT OF ENDEMIC GOITER

The chief value of iodine is in the prevention rather than in the treatment of endemic goiter. Iodine has been used successfully (1) to prevent the development of goiter in children, (2) to prevent the development of goiter in pregnancy in both mother and child, and (3) in the treatment of adolescent goiter.

In certain parts of the country, such as in the region of the Great Lakes, the hills of West Virginia, parts of Pennsylvania, and on the northwest Pacific coast, endemic goiter is prevalent. Here the iodine content of water and the iodine intake of the average person are low. Although the iodine intake may be sufficient for ordinary requirements, it may in certain individuals, or in the presence of unknown goitrogens, fall below the level of physiologic necessity for the maintenance of a normal thyroid. A compensatory hyperplasia of the thyroid then ensues (Fig. 9). It is estimated that the normal thyroid gland requires approximately 0.22 mg. iodine daily (Else).

Although subsequent involution to the colloid phase occurs, these changes produce permanent alterations of thyroid structure, lay the foundation for endemic goiter, and may result in the development of adenomas with their attendant complications of hyperthyroidism, growth to deforming size, and development of carcinoma.

In recent years, the widespread use of canned and frozen foods shipped from all over the country probably has helped to diminish the incidence of goiter in endemic areas, partly by effecting a change in diets that may have contained goitrogens and partly by affording more iodine.

Iodine Deficiency in Pregnancy

The appearance of or enlargement of a goiter at the time of pregnancy is commonly observed in patients in regions where goiter is prevalent. The basal metabolic rate in pregnancy may be increased to as much as plus 30 per cent. For this reason every pregnant woman who lives in regions where endemic goiter is prevalent should receive prophylactic maintenance doses of iodine.

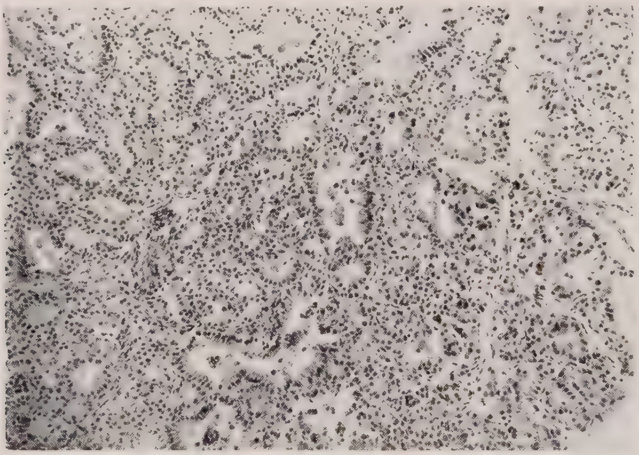


Fig. 9. Marked hyperplasia of thyroid in a sixteen year old girl from Niagara Falls, New York. Thyroidectomy at age of 12 followed by recurrence. No hyperthyroidism at any time. Basal metabolic rate minus 10 per cent. Goiter again recurred after second operation but was controlled by administration of iodine and desiccated thyroid. (Courtesy of Ohio State Medical Journal.)

Iodized salt, in the early years of its use, fell into some disrepute because of the relatively enormous physiologic quantities of iodine it contained, as it was thought that in some instances these large doses of iodine had induced hyperthyroidism in previously inactive adenomas. But at the present time the common brands of iodized salt contain only 1 part per 10,000 of potassium iodide (editorial, J.A.M.A.), representing 75 to 80 parts of iodine for each 1,000,000 parts of salt, and the daily intake of iodine by a person who lives in a region of endemic goiter and uses iodized salt is no greater than that of a person who lives by the sea and uses uniodized salt.

If prophylactic doses of iodine are to be prescribed, administration of a 25 per cent solution of *potassium iodide* in doses of 1 minim once a week is a practical method. If tablet form is preferred, one tablet containing 10 mg. of iodine may be taken once a week. By supplying the physiologic demands of pregnancy, not only is goiter in the mother prevented, but congenital goiter and cretinism in the child may be avoided.

Iodine Deficiency in Puberty and Adolescence ("Adolescent Goiter")

At puberty the thyroid enlarges, becomes more vascular, and, if any iodine deficiency exists, the gland may undergo a rapid hypertrophy and hyperplasia. In the presence of such an iodine deficiency the superior thyroid arteries may pulsate forcibly, and occasionally cases have been observed in which the gland becomes so vascular that a bruit can be detected in spite of the fact that the basal metabolic rate is normal and there is no clinical evidence of hyperthyroidism. The involution of such a gland to the colloid phase results in the formation of the typical adolescent goiter. These changes can be prevented by the administration of iodine in the same form and doses as those prescribed for iodine deficiency during pregnancy.

Adolescent goiter often can be prevented but, once established, can rarely be cured by medical treatment. A gradual diminution in the size of the gland may be noted if the changes have been present for a relatively short time and if the patient is in the early "teens." Adequate doses of iodine should be supplemented by *desiccated thyroid* in doses up to ½ grain daily when the basal metabolic rate is normal or in quantities sufficient to correct any hypometabolism that may be present. Desiccated thyroid supplies the hormone to the body and produces physiologic rest of the thyroid gland. In older children and in adults little or no regression can be expected, and the most that can be anticipated is prevention of further enlargement. There is no reason, however, to consider the surgical removal of a diffuse goiter in an adolescent unless it is extremely large and its removal is desired for cosmetic reasons. Goiters that may be conspicuous in children are not readily noticeable later when subcutaneous fat is deposited in the neck. Even when the gland does not change in size the ultimate cosmetic effect usually is good.

Fig. 10. Large multinodular goiter. Gradual enlargement since childhood.
Fig. 11. Same patient as shown in Fig. 10 shortly after thyroidectomy.

Multinodular Goiter

In areas of endemic goiter, the diffuse enlargement of the thyroid that occurs in adolescence almost invariably becomes nodular if the patient lives long enough. The serious complications of nodular goiter are: (1) hyperthyroidism, (2) intrathoracic growth, (3) growth to excessive size (Figs. 10 and 11), and (4) the development of malignant tumors. Hyperthyroidism, aside from that seen in true Graves' disease, is associated with an adenomatous type of gland. Almost all large goiters are nodular. Practically all intrathoracic goiters are adenomas which have grown downward into the thorax. Malignant tumors of the thyroid are seven times as common in regions of endemic goiter as in nongoitrous areas.

The removal of all nodular goiters would be impractical. In the first place, the incidence of adenomatous goiter is extremely high, and in some regions the majority of the population may be affected. In the second place, the type of adenomatosis which is present in these cases appears, as Reinhoff's studies (1930) have indicated, to be a physiologic process of degeneration and regeneration that involves the entire gland, so that even after a sub-total thyroidectomy has been performed a certain amount of adenomatous tissue remains. And lastly, experience has shown that malignant change is a relatively rare finding in multinodular goiters. Hyperthyroidism, moreover, can be treated safely after it has appeared, and a substernal goiter can likewise be removed with safety after its symptoms bring the patient to the physician. In multinodular goiter, therefore, prophylactic thyroidectomy need not be recommended unless the gland is large enough to be of cosmetic importance or unless it contains discrete adenomas suggesting the possibility of cancer.

The indications for thyroidectomy in a patient with a multinodular goiter are: (1) enlargement of an adenoma; (2) development of hyperthyroidism; (3) pressure symptoms denoting growth, intrathoracic extension, or tracheal compression; and (4) cosmetic reasons. The removal of a large goiter is also indicated in the presence of symptoms such as fatigue, palpitation, and dyspnea, which are perhaps the result of a combination of psychic and mechanical factors as well as of the presence of a large vascular bed which may place strain on the myocardium (Fig. 12).

Discrete Adenoma

A different problem is presented by the finding of a firm, circumscribed, discrete adenoma. Even if there is no evidence of hyperthyroidism, even if the adenoma is of relatively small size, and regardless of whether or not the tumor is enlarging, its removal should be advised.

The discrete adenoma has certain clinical and pathologic qualities of neoplastic growth which render its management a different problem from that of the multinodular goiter. It is

Fig. 12. Large colloid adenoma of the thyroid.

in this type of tumor that malignant change is more commonly seen. At least 5 per cent of such adenomas are found by the pathologist to be malignant despite the fact that the diagnosis is not suspected before operation. For this reason I believe that discrete adenomas should be removed not because of the possibility of the tumor's becoming malignant later but because the tumor may be malignant at the time it is first seen. The following case report illustrates this point.

The patient was a married woman, aged 42. Examination showed a small discrete adenoma of the thyroid. Thyroidectomy was advised but the patient refused operation.

Three years later she returned complaining of enlargement of the thyroid and of pain in the left side of the neck radiating upward behind the ear. Examination showed a large, hard, fixed carcinoma of the thyroid.

Complete removal of the tumor was impossible. Roentgenotherapy was given and temporary improvement followed, but the tumor recurred. The patient died as a result of invasion of the trachea by the tumor.

Fig. 13. Calcified adenoma of the thyroid.

Calcified Adenomas. Occasionally calcium is deposited in adenomas of the thyroid so that the entire tumor becomes as hard as a stone. Calcified adenomas usually are harder than carcinomas or inflammatory lesions of the thyroid and can be diagnosed clinically on the basis of their hardness. A roentgenogram confirms the diagnosis (Fig. 13). The etiology of the calcification is not known. Possibly it is the end result of a hemorrhage into an adenoma. Calcified adenomas do not enlarge and usually do not cause symptoms. I have seen one patient, however, who had a persistent irritative cough which was relieved by removal of a calcified adenoma.

If the calcified adenoma gives no symptoms and is of no cosmetic importance, it can be assumed that it is quiescent and without clinical consequence. Only once have I seen carcinoma in the same gland with a calcified adenoma. There is no reason, however, why this association cannot occur, as one adenoma may be calcified and another in the same gland malignant. Hence the presence of calcification does not rule out carcinoma any more than does the presence of hyperthyroidism. The calcification merely affords an acceptable explanation of the hardness of certain tumors in which carcinomas would otherwise have to be considered. Papillary adenomas or low-grade papillary carcinomas may contain small areas of calcification.

Hemorrhage into an Adenoma

Acute hemorrhage may occur into an adenoma of the thyroid. The symptoms are pain and sudden swelling of the neck. The pain usually persists for several days, then subsides, and the swelling gradually resolves as the blood is absorbed. If the residual tumor is not of sufficient size to be of cosmetic importance and if the pain has subsided in a few days, it is not necessary to remove the adenoma. The swelling associated with hemorrhage into an adenoma is more localized than that seen in most cases of subacute thyroiditis, and the onset usually is more sudden.

Recurrent Adenomas

Since it is impractical to perform a total ablation of the thyroid for adenomatous goiter, and since multinodular goiters may involve almost the whole gland, it is not surprising that adenomatous goiters recur occasionally. The scar tissue of the first operation often prevents the recurrent adenoma from growing forward into the neck and tends to drive it backward behind the trachea. The adenoma expanding within a dense inelastic capsule of scar tissue often feels as hard as a carcinoma, and it may compress the trachea and cause severe symptoms of respiratory obstruction (Fig. 14).

Sometimes the recurrent nerve is found high on the lateral or even on the anterior surface of such tumors and may be injured unless the greatest care is used in the dissection.

Fig. 14. Recurrent nodular goiter without hyperthyroidism. Symptoms of tracheal compression.

It is unwise to remove a small symptomless goiter recurring years after the removal of an adenomatous goiter. In these cases there is little danger of carcinoma and considerable danger of injuring the recurrent nerve or of damaging the parathyroids and causing tetany. Only if the recurrent nodule is enlarging, causing symptoms, or is large enough to be of cosmetic importance, is it desirable to remove such adenomas. Only twice have

3

I found carcinomas in recurrent goiters, and in each case the diagnosis was obvious.

Cretinism and Childhood Hypothyroidism

True cretinism is a rare condition in this country, but textbooks have made everyone familiar with the clinical picture

Fig. 15. Cretin (Courtesy of Dr. E. Perry McCullagh).

of the mentally and physically retarded, pot-bellied, big-tongued cretin (Fig. 15).

Cretinism may be difficult to differentiate from mongolism, although the appearance of the mongol usually is typical, is recognizable at birth, and is sufficient in itself to establish the diagnosis.

Older mongols tend to be active, whereas cretins are more often inactive. Looseness of the joints suggests mongolism, but both mongols and cretins may have delayed union of the epiphyses. The tongue may appear to be large in both cretins and mongols. The skin of the cretin is coarse and myxedematous as compared to the fine skin of the mongol. If the blood cholesterol is high, cretinism is suggested.

Often it is impossible to establish a definite clinical diagnosis, and when this is the case an empiric trial of thyroid feeding should be given. If cretinism is recognized in the first year or two of life and if adequate therapy is given, satisfactory development may occur. But the longer the treatment is delayed the less response is obtained in respect to correction of the mental retardation. Means gives the following table for United States Pharmacopeia thyroid dosage for the treatment of cretinism.

2 to 4 months	$\frac{1}{10}$ grain daily
4 to 8 months	$\frac{1}{5}$ grain daily
8 to 12 months	$\frac{3}{10}$ grain daily
12 to 14 months	$\frac{2}{5}$ to $\frac{3}{4}$ grain daily
2 to 4 years	$\frac{1}{2}$ to $1\frac{1}{2}$ grains daily
4 to 12 years	1 to 3 grains daily

Childhood hypothyroidism (Fig. 16) must be differentiated from pituitary dycrasias, chondrodystrophy, mental retardation, as well as from dwarfism secondary to infectious or nutritional disorders. Often a therapeutic trial of desiccated thyroid is the best way of differentiating these conditions.

The presenting symptom of hypothyroidism in children frequently is mental retardation and failure of the child to do well in school. The basal metabolic rate is not a satisfactory diagnostic criterion in children. Of more clinical significance is shortness of stature, the presence of retarded dentition, and delayed epiphyseal development. Since illnesses may cause epiphyseal retardation, a skeletal age which is retarded less than two years is of little significance (McCullagh).

The level of blood cholesterol usually is high in childhood hypothyroidism. Levels of less than 300 mg. per 100 cc. are not considered significant. A normal cholesterol level does not exclude hypothyroidism, although this finding is rare.

The determination of the blood iodine level is of little or no value in the diagnosis of hypothyroidism. The protein bound blood iodine, however, usually is low, and its measurement may

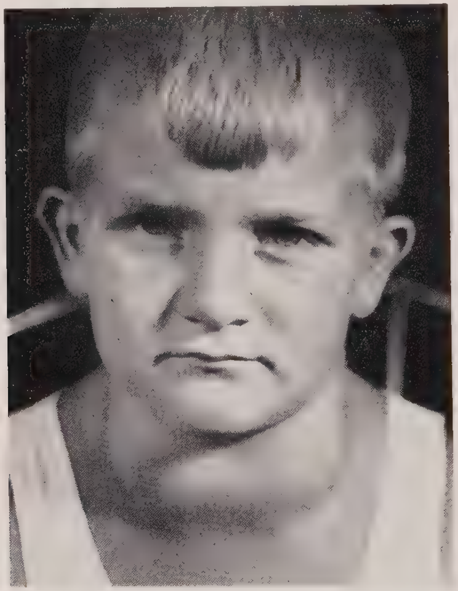
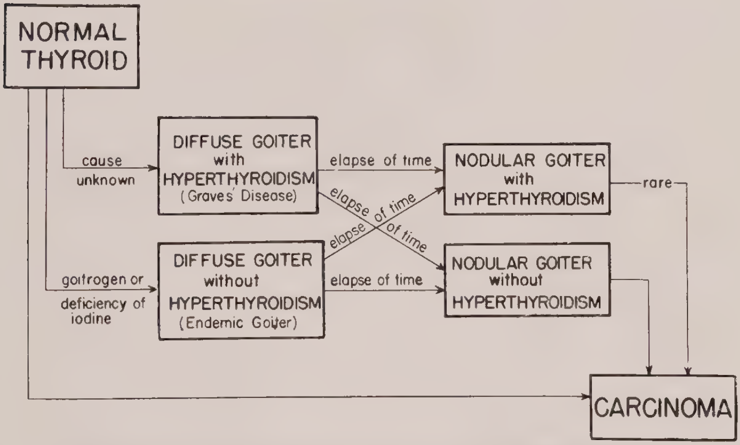


Fig. 16. Congenital goiter and childhood hypothyroidism. Patient is brother of girl whose thyroid is shown in Fig. 6. The boy's thyroid showed colloid goiter and exhaustion atrophy.

be of value if accurate determinations are made and if the patient has been taking no iodine.

Daily doses of from 1 to 3 grains of U.S.P. desiccated thyroid are necessary to correct childhood hypothyroidism. The dose should be adjusted in accordance with the clinical response of the patient and the level of the blood cholesterol. It is usually well to begin with small doses, which may be increased gradually. Growth and skeletal development of patients with childhood hypothyroidism may progress satisfactorily in response to treatment, but cretinism is rarely recognized in time for treatment to compensate for the mental retardation. Transplantation of thyroid tissue has not been effective.

The accompanying chart shows in outline form the relation of the various types of goiter to one another and to a deficiency of iodine.



The evolution and interrelationship of various types of goiter.

Bibliography

1. Iodine and table salt. J. A. M. A. *135:* 434–435 (Oct. 18) 1947.
2. Eaton, J. C.: Treatment of thyrotoxicosis with thiouracil. Lancet *1:* 171–174 (Feb. 10) 1945.
3. Else. J. E.: Relationship of iodine to human thyroid gland. Northwest Med. *25:* 419–422 (Aug.) 1926.
4. Hartsock, C. L.: Iodized salt in prevention of goiter; is it safe measure for general use? J. A. M. A. *86:* 1334–1338 (May 1) 1926.
5. McCullagh, E. P.: Personal communication.
6. Means, J. H.: The Thyroid and Its Diseases. Being an Account Based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital. Page 306. Philadelphia: J. B. Lippincott Co., 1937.
7. Reinhoff, W. F., Jr.: New conception of some marked changes in diseases of thyroid gland. Tr. Am. A. Study Goiter 167–189, 1930.

Chapter 4

INTRATHORACIC GOITER

Incidence

Although many large goiters dip beneath the clavicles for a short distance, true intrathoracic goiters, with extension downward as far as the arch of the aorta, are relatively rare. In a series of 11,800 thyroidectomies performed at the Cleveland Clinic Hospital, there were only ninety-seven cases in which the goiter descended to the arch of the aorta or below it, an incidence of less than 1 per cent.

Pathology

It is a safe rule to consider all intrathoracic goiters to be adenomas originating in normally situated thyroid glands. All large intrathoracic goiters are adenomatous. In no instance in this series did a diffuse goiter descend to the arch of the aorta. In all cases the adenomas had their origin in normally situated thyroid glands.

Intrathoracic goiter is a disease of the middle and latter span of life, the average age of the patients in this series being fifty-three years. The youngest patient was thirty-two years of age and in only 7 per cent of the cases were the patients under forty years of age. Since only adenomatous goiters become intrathoracic, it is not surprising to find the incidence of intrathoracic goiter highest in the older age groups in which adenomas are more common.

Etiology

There is little doubt that the musculature of the neck plays a large part in directing the growth of an adenomatous goiter. Intrathoracic goiters, as compared with other forms of endemic goiter, are relatively more common in men than in women. They are also more commonly seen in stocky, short-necked individuals in whom the prethyroid muscles are well developed. The pressure from these muscles tends to prevent the outward expansion of the goiter in the neck and gradually forces the adenoma downward into the superior mediastinum. Here for a time the adenoma may be freely movable, rising with deglutition or with straining, and descending again into the thorax. As the adenoma enlarges, it delivers from its intrathoracic position with less ease but still retains its attachment to the thyroid. Finally it becomes imprisoned in the thorax and continues to expand downward and laterally. The narrow thoracic outlet prevents its emergence into the neck.

Symptoms

Patients with intrathoracic goiters may be divided according to symptoms into three groups: first, those with no symptoms; second, those with symptoms resulting from an associated hyperthyroidism; and third, those with symptoms resulting from pressure on the trachea and the great vessels.

Large intrathoracic goiters are often completely symptomless and may appear completely harmless. On the other hand, relatively small intrathoracic goiters situated in certain positions may produce intolerable symptoms of pressure and of tracheal obstruction.

The most severe symptoms occur in the cases in which the pressure of the enlarging adenoma is exerted exactly at the level of the thoracic outlet. The narrow bony outlet at this level renders it impossible for the tumor to expand without compressing the trachea. The most common type of tracheal compression seen at this level is the result of a dumbbell-shaped goiter, part of which lies above the thoracic outlet in the neck and the other part below the outlet and in the thorax (Figs. 17 and 18). The isthmus of the dumbbell-shaped goiter compresses the trachea between itself and the bony structures of the thoracic outlet, often producing severe obstructive symptoms. To make matters still worse, extension of the neck, straining, or swallowing tends to lift the lower half of the dumbbell out of the thorax and through the contracted outlet causing further pressure. Flexing of the neck, on the other hand, forces the cervical enlargement downward through the rigid outlet and again increases the pressure symptoms. Hence it is common for patients with intrathoracic goiter to complain that flexing

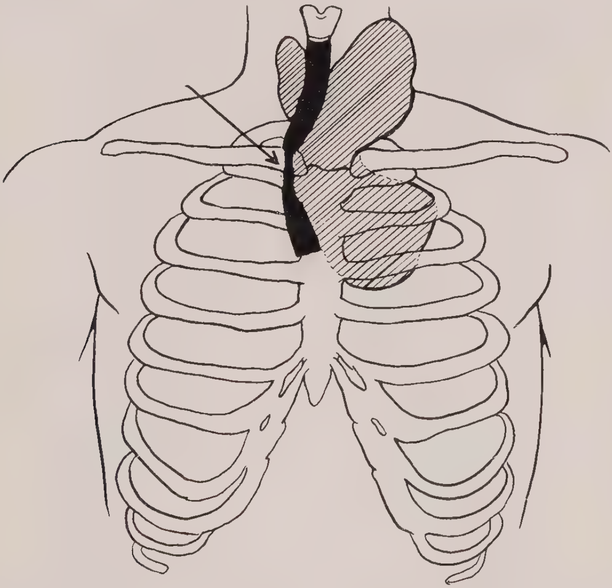


Fig. 17. Dumbbell type of intrathoracic goiter compressing trachea at thoracic inlet.

or extending the neck, as in bending forward or in lying flat on the back, produces an unpleasant sensation of choking.

A second type of intrathoracic goiter which may produce obstruction of respiration is a relatively small adenoma located at the level of the thoracic outlet. It is situated either directly anterior to the trachea, compressing it backward against the vertebral column, or directly behind the trachea and compressing it forward against the sternum. The trachea may be considerably angulated and distorted by relatively small adenomas in these locations, and the resulting obstructive symptoms may be severe.

Nearly 50 per cent of the patients in this series had no symptoms referable to pressure or to tracheal obstruction. If the cervical portion of the thyroid is not enlarged sufficiently to result in fixation of the tumor, there is nothing to prevent an

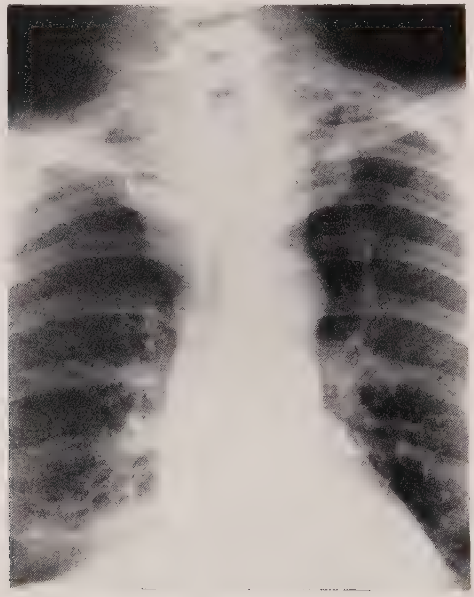


Fig. 18. X-ray of dumbbell type of intrathoracic goiter compressing trachea at thoracic inlet.

adenoma of the lower pole from growing downward into the thorax and expanding into the thoracic cavity without producing symptoms of tracheal compression. In one case (Fig. 19) an enormous intrathoracic goiter entirely filled the right upper half of the thoracic cavity without compressing the trachea or producing the slightest symptom of pressure. The degree of tracheal obstruction depends not so much on the size of the tumor as upon its ability to expand without producing pressure on the trachea at the level of the thoracic inlet.

Hyperthyroidism was present in 50 per cent of all patients operated upon for large intrathoracic goiters and manifested itself in the usual way. The most common symptom associated with intrathoracic goiter is *dyspnea*, but in a high percentage of cases the dyspnea is secondary to an associated hyperthyroidism and the myocardial changes incidental to advancing age. In about 50 per cent of the cases dyspnea was a leading complaint

Fig. 19. Huge intrathoracic goiter filling upper right lung field removed without splitting sternum.

and could not be explained solely on the basis of hyperthyroidism or myocardial damage. This symptom was relieved following operation in the majority of these cases.

In 27 per cent of the cases the patients complain of *choking sensations*, usually brought on by swallowing, extending, or flexing the neck. The relation of the symptoms of pressure to the position of the head is a good indication that the symptoms are the result of an intrathoracic goiter.

A late symptom of tracheal obstruction is the development of *stridor*, which was noted in only 12 per cent of the cases. The stridor associated with intrathoracic goiter occurs usually when the patient is in certain positions and most commonly during sleep. The stridor tends to be of a lower pitch than a laryngeal stridor.

Cough is rare and frequently represents a late symptom of intrathoracic goiter. When present it is often of a peculiar brassy quality. Long-standing obstruction of the trachea may result in bronchiectasis, which signifies its presence by a productive cough.

Although the esophagus may be displaced by an intrathoracic goiter, *dysphagia* is rare and did not occur in any case in this series.

Hoarseness is seldom caused by an intrathoracic goiter. In only 2 per cent of the cases, in all of which the goiter descended to the arch of the aorta or below, was there a preoperative paralysis of the recurrent laryngeal nerve. A change in the quality of the voice, secondary to distortion of the larynx and trachea, is more commonly seen. In some instances the patients noticed difficulty in singing.

Many patients who had no complaints prior to operation noted an improvement in their general sense of well-being after the removal of a large intrathoracic goiter. In these cases the pressure symptoms had come on so gradually that the patient had become accustomed to their presence and was scarcely conscious of them until the tumor was removed.

The most reliable sign of obstruction is the sound of the breathing. When the patient takes a deep breath there is a peculiar, hollow, cavernous sound, as when a seashell is held up to the ear. It resembles the sound made by blowing into a large pipe and is quite different from a laryngeal stridor. This type of breathing denotes obstruction below the larynx.

Diagnosis

An intrathoracic goiter often is overlooked unless roentgenograms of the chest are taken. The majority of intrathoracic goiters are palpable. Percussion is not of much diagnostic value. Although the symptoms of tracheal obstruction or the presence of dilated veins over the thorax may indicate the presence of an intrathoracic goiter, the final decision as to the nature and extent of the mediastinal tumor usually depends on the roentgenologic findings.

Fig. 20. Large intrathoracic goiter barely palpable in neck. Patient's brother had a similar intrathoracic goiter.

In the anteroposterior view of the chest, the trachea can be seen compressed or displaced by a smooth shadow descending from the neck (Fig. 20). This shadow completely fills the area just below the thoracic inlet and becomes narrower as it descends to meet the shadow of the aorta. As Nichols has pointed out, the demonstration of an angle between the mediastinal tumor and the arch of the aorta differentiates an intrathoracic goiter from an aortic aneurysm. The absence of expansile pulsation proved by fluoroscopy or kymographic studies and the tendency of the tumor to rise when the patient swallows will further distinguish an intrathoracic goiter from an aortic aneurysm. Finally, a lateral view is indispensable in demonstrating the relationship of the tumor to the trachea and in revealing small adenomas compressing or displacing the trachea from the front or from behind.

Treatment

The treatment of intrathoracic goiter is surgical. Roentgenotherapy is ineffective in reducing the size of an intrathoracic goiter or in alleviating its symptoms. These tumors are adenomas, are not sensitive to irradiation therapy, and do not diminish in size in response to treatment with iodine.

When intrathoracic goiter is large enough to descend to or below the arch of the aorta, its removal may present technical difficulties, and the risk of thyroidectomy is considerably increased. Therefore, in older patients who have large but symptomless intrathoracic goiters, it is not always wise to advise their removal. This is particularly true in patients past sixty-five years of age, in whom life expectancy may be shortened by the presence of arteriosclerosis, hypertension, or myocardial damage. In such cases, if the goiter is not enlarging, if it gives no symptoms, and if hyperthyroidism is not present, it is more than likely that the patient will die of other causes before the goiter produces any discomfort. But in younger patients, in patients with hyperthyroidism, and in patients in whom obstructive symptoms are present, thyroidectomy should be performed unless strong contraindications are present.

Technic

Since intrathoracic goiters are adenomas originating in normally situated thyroid glands, it is clear that the operation for intrathoracic goiter should be directed primarily to the cervical portion of the tumor (Guthrie) (Figs. 21 and 22). The operation can be divided into six steps: (1) The cervical portion of the thyroid is dissected free of its capsule of muscle and fascia.

(2) The superior pole is clamped and divided. (3) The inferior thyroid artery is located by palpation as it enters the thoracic outlet and is ligated in continuity. (4) The tracheal attachments of the thyroid are cut over hemostats, whose points are always directed laterally, and into the thyroid tissue where there is no possibility of injury to the recurrent nerve.

Up to this point, no direct attack on the intrathoracic portion of the gland has been made. With the cervical portion

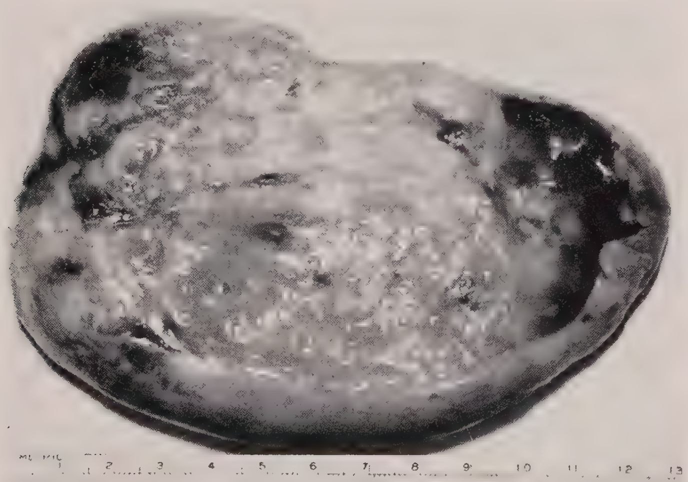


Fig. 21. Intrathoracic goiter. No enlargement of the thyroid was palpable in the neck.

of the gland freed from the trachea, with the superior pole cut and tied, and with the isthmus of the gland divided, the intrathoracic portion tends spontaneously to slide upward into the incision. (5) Gentle traction is made on the intrathoracic portion, using the cervical portion of the gland as a handle. (6) As the gland delivers upward out of the thorax the lateral thyroid vein and the branches of the inferior thyroid vessels are clamped, cut, and tied as they present themselves in the field. There is rarely any bleeding from adhesions or fibrous bands that may be present at the base of the intrathoracic extension. The operation should be practically bloodless if a careful dissection is performed and if the blood supply of the adenoma is meticulously ligated before making a forcible attempt to withdraw the intrathoracic extension.

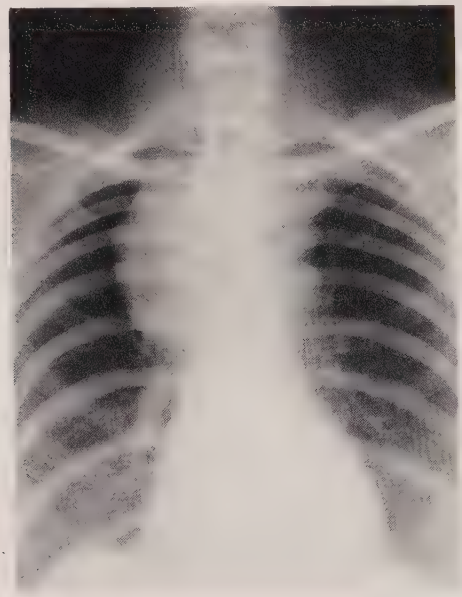


Fig. 22. X-ray photograph of gross specimen shown in Fig. 21. Benign adenoma.

The recurrent nerve is rarely displaced by an intrathoracic goiter except as it is pressed further medially into its normal position in the tracheo-esophageal groove. Hence, if the operation is performed gently and if adhesions to the capsule are divided under direct vision as the gland is delivered into the wound, there is little danger of injury to the intrathoracic portion of the nerve. The greatest danger of injury to the nerve is at the point where it comes forward to enter the larynx.

Collapse of the trachea probably never occurs except secondarily to injury to the recurrent nerves. The appearance of collapse is the result of strong inspiratory efforts to suck air through the narrow chink between the paralyzed cords. The suction draws the walls of the trachea together and gives the appearance of spontaneous collapse.

Occasionally during the delivery of a large adenoma, compression of the trachea will take place, but the normal shape of the trachea is restored as soon as the pressure is removed. Since force should not be used in delivering the goiter, this complication should rarely occur.

It is nearly always possible to remove an intrathoracic goiter without splitting the sternum or resorting to a transthoracic approach. I never have seen an intrathoracic goiter that could not be removed through the neck, although such cases have been reported. Splitting the sternum produces considerable shock and increases the incidence of postoperative pulmonary complications. In this series of ninety-seven cases in which the goiter descended to or below the arch of the aorta, it was necessary to split the sternum in only one case, and the outcome in this instance was fatal, the patient dying as the result of a mediastinal hemorrhage.

In all but three of the remaining ninety-six cases the goiter was removed through the usual cervical incision. In two of these three cases, large cervical adenomas were removed with relief of the pressure symptoms. In view of the patients' debilitated condition and the technical difficulties involved, it was not thought advisable to attack the intrathoracic portion of the gland. In a third case, every effort was made to remove the intrathoracic portion, but the lobes had extended bilaterally behind the trachea and into the mediastinum for a distance of 3 inches below the arch of the aorta. It was technically impossible to remove the tumor. The situation was further complicated by the presence of advanced bronchiectasis, which afforded a strong contraindication to splitting the sternum.

In over 95 per cent of the cases the entire tumor was removed through usual incision without disturbing the bony structures of the thorax. In several instances the tumor was too large to be delivered intact through the thoracic outlet, but its complete removal was successfully accomplished by ligating the blood supply, opening the capsule of the adenoma, and breaking up the tumor and removing it piecemeal. This procedure is accompanied by little or no bleeding. After the removal of sufficient tissue, the capsule of the adenoma can be delivered through the thoracic outlet and excised. Preliminary extracapsular ligation of the inferior as well as the superior thyroid arteries is helpful in reducing the oozing to a minimum.

There has been considerable controversy as to the treatment of the cavity left by removal of an intrathoracic goiter. Some advocate packing the cavity in order to control bleeding and prevent mediastinal extravasation of blood or serum. This technic is valuable in the rare case in which there is persistent and uncontrollable oozing from the wall of the cavity. However, in the majority of cases the cavity left by the removal of an intrathoracic goiter is merely a *potential* space and in nearly every instance is quickly obliterated by the pleura and mediastinal tissues as they are forced into it by the intrathoracic pressure. By the use of packing, this potential space is transformed to a true cavity which is highly susceptible to infection and may drain for weeks.

For the past eight years, since adopting nonabsorbable suture material, I have not drained any thyroid wounds. Large cavities incident to the removal of intrathoracic goiters have healed as promptly as ordinary incisions, and there have been no complications incident to extravasation of blood or serum in the mediastinum.

The operation can be performed under local or cervical block anesthesia with little discomfort to the patient. Intratracheal anesthesia is satisfactory but in older patients may be undesirable because of its tendency to produce tracheal irritation and increase the amount of postoperative mucus. In addition, the use of tracheal intubation necessitates deep anesthesia with its attendant predisposition to pneumonia. If the operation is performed under regional anesthesia, if the upper attachments of the goiter are completely freed, and if the goiter is delivered with extreme gentleness there should be no interference with respiratory exchange.

Bibliography

1. Clinics of G. W. Crile and Associates: The Thyroid Gland. Page 123. Philadelphia: W. B. Saunders Co., 1922.
2. Guthrie, C., and Evans, R. L.: Dangers of air embolism in thyroidectomy. West. J. Surg. *41:* 497–506 (Sept.) 1933.
3. Lahey, F. H.: Goiter incisions. Ann. Surg. *117:* 332–347 (March) 1943.

Chapter 5

CLINICAL AND PATHOLOGIC ASPECTS OF HYPERTHYROIDISM

Etiology

Although the etiology of hyperthyroidism is unknown, different factors appear to be responsible for the development of hyperthyroidism in Graves' disease and in nodular goiters.

Graves' disease is a systemic disorder involving widespread disturbances of the neuro-endocrine system. The diencephalon and the pituitary may be involved in the mechanism of its production. The pituitary gland probably plays a part, and it is thought by some that the overactivity of the thyroid is entirely secondary to stimulation by the pituitary. The exophthalmos so commonly seen in Graves' disease also appears to be related to hyperfunction of the pituitary and does not bear any relationship to the presence or absence of hyperthyroidism.

There are certain solitary adenomas of the thyroid occurring in an otherwise normal gland which are solely responsible for the production of hyperthyroidism. Cope has shown that in some cases a solitary adenoma takes up most of a tracer dose of radioactive iodine, leaves the remainder of the gland in a state resembling atrophy of disuse, and is apparently the sole cause of hyperthyroidism. This type of tumor is analogous to a hyperfunctioning adenoma of the pancreas or parathyroid and appears to be an autonomous neoplastic process growing and functioning independently of the neuro-endocrine system.

The etiology of the hyperthyroidism associated with multinodular goiters is more difficult to determine. In this type of goiter there are involutionary nodules and/or true adenomas scattered throughout the parenchyma of the gland. Some of these nodules take up radioactive iodine and appear to function; others do not. Sometimes the parenchyma takes up most of the radioactive iodine and the nodules have no apparent activity. Again the nodules may take up iodine and show great activity in contrast to an atrophic and apparently nonfunctioning parenchyma.

In such goiters there is no way of telling, without studies made with radioactive iodine, which if any of the nodules are causing the hyperthyroidism or whether the hyperthyroidism is coming from the parenchyma of the gland. In view of these findings, it is not wise to treat hyperthyroidism by the enucleation of an adenoma unless the appearance of the remainder of the gland makes it apparent that the hyperthyroidism is not produced by the parenchyma but by the adenoma.

Even the pathologist cannot with certainty correlate functional activity with the histologic appearances of the thyroid. The only known means of determining just which part of a thyroid gland is hyperfunctioning is by radioautograph after a tracer dose of radioactive iodine. In all cases the hyperthyroidism is the same and the treatment is identical.

Correlation of Clinical and Pathologic Findings

The classification of goiter has remained in a state of confusion because there has been a persistent and futile attempt on the part of clinicians to correlate the clinical with the pathologic findings. Since hyperplasia of the thyroid gland is a common finding in exophthalmic goiter, many believe that the finding of a hyperplastic gland is equivalent to the presence of clinical evidences of hyperthyroidism. Yet marked hyperplasia of the thyroid, indistinguishable from that found in the most severe case of Graves' disease, can occur spontaneously or following ingestion of goitrogens, such as thiocyanates and the antithyroid drugs, and is usually accompanied by a mild hypothyroidism. Conversely, hyperthyroidism occasionally is seen in patients whose thyroid glands, as the result of prolonged treatment with iodine, are in the pure colloid phase and are indistinguishable, histologically, from a simple endemic goiter.

Similarity of Hyperthyroidism Occurring in Graves' Disease and in Nodular Goiter with Hyperthyroidism

It is difficult and often impossible to draw sharp lines of differentiation between Graves' disease and nodular goiter with hyperthyroidism.

The goiters of patients with Graves' disease obey the same law that Wegelin has so clearly demonstrated in the incidence of involutionary nodules and adenomas in the endemic goiters of Switzerland. Elderly patients with longstanding Graves' disease usually have nodules in their thyroid glands. The glands of children and young adults with Graves' disease of short duration rarely are nodular.

Although their causes may be different, there is no reason to believe that the hyperthyroidism associated with the diffuse goiter of Graves' disease is qualitatively different from that associated with toxic adenomas. The exophthalmos that is seen in Graves' disease is not dependent on the hyperthyroidism and may occur in the absence of any demonstrable disturbance in the morphology or function of the thyroid gland. The increased incidence of cardiac complications in patients with nodular goiter is not dependent upon any qualitative difference in the thyroid hormones but results from the increased incidence of organic heart disease in the older group of patients who more commonly have nodular goiters. In short, the disease is hyperthyroidism, and, aside from exophthalmos, its manifestations will vary more with the age of the patients than with the type of goiter.

The average age of patients having hyperthyroidism associated with nodular goiter is approximately thirteen years greater than that of patients with Graves' disease. In the older patients, cardiac complication often will occur regardless of whether the goiter is diffuse or nodular.

There is not only little clinical difference between the hyperthyroidism associated with Graves' disease and that associated with nodular goiters, but also it is impossible always to determine before operation whether or not adenomas are present. Early adenomatous changes cannot be palpated with certainty.

A symmetrical adenomatosis of the thyroid is easily confused with a lobulated diffuse goiter. An asymmetrical diffuse goiter may be indistinguishable from an adenoma. And true Graves' disease, with a diffuse parenchymatous hyperplasia, may occur in a patient who has a preexisting nontoxic adenoma.

Hyperthyroidism associated with nodular goiters may respond to preoperative treatment with iodine in much the same way as Graves' disease. The response is less dramatic than is commonly seen in patients with diffuse hyperplastic glands but may be none the less definite. The response is most dramatic when the hyperthyroidism is the result of Graves' disease occurring in a thyroid which accidentally contained a quiescent adenoma. Since there is little or no clinical difference between the hyperthyroidism associated with diffuse and with nodular goiters, since the response of both types to iodine and the antithyroid drugs is favorable, since there is no reliable evidence that iodine induces an exacerbation of the hyperthyroidism associated with any type of goiter, and finally, since it is not possible before operation to differentiate with certainty diffuse goiters from nodular goiters or Graves' disease from nodular goiter with hyperthyroidism, it is needless, from the therapeutic standpoint, to try before operation to differentiate between the various types of goiter that produce hyperthyroidism.

At the time of operation the activity of the parenchyma of the thyroid often can be estimated by its appearance and vascularity. In Graves' disease recurrences of hyperthyroidism after operation are more common than following removal of adenomas, and hence a more complete thyroidectomy should be performed.

The fundamental issue in hyperthyroidism is the age of the patient and his reaction to the disease rather than the presence or absence of nodules in the thyroid.

Bibliography

1. Cope, O., Rawson, R. W., and McArthur, J. W.: Hyperfunctioning single adenoma of thyroid. Tr. Am. A. Study Goiter, 1942–1946, 156–174, 1946.
2. Wegelin, C.: In Handbuch der speziellen pathologischen Anatomie und Histologie. (Henke, F., and Lubarsch, O., editors.) Achter Band—Drüsen mit innerer Sekretion. Berlin: Julius Springer, 1926.

Chapter 6

DIAGNOSIS OF HYPERTHYROIDISM

Relation of Symptoms and Signs of Hyperthyroidism to the High Basal Metabolic Rate

Hyperthyroidism is an organic disease that produces characteristic objective signs. Its symptoms, on the other hand, may be simulated by many functional disturbances. Symptoms alone, in the absence of signs, do not afford a reliable basis for establishing the diagnosis of hyperthyroidism.

The rate of metabolic activity is consistently increased in hyperthyroidism and the symptoms and signs are largely dependent on this increase in the metabolic rate. The increase in the metabolic rate implies an increase in the amount of oxidation that the body performs day and night, at work and at rest.

In hyperthyroidism, the appetite increases in order to furnish additional fuel for the increased metabolic demands. If the food intake is not enlarged in proportion to the increased demands, the body is forced to oxidize its own tissues, and weight is rapidly lost.

The increased oxygen requirement of the tissues necessitates a speeding up of the circulatory mechanism. This increase can be obtained in one of two ways, either by accelerating the rate of the heart or by increasing the stroke volume of each beat. Both mechanisms are brought into play and express themselves as tachycardia and increased pulse pressure. To increase the speed of circulation, the arterioles dilate, diminishing the peripheral resistance and lowering the diastolic blood pressure. The systolic pressure remains high as a result of the increased output of each beat of the heart. The arteriolar dilatation expresses itself as a flushing and warming of the skin and by the presence of capillary pulsations, as seen in the nail beds. Excessive perspiration is present, and the patient may complain of intolerance of heat. The hyperhidrosis has not been satisfactorily explained, but it may be a compensatory mechanism adapted to disperse the heat produced by the increased metabolism.

Of all the symptoms of hyperthyroidism, those referable to the circulatory system are the most constant and dependable. A persistent, forceful, afebrile tachycardia with an increase of pulse pressure must be considered the result of hyperthyroidism until proved otherwise. An increased precordial thrust is a nearly constant finding in patients with hyperthyroidism, and palpitation is present. It is inconceivable that any appreciable degree of hyperthyroidism could be present without exhibiting itself in stimulation of the cardiovascular system.

Examination of the Thyroid

Examination should begin with inspection. Small nodules which are clearly visible when the patient swallows may be so soft that they escape detection by palpation.

Most patients with hyperthyroidism have a palpable enlargement of the thyroid. Short-necked, heavy-muscled men may have a soft, diffuse, low-lying goiter that may escape recognition even by an expert. An intrathoracic goiter may be so deep that it will not be palpable. Sometimes the gland is not enlarged, but its consistency has a firm rubbery quality that distinguishes it from the ordinary soft normal thyroid or endemic goiter. Occasionally active hyperthyroidism is present in the absence of any palpable abnormality of the thyroid but these cases are exceptions to the rule.

During the examination of the thyroid the patient should sit with the head slightly forward, lie with the neck nearly fully extended, or, best of all, stand with the head held erect. If the neck is flexed, as it will be with the patient reclining on a pillow, a low-lying gland will nearly always escape palpation, and if the neck is hyperextended the tightening of the pretracheal muscles may render palpation difficult.

It is helpful to have the patient swallow. The gland is fixed to the trachea, rises with deglutition, and rolls beneath the fingers or thumb as the patient swallows.

The most satisfactory method of palpating the thyroid is with the thumb. The examiner stands directly in front of the standing patient, the thumb is then placed on the thyroid, and the patient is asked to swallow (Fig. 23).

Fig. 23. Examination of the thyroid.

The thyroid may also be palpated with the fingers, the examiner standing behind the patient. This method is perhaps the most sensitive way to determine the presence or absence of small nodules.

A third method of palpation, recommended by Lahey (1931) and of particular value in examining patients with retrotracheal or deep-lying adenomas, is accomplished with the examiner standing in front of the patient. To examine the right lobe, the larynx is displaced to the right with the thumb of the right hand. With the fingers of the left hand behind the sternomastoid muscle and the thumb of the left hand anterior to this muscle, the gland is palpated between the fingers and thumb.

Exophthalmos

Hyperthyroidism induced by feeding desiccated thyroid does not produce exophthalmos, nor does exophthalmos occur in patients whose hyperthyroidism is caused by a nodular goiter unless Graves' disease is present.

Quite inexplicable, on the basis of our present knowledge, is the tendency for patients with Graves' disease to develop exophthalmos. The administration of the thyrotropic hormone of the pituitary is known to produce exophthalmos in animals that have been subjected to complete thyroidectomy. It is on the basis of these observations that some believe exophthalmos to be the result of pituitary overactivity. Since the eye signs of Graves' disease may be present in the complete absence of morphologic or functional changes in the thyroid (ophthalmopathic Graves' disease without hyperthyroidism) (Means) there are probably other factors besides the thyrotropic hormone of the pituitary gland that cause the exophthalmos. One of these may be a pituitary hormone closely related to the thyrotropic hormone but not identical with it.

The first eye sign of Graves' disease, usually apparent before the development of a measurable exophthalmos, is a staring expression due to widening of the palpebral fissures (Stellwag's sign). Associated with this widening is lid-lag (von Graefe's sign), best demonstrated by having the patient hold his head still and follow a series of up and down movements of the examiner's hand. On downward motion of the hand the retracted upper lid fails to cover the white of the eye above the pupil and confirms the presence of lid-lag.

Measurable exophthalmos is less common than the other eye signs of Graves' disease. It is often impossible without the use of the exophthalmometer to state whether or not exophthalmos is present. Measurements in excess of 22 to 23 mm. in the anterior-posterior position of the eyes are considered abnormal. If the palpebral fissures are widened the eyes have a staring expression suggestive of exophthalmos even when no measurable exophthalmos is present. On the other hand, rather marked exophthalmos, particularly after operation, may be masked by the absence of widened fissures (Figs. 24 and 25). The degree of exophthalmos can be estimated better with the lids closed than with them open because the examiner is not then led astray by the widening of the fissures (Rundle).

Fig. 24. Exophthalmos persisting after operation but rendered inconspicuous by absence of widened palpebral fissures. Eyes measure 30 mm. in anterior-posterior position.

Other Symptoms and Signs of Hyperthyroidism

Nervousness and an exaggeration of all emotional reactions are almost invariably present in patients with hyperthyroidism. Weeping is a common complaint, particularly in women.

In the presence of severe hyperthyroidism all systems are affected. There is a diminution of gastric acidity, a tendency to hypermotility of the gastrointestinal tract, and a negative calcium balance resulting in a tendency toward skeletal decalcification. Menstruation may be interrupted in severe cases.

The skeletal muscles are weakened, often so strikingly that the patient is unable to step up onto a chair. The metabolism of muscle is disturbed so that muscular work is performed less efficiently. The muscle may become infiltrated with fat. The excretion of creatine is increased, and there may be a decreased

Fig. 25. Appearance of unilateral exophthalmos given by unilateral widening of palpebral fissure. Both eyes show measurable exophthalmos.

tolerance to administered creatine. The fine tremor, so commonly seen in hyperthyroidism, probably is the result of these disturbances in the metabolism of muscle. The tremor is best demonstrated by having the patient outstretch his hand with the fingers rigidly extended and separated. The tremor may be so fine that it is easier to feel than to see.

Carbohydrate metabolism is disturbed, probably due to impairment of the glycogen storage function of the liver. Abnormal glucose tolerance curves are observed, and sometimes there is glycosuria.

A mild lymphocytosis is often present, and there is some tendency to a generalized hyperplasia of lymphoid tissue.

Laboratory Tests as Diagnostic Aids

The *basal metabolic rate* is the most useful laboratory test in the diagnosis of hyperthyroidism. Although there are a few cases in which the basal metabolic rate is within the normal limits of 0 to plus 15 per cent, I have never seen a patient with active hyperthyroidism untreated by iodine, antithyroid drugs, or roentgenotherapy whose basal metabolic rate was consistently less than 0 per cent. The occasional patient who has hyperthyroidism associated with a high-normal basal metabolic rate probably had a basal metabolic rate that was below normal before he developed hyperthyroidism.

An analysis of the results of thyroidectomy in relieving the symptoms that were thought to be attributable to hyperthyroidism confirms the importance of the basal metabolic rate as a diagnostic test for hyperthyroidism. In 142 consecutive cases of Graves' disease in which the patients' basal metabolic rates were over plus 20 per cent, the symptoms of hyperthyroidism were specifically relieved by thyroidectomy. In sixty-nine cases of nodular goiter with hyperthyroidism, symptoms were similarly relieved except in the case of one patient who developed a major psychosis. The diagnosis of hyperthyroidism was probably an error, as it appears that the psychosis was the chief cause of her symptoms.

In twenty-five cases in which the diagnosis of Graves' disease was made on patients with basal metabolic rates between 0 and plus 20 per cent there were ten cases in which thyroidectomy failed to relieve the symptoms. Two-thirds of the patients had had iodine before the basal metabolic rate was recorded. Three of seven patients whose basal metabolic rates were under plus 20 per cent and who had had no iodine failed to improve after operation. The lowest basal metabolic rate occurring in a patient with Graves' disease who received the expected benefit from operation was plus 4 per cent. This was a child who had had iodine before the basal metabolism test. In thirty nodular goiters with symptoms of hyperthyroidism and with basal metabolic rates between 0 and plus 20 per cent, there were seven cases in which the operation failed to relieve the symptoms.

It is apparent from these figures that the basal metabolism is an extraordinarily reliable index of whether or not the symptoms are the result of hyperthyroidism. Regardless of the history and physical examination, a high proportion of operations for hyperthyroidism performed on patients with basal metabolic rates within the normal range fail to relieve the symptoms. This is more often the case when the patient has not taken iodine before the basal metabolic rate was determined.

An elevation of the basal metabolic rate does not necessarily imply that hyperthyroidism is present. Leukemia may produce a striking elevation of the basal metabolism, probably as a result of the enormous activity of the bone marrow. In certain cases of severe essential or malignant hypertension the basal metabolic rate may be elevated to as much as plus 50 per cent. The cause of this elevation is not understood, but it is well established that the hypermetabolism does not originate in the thyroid. In the presence of dyspnea secondary to cardiac decompensation, the increased work performed by the muscles of respiration then results in an elevation of the basal metabolic rate.

In patients with hyperthyroidism the *blood cholesterol* level is low or in the lower limits of the normal range (Hurxthal). A low blood cholesterol of itself is of little or no clinical significance, because a number of conditions other than hyperthyroidism can influence its level. But the finding of a high fasting blood cholesterol in a patient suspected of having hyperthyroidism is strong evidence against the presence of hyperthyroidism. Even in patients with diabetes who have hyperthyroidism high levels of cholesterol rarely are observed.

Considerable experimental and clinical investigation of the *blood iodine* levels in patients with hyperthyroidism has been carried out (Perkin), but the findings are too irregular and inconsistent to be of clinical value.

The level of the protein bound blood iodine correlates well with the basal metabolic rate and the clinical findings (Curtis), but this test is difficult and expensive and not adaptable to performance in the average laboratory. Intake of iodine, moreover, may invalidate its results.

Fig. 26. Graves' disease with severe exophthalmos. (Courtesy of Surgery, Gynecology and Obstetrics.)

Differential Diagnosis

Active hyperthyroidism in a young adult can be recognized as readily as the face of an intimate friend (Fig. 26). The characteristic quickness of the motions, the restlessness of the behavior, and the bright-eyed alertness of the patient cannot fail to suggest the true nature of the disease. On the other hand, in patients of advanced years with mild hyperthyroidism, in patients with goiters complicated by other medical problems, such as diabetes, tuberculosis, hypertension, or organic heart disease, the diagnosis may tax to the utmost all available clinical and laboratory facilities (Figs. 27 and 28).

Any infectious process, and especially the chronic types of infection such as tuberculosis and undulant fever, may simulate

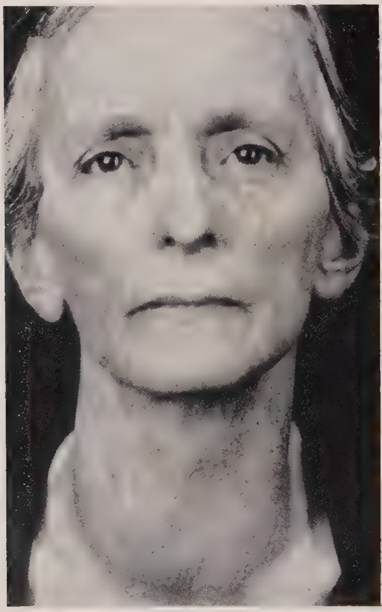


Fig. 27. Hyperthyroidism in an elderly patient manifesting itself by cardiac symptoms. Note the absence of the appearance of stimulation. (Courtesy of Surgery, Gynecology and Obstetrics.)

Fig. 28. Hyperthyroidism in an elderly patient. The patient had kidney stones and the presence of severe hyperthyroidism was not suspected until she became confused, fell out of bed, and developed a mild thyroid crisis. (Courtesy of Surgery, Gynecology and Obstetrics.)

hyperthyroidism. There is a tendency to tachycardia, loss of weight, nervousness, and fatigue. In borderline cases of suspected hyperthyroidism, all possibilities of chronic infection should be eliminated before treatment of the suspected hyperthyroidism is begun.

Essential Hypertension. The most difficult condition to differentiate from hyperthyroidism is severe essential hypertension. Here a moderate elevation of the basal metabolic rate is a relatively common finding, and in a small percentage of the cases elevations of the basal metabolic rate up to plus 50 per cent may be present in the complete absence of true hyperthyroidism.

In one case of malignant hypertension the basal metabolic rate at bed rest in the hospital remained persistently in the neighborhood of plus 45 per cent. There was no clinical evidence of hyperthyroidism, and the thyroid was not palpably enlarged. The patient's chief complaints were referable to paroxysmal dyspnea. However, dyspnea was not constantly present, and the elevation of the basal metabolic rate could not be attributed to increased work by the muscles of respiration.

In view of the striking and persistent elevation of the basal metabolic rate, a total ablation of the thyroid gland was performed* in an attempt to decrease the work of the heart and restore its compensation. Every vestige of thyroid tissue was removed. Following the operation the patient's blood pressure remained unchanged, but the symptoms improved. The basal metabolic rate fell to only plus 8 per cent instead of falling to the level of minus 30 to minus 40 per cent, as one would expect in the absence of all thyroid tissue. Some months later the patient died and the complete absence of the thyroid was confirmed at postmortem examination. It is clear that in this case the patient's basal metabolic rate was elevated by the hypertension and that this elevation of the basal metabolism could be maintained at the level of plus 8 per cent even in the absence of all thyroid tissue.

In many cases of essential hypertension the basal metabolic rate is elevated to from plus 20 to plus 60 per cent. The symptoms experienced by these patients closely simulate those of patients with hyperthyroidism. An elevation of the basal metabolic rate, whether it be the result of hypertension or of

---

* Operation by Dr. Glover Copher.

thyroid activity, must stimulate the circulatory system, and must increase the demands of the body for food. So closely may hypertension simulate hyperthyroidism that it is not surprising that some of these patients have had thyroidectomies performed without relief of symptoms.

There are many cases of hypertension in which the basal metabolic rate is elevated, the history is consistent with hyperthyroidism, and the physical findings do not rule out its presence. A high or a normal blood cholesterol is strong evidence against the presence of hyperthyroidism. In the final analysis the clinical picture of the patient is the most valuable aid in determining whether a patient with hypertension has hyperthyroidism as well. Thyroidectomy in the presence of hypertension will not lower the diastolic blood pressure even if hyperthyroidism is present.

Cardiac Decompensation. The basal metabolic rate is elevated in patients with dyspnea of cardiac origin. It is often difficult to determine whether or not the cardiac decompensation is the result of a "masked" hyperthyroidism. Unless the diagnosis is perfectly clear, the basal metabolic rate should be rechecked after compensation has been restored by a period of bed rest and digitalization. If the basal metabolic rate remains elevated at rest in the absence of dyspnea, hyperthyroidism presumably is present.

Neurocirculatory Asthenia. Occasionally the symptoms of neurocirculatory asthenia simulate hyperthyroidism so closely that thyroidectomy is performed. The symptoms of neurocirculatory asthenia are unchanged or aggravated by such an operation. Although nervousness, palpitation, tachycardia, and tremor are present in neurocirculatory asthenia, the physical findings and the basal metabolic rate should facilitate the differentiation of the two conditions.

Neurocirculatory asthenia is a functional disturbance characterized by its occurrence in a nervous type of person, by the paroxysmal nature of its symptomatology, and by the absence of any consistent alterations in the basal metabolic rate. The tachycardia of neurocirculatory asthenia tends to disappear with bed rest. Sinus arrhythmia is often present and is easily elicited by holding the breath or by flexion of the trunk, whereas the tachycardia of true hyperthyroidism is little if at all slowed by these measures. In neurocirculatory asthenia the pulse pressure is not increased, and the systolic blood pressure is often low. The apex impulse of the heart is forceful only during the paroxysms of tachycardia. The patient may enter the hospital with a forceful tachycardia of 120 beats per minute and the pulse rate the next morning will have fallen to 80.

The circulatory manifestations of hyperthyroidism are constant rather than paroxysmal. The heart is necessarily subjected to a constant stimulation as a result of the increased metabolic demands. At bed rest in the hospital, the pulse rate of the patient with hyperthyroidism will fall slowly in response to the slow decline of the basal metabolic rate. The pulse pressure is nearly always increased and the systolic blood pressure is almost invariably a high rather than a low normal.

The hands of the patient with neurocirculatory asthenia are mottled, cold, and moist, in sharp contrast to the warm flushed skin of the patient with hyperthyroidism. One should beware of performing a thyroidectomy for hyperthyroidism on a patient with cold hands. Tremor, if present in a patient with neurocirculatory asthenia, is coarse and irregular, as a rule appetite is either unchanged or diminished, and significant loss of weight is absent unless the patient refuses to eat.

In differentiating hyperthyroidism from functional states the history is of little value. The most important thing to remember is that hyperthyroidism is an organic disease characterized by hypermetabolism and that this hypermetabolism is bound to give objective evidence of its presence. It is the signs and not the symptoms that count.

Psychosis. Major organic psychosis can closely simulate hyperthyroidism. Patients with involutional psychosis may have a persistent forceful tachycardia, may lose considerable weight, and may have a facial expression closely resembling that of hyperthyroidism. This stimulation of the circulatory system and of the mechanism of emotional expression arises from the disorientation of the patient's mind and from his inexpressible fear of some terrible fate evident to himself alone. In these cases the basal metabolic rate is likely to be unreliable, and the diagnosis must be determined largely by clinical means.

Patients who are disoriented or delirious and who are suspected of having hyperthyroidism should not be subjected to thyroidectomy until mental clarity has returned and the basal metabolic rate has been brought to normal by treatment with the antithyroid drugs. If the psychosis is due to hyperthyroidism, the patient is apt to have a severe or even fatal postoperative thyroid crisis. If the psychosis is not due to hyperthyroidism, operation will not help it. Patients with psychosis are best treated by conservative measures.

Globus. Sensations of pressure and choking are not symptoms of goiter unless thyroiditis, carcinoma, or a large adenoma which exerts pressure on the trachea is present. Choking sensations are rarely seen in patients with hyperthyroidism. These symptoms are due to an involuntary contraction of the pharyngeal musculature such as occurs in states of nervous tension, a so-called "lump in the throat" or "globus hystericus." Thyroidectomy usually aggravates the symptoms, and afterward the patient complains of "adhesions" of the scar.

Therapeutic Test with an Antithyroid Drug

One of the most valuable methods of determining the presence of hyperthyroidism in any of the conditions mentioned is the therapeutic test with propylthiouracil. If a patient is suspected of having hyperthyroidism the basal metabolic rate should be established accurately. The patient is then given 250 mg. of propylthiouracil daily for a period of two months, after which the basal metabolic rate is again determined. The pulse rates and blood pressure readings of the two periods of observation are compared, as are the weights of the patient and his evaluation of the severity of the symptoms. If there has been striking objective and subjective evidence of improvement it is probable that hyperthyroidism is present. On the other hand, if there is no subjective or objective improvement it is unlikely that hyperthyroidism is a factor in the production of the symptoms.

If the patient has been taking iodine continuously over a long period of time, or if the gland is large, it may require a longer period of treatment, as the action of the drug may be delayed. Propylthiouracil does not, as a rule, effect a significant reduction in the basal metabolic rate in two months if the thyroid is normal.

Tracer doses of radioactive iodine may prove to be of value in the diagnosis of selected cases, but these studies by Astwood have not as yet been completed.

Bibliography

1. Astwood, E. B.: Pending publication.
2. Curtis, G. M., and Fertman, M. B.: Blood iodine studies; analysis of blood iodine in thyroid disease. Arch. Surg. *50:* 207–213 (April) 1945.
3. Hurxthal, L. M.: Blood cholesterol and thyroid disease; myxedema and hypercholesteremia. Arch. Int. Med. *53:* 762–781 (May) 1934.
4. Lahey, F. H.: Surgical management of intrathoracic goiter. Surg., Gynec. & Obst. *53:* 346–354 (Sept.) 1931.
5. Means, G. H.: Diseases of thyroid gland. New England J. Med. *221:* 820–825 (Nov. 23) 1939.
6. Perkin, H. J.: Value of blood iodine estimations in treatment of clinical hyperthyroidism. S. Clin. North America *16:* 1509–1511 (Dec.) 1936.
7. Rundle, F. F.: Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to effect of thyroidectomy. Clin. Sc. 5*:* 177–194 (Dec.) 1945.

Chapter 7

IODINE IN THE TREATMENT OF HYPERTHYROIDISM

Physiologic Action of Iodine in the Treatment of Hyperthyroidism

When a patient with Graves' disease is given iodine, the hyperplastic gland fills with colloid, the pulse rate falls, the basal metabolic rate is lowered, and a partial remission of the hyperthyroidism is induced (Plummer).

The mechanism of this reaction is not understood, but iodine does exert a direct action on the secretory activity of the thyroid gland causing a diminution but not a complete interruption of its output of active thyroid hormone. The block appears to be in the release of active thyroid hormone from the gland rather than in its production or storage. This reaction appears within twenty-four hours after the administration of iodine, and its maximum general effect is noted from one to three weeks after the initiation of treatment. The hyperthyroidism is improved but not completely controlled, and the disease persists indefinitely in modified severity as long as the iodine is given.

Many believe that iodine loses its effectiveness after a few weeks of continuous administration and that patients who take iodine over long periods of time become "iodine-fast" or "iodine-tolerant" so that the drug no longer exerts any control over the hyperthyroidism. In many cases the severity of the disease progresses in spite of the administration of iodine, so that neither larger doses nor a continuation of the same doses of iodine produces any further remission. Yet as Means and Lerman have shown, the hyperthyroidism in these so-called "iodine-fast" cases undergoes an exacerbation when iodine is withdrawn. This indicates that the administration of iodine exerts a continuous effect, perhaps more striking in the first few weeks, but nevertheless present as long as it is given. Iodine escape (an exacerbation of the patient's symptoms while iodine is being given) is not to be interpreted as the failure of iodine to exert a continuous depressant effect on the secretory activity of the thyroid. Rather it should be considered the result of an exacerbation of the disease itself which has occurred in spite of the iodine and which would be more severe if the iodine were withdrawn.

Spontaneous or Iodine-Induced Remissions

There is some tendency for Graves' disease to enter a spontaneous remission. This tendency is not apparent in the hyperthyroidism secondary to nodular goiters. Means states that the course of Graves' disease is variable, with some tendency to self-limitation. In some cases the disease "burns itself out" and produces myxedema. In others the cause of the disease subsides spontaneously and the function of the thyroid returns to normal.

Since there is this tendency toward remission in Graves' disease "cures" are sometimes seen following prolonged treatment with iodine. Whether or not these cures would have occurred spontaneously if iodine had not been given has never been determined.

Thompson *et al.* reported a series of twenty-four patients treated by prolonged administration of iodine. The results were satisfactory in the majority of cases in which the hyperthyroidism was mild, and in half of them the patients remained well after withdrawal of iodine. In ten cases of moderate to severe hyperthyroidism, however, the disease was controlled in only one case and in five it became more severe.

In general, there is little evidence to indicate that the administration of iodine will cure patients with severe hyperthyroidism or permanently modify the severity of the disease except as it depresses the secretory activity of the thyroid during the time it is given.

Preoperative Administration of Iodine in Patients with Hyperthyroidism

It is advantageous to see the patient with hyperthyroidism before iodine is given in order to estimate the true severity of the disease and to plan treatment accordingly. Prolonged treatment with iodine has little to recommend it in this era when safe and effective means of inducing a remission are available. Futile attempts to treat hyperthyroidism with iodine often result in prolonged periods of disability followed by the ultimate necessity of a more definitive treatment. If hyperthyroidism is recognized when the symptoms first appear and is treated definitively without delay, the mortality rate is negligible and the period of disability is short.

If the patient is to be prepared for operation with iodine the ideal time for performing a thyroidectomy is after two to four weeks of therapy. One cubic centimeter of Lugol's solution three times daily or sodium or potassium iodide in equivalent doses provides more than an ample intake of iodine. One drop of saturated solution of potassium iodide is equivalent to six drops of Lugol's solution. Determinations of the blood iodine, taken one hour after the first dose of iodine, show values ranging from 125 micrograms to 175 micrograms per 100 cc. of blood, as compared with the normal blood iodine level of 7 micrograms to 11 micrograms. No convincing or controlled evidence has been produced to indicate that the remission induced by the intravenous administration of iodides results in either a more rapid or a more complete remission of the hyperthyroidism. In fact, Thompson has shown that doses as small as 6 mg. of iodine daily given by mouth are as effective as the larger doses that are commonly used.

When in response to iodine the pulse curve has fallen and has established a plateau at a lower level, when the patient is eating well and the weight is increasing, when the patient's nervousness and restlessness are diminished, the time for operation has arrived. The disease has entered a remission and has gained an impetus or "momentum" in the direction of recovery. After such a response, severe thyroid reactions are rare and operation is relatively safe (Fig. 29).

If, on the other hand, the pulse curve fails to fall in response to bed rest and iodine, if the patient loses weight and becomes more nervous, the disease has failed to enter a remission and is capable at the slightest provocation of evoking a dangerous thyroid crisis (Fig. 30). This type of reaction is commonly seen in patients who have had iodine for long periods of time prior to admission. The risk of operation is greater in them

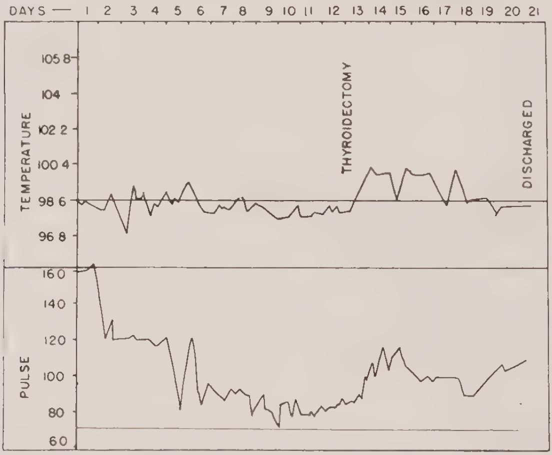


Fig. 29. Good response of the pulse curve to iodine. Operation was followed by a minimum reaction. (Courtesy of Surgery, Gynecology and Obstetrics.)

than in the patient whose preoperative response has been favorable (Fig. 31). Further treatment with iodine will not accomplish any added improvement. Under such circumstances the risk of operation is too great to be undertaken without completely controlling the hyperthyroidism by administration of an antithyroid drug. Iodine should not be withdrawn until the hyperthyroidism is well controlled lest the withdrawal induce a fatal exacerbation of hyperthyroidism before the antithyroid drug can exert its effect (Fig. 32).

Iodine is effective in modifying the hyperthyroidism of both

Graves' disease and nodular goiters. Although the most rapid and dramatic iodine remissions are apt to occur in patients with diffuse hyperplastic goiters the remission induced in patients with nodular goiters may be striking.

Postoperative Use of Iodine

After iodine has been administered for three weeks, the remission of the hyperthyroidism is as great as can be obtained

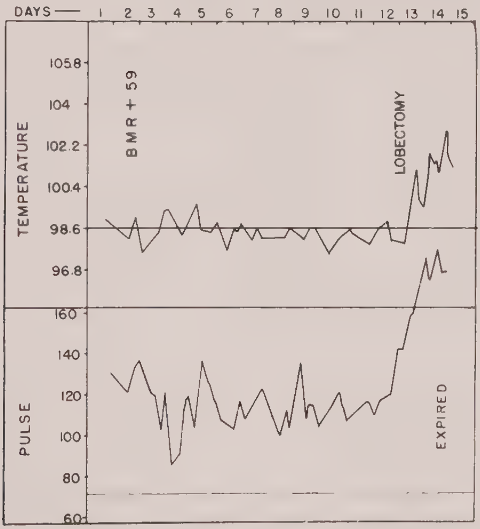


Fig. 30. Fatal thyroid crisis following hemithyroidectomy in a patient with Graves' disease whose pulse curve failed to respond to preoperative treatment with iodine. (Courtesy of Surgery, Gynecology and Obstetrics.)

by means of iodine therapy. In these cases, the level of iodine in the blood is extremely high and the thyroid gland has undergone as much involution as iodine can be expected to produce. Since iodine does not have any effect on the active thyroid hormone which is already circulating in the blood, and since the thyroid in properly prepared cases has undergone as much involution as iodine can produce, it is quite useless to administer huge doses of iodine either by mouth, by rectum, or intravenously. If the patient has been properly prepared for operation, the most that can be accomplished by giving iodine after operation is to maintain the effects of the iodine given before. This can best be done by continuing to give 1 cc. of Lugol's solution three times daily, either by mouth or by rectum for the first two or three days after operation. When the peak of the thyroid reaction has passed, the administration of iodine can be discontinued with safety.

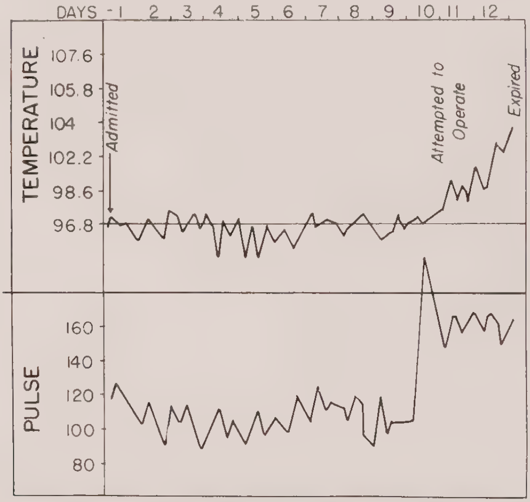


Fig. 31. Graves' disease. Unsatisfactory response to iodine. Fatal thyroid crisis followed preparation for operation. Operation cancelled because of patient's emotional reaction to the operating room.

If by any chance a patient has been improperly prepared for operation and has not had sufficient iodine to produce a maximum remission, and if a severe postoperative reaction should develop, Lugol's solution in doses up to 30 minims can be given intravenously in a solution of 10 per cent glucose. This same treatment is effective for patients admitted to the hospital in thyroid crisis, especially if iodine has not been administered previously.

Iodine tends to produce remissions in some cases of mild recurrent hyperthyroidism and sometimes appears to induce a permanent remission. It is logical, therefore, to believe that iodine might prevent recurrence if given in selected cases after thyroidectomy. Small doses of iodine (1 minim of Lugol's solution daily) for a period of six months after operation may be given in cases in which severe hyperthyroidism is associated with an extremely hyperplastic gland. It is my impression that the residual symptoms of hyperthyroidism are more promptly and completely controlled in these patients than in

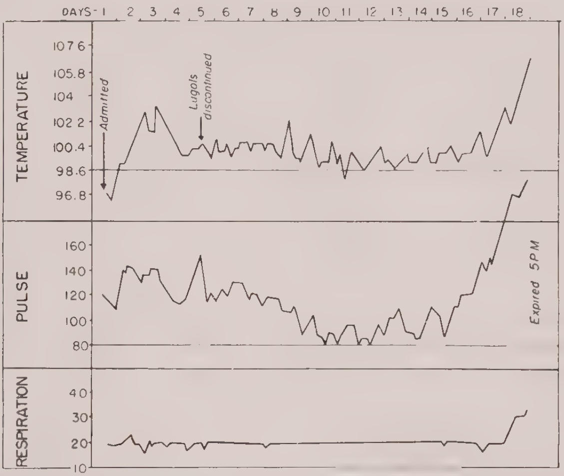


Fig. 32. The patient was given iodine for four days but because the reaction to iodine seemed unfavorable its administration was discontinued. The patient made a good response to the iodine but then, as soon as its effect wore off, developed a thyroid crisis and expired. This chart dates from the early days of the use of iodine when its effects were not understood clearly.

those who are discharged without iodine and with the remnants of thyroid tissue in a hyperplastic state. This procedure seems even more logical in view of the fact that iodine prevents the compensatory hyperplasia which develops in the thyroids of experimental animals after the greater portion of the gland has been removed.

It is also reasonable to expect that iodine would exert a beneficial effect on the hyperplastic remnants of a gland which had been prepared for operation by administration of an antithyroid drug. In one case a goiter recurred within a few weeks in a patient who had received thiouracil preoperatively. The gland did not enlarge further after iodine was given.

Iodine may also be used in conjunction with the antithyroid drugs to prevent excessive hyperplasia and vascularity of the thyroid. Doses as small as 10 mg. daily are effective in preventing the development of a thrill and bruit. Ten minims of Lugol's solution should be given three times daily for at least ten days before thyroidectomy is performed upon a patient being treated with an antithyroid drug. The administration of iodine causes an involution of the thyroid and prevents the excessive vascularity which otherwise follows the use of the antithyroid drugs.

Occasionally a deficiency of iodine or ingestion of some unknown goitrogen induces hyperplasia in a simple diffuse goiter. In the following case report, although the patient did not have hyperthyroidism, the thyroid gland was extremely hyperplastic. Had iodine in physiologic doses been administered from the time of operation, the recurrence probably could have been avoided.

A 19-year-old school girl from Niagara Falls, N. Y., entered the hospital for treatment of a congenital goiter. A thyroidectomy had been performed elsewhere at the age of 15. She had had no symptoms of hyperthyroidism. After operation, the goiter recurred promptly and grew until it was nearly as large as before.

Examination showed a recurrent, diffuse goiter of soft consistency. The basal metabolic rate was minus 7 per cent; the pulse was 78. There was no clinical evidence of hyperthyroidism.

Subtotal thyroidectomy was performed, and the patient was discharged after an uneventful convalescence. At the time of discharge, the incision was well healed and no thyroid tissue was palpable

One month later the patient returned, complaining that the goiter again had begun to enlarge. Examination revealed a soft, diffuse enlargement of both lobes of the thyroid to approximately three times the normal size. There was no evidence of hyperthyroidism.

The thyroid gland at the time of the second operation was extremely hyperplastic and contained no colloid whatsoever. The second recurrence was treated with small doses of iodine and thyroid extract and, over a period of years, has decreased slightly. Had iodine been given immediately following the second thyroidectomy, the second recurrence probably could have been prevented.

The brother of the patient had three operations for a congenital goiter associated with childhood hypothyroidism. The thyroid gland showed colloid goiter and exhaustion atrophy.

The Dangers of Withdrawing Iodine

In 1926, iodine often was given over long periods of time in an attempt to cure patients with hyperthyroidism. The danger of withdrawing iodine from patients with severe hyperthyroidism who had been taking iodine for a long period of time was not appreciated, and iodine was not given between the stages of divided operations. Consequently, as many patients died at home between stages as died in the hospital after operation. The patients left the hospital in good condition, but fatal thyroid crises or cardiac failure soon developed. The exacerbation resulting from the withdrawal of iodine was more severe than the remission induced by the operation.

It is equally dangerous to withdraw iodine from a patient with severe hyperthyroidism who is to be treated with an antithyroid drug. The exacerbation due to withdrawal of iodine may take place before the antithyroid drug becomes effective, and death may ensue. Under these circumstances it is preferable to give both iodine and the antithyroid drug simultaneously.

Bibliography

1. Haines, S. F.: Use of iodine in recurrent exophthalmic goiter. West. J. Surg. *42:* 449–455 (Aug.) 1934.
2. Means, J. H., and Lerman, J.: Action of iodine in thyrotoxicosis with special reference to refractoriness. J. A. M. A. *104:* 969–972 (Mar. 23) 1935.
3. Means, J. H.: The Thyroid and Its Diseases. Being an Account Based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital. Philadelphia. J. B. Lippincott Co., 1937.

4. Plummer, H. S.: Results of administering iodin to patients having exophthalmic goiter. J. A. M. A. *80:* 1955 (June 30) 1923.

5. Thompson, W. O., Brailey, A. G., Thompson, P. K., and Thorp, E. G.: Range of effective iodine dosage in exophthalmic goiter; effect of basal metabolism of rest and of daily administration of one drop of compound solution of iodine. Arch. Int. Med. *45:* 261–281 (Feb.) 1930.

Chapter 8

ANTITHYROID DRUGS IN THE TREATMENT OF HYPERTHYROIDISM

The Contribution of the Antithyroid Drugs to the Safety of Thyroid Surgery

In June, 1942, Astwood first treated hyperthyroidism with an antithyroid drug. The patient was given 2 gm. of thiourea daily and the basal metabolic rate fell to normal in two weeks.

Since this time thousands of patients have been treated with the antithyroid drugs. Thiouracil was first used but proved too toxic to find widespread acceptance except as a means of preparing seriously ill patients for operation. Now the newer and less toxic thiouracil derivatives, propyl- and methylthiouracil, are effective in controlling and possibly in curing hyperthyroidism.

Before the introduction of thiouracil the mortality rate of hyperthyroidism treated by experienced surgeons had fallen to less than 1 per cent. Improvement in anesthesia, in surgical technic, in preoperative and postoperative care, a keener appreciation of factors that increased the risk of operation, and the judicious use of x-ray therapy in preparing seriously ill patients for operation all contributed materially to this advance. Yet it was impossible to lower the mortality rate in a large series of cases to levels much below the apparently irreducible minimum of 1 per cent and still to operate on all the desperately ill patients whose life depended on control of their hyperthyroidism.

Although operations for hyperthyroidism still carried a low but significant risk, operations for simple goiter, often more difficult from a technical standpoint, were attended by a mortality rate of less than one in a thousand. The mortality of operations for hyperthyroidism was thus ten times that of simple goiter.

The postoperative fatalities usually occurred in a group of patients who could be picked out preoperatively as presenting an increased risk. Thiouracil, although dangerous in itself, afforded a means of abolishing this risk and of rendering these patients as safe for operation as they would have been if they had had simple goiters.

Since the risk of fatal agranulocytosis during treatment with thiouracil was estimated to be approximately 0.5 per cent, few surgeons chose either to maintain treatment with this drug indefinitely or to use it routinely to prepare patients for operations which involved no special dangers. Hence only a small percentage of all patients with hyperthyroidism were prepared with thiouracil, and most were treated with iodine and operated upon as before.

Since the seriously ill patients were generally treated before operation until the hyperthyroidism was completely controlled, the mortality rate of thyroidectomy immediately fell to levels never before attained, and only a small fraction of a per cent of the patients operated upon were lost. The advent of the newer antithyroid drugs, propyl- and methylthiouracil, has increased the safety of preoperative preparation to the point that it is now safe to prepare the majority of patients with hyperthyroidism with these drugs.

Today the mortality rate of the surgical treatment of hyperthyroidism in the hands of competent surgeons who prepare the majority of their patients with propylthiouracil has fallen almost to the vanishing point. There have been no deaths following operations for hyperthyroidism at the Cleveland Clinic Hospital in the last 800 consecutive cases. The morbidity of thyroidectomy in the hands of competent surgeons is likewise low, injuries to the recurrent laryngeal nerves and tetany occurring in only a fraction of a per cent of the cases. The consideration of the scar is not often a serious one. Hence it is fair to say that both the mortality and morbidity of thyroidectomy for hyperthyroidism are now on an eminently satisfactory level approximating that of removal of a simple goiter.

Unfortunately in the hands of unqualified surgeons, the morbidity of thyroid surgery, including injury to the recurrent laryngeal nerves, tetany, recurrent hyperthyroidism, and unsatisfactory scars, still appears to be much higher than it should be. As nearly as can be judged from examination of the vocal cords of the patients who are seen at the Cleveland Clinic with recurrent goiters after operations performed elsewhere, the incidence of unilateral vocal cord paralysis is greater than 8 per cent. This may not be a true sampling of the over-all incidence of this complication, but since figures of this nature are not reported, I know of no other way to arrive at an estimate.

There always has been a marked disparity between the mortality rates reported by surgeons who are particularly interested in surgery of the thyroid and those reported from general hospitals where no one surgeon or group of internists and surgeons has become interested in the study of thyroid disease. Thus, before the introduction of thiouracil mortality rates following operation for hyperthyroidism were as high as 11.5 per cent in certain unspecialized hospitals while some of the more specialized institutions were losing less than 1 per cent of the patients operated upon. The type of patient and the severity of the disease may have played a part in these results, but it is noteworthy that the results in respect to morbidity following thyroid surgery follow a similar pattern. Technical accidents, tetany, injury to the recurrent laryngeal nerves, and persistent and recurrent hyperthyroidism are much lower in the hands of surgeons who are specially trained in the surgery of the thyroid than in those of the surgeon who only occasionally performs a thyroidectomy.

The purpose of this discussion is not to emphasize the relative risks of thyroidectomy in the specialized as compared to the unspecialized institution but is rather to point out that, when deciding as to the merits of medical versus surgical treatment of hyperthyroidism, there are important considerations other than those of the methods involved. If there were available a surgeon, well trained to perform a safe thyroidectomy, thyroidectomy might be the treatment of choice. But if the patient were to be subjected to operation by a surgeon whose record of mortality and morbidity following thyroidectomy is high, certainly a prolonged trial, if not indefinite treatment, with one of the antithyroid drugs would be the wisest course to follow.

Rationale of Treatment with the Antithyroid Drugs

Recurrence Following Operative Treatment. When hyperthyroidism comes about as the result of functional activity in a longstanding adenoma, it is not surprising that removal of the benign tumor which is responsible for the hyperthyroidism is followed by cure of the disease and an almost negligible incidence of recurrent hyperthyroidism. The factors responsible for the development of the original adenoma are no longer in operation, and if excision has been complete, there is no reason for the hyperthyroidism to recur.

In Graves' disease, however, the entire gland is stimulated to hypertrophy, hyperplasia, and hyperfunction by causes which are not fully understood. It seems likely that the primary seat of the disease is in the thyroid gland itself. Subtotal thyroidectomy does nothing to eliminate the factors that originally stimulated the hyperplasia and hyperfunction. Hence, the surprising clinical feature is not that hyperthyroidism occasionally recurs but rather that the disease does not *always* recur.

The incidence of persistent hyperthyroidism following operation is easy to determine. Persistence of the hyperthyroidism represents a technical error resulting from insufficient removal of thyroid tissue. This complication is rare and occurs only in a fraction of 1 per cent of all cases of hyperthyroidism if thyroidectomy has been well done.

On the other hand, the true incidence of hyperthyroidism recurring a year or more after operation is difficult to determine and will depend upon the length of the follow-up. Although the greatest incidence of recurrent hyperthyroidism is in the first two years following thyroidectomy, it may recur at any time. A patient may remain well for twenty years only to develop, late in life, recurrent hyperthyroidism. Thompson, in a group of patients some of whom were followed only three months, found that 19.5 per cent showed residual or recurrent hyperthyroidism. It is estimated that the over-all incidence of persistent and recurrent hyperthyroidism following an adequate thyroidectomy does not exceed 5 per cent. (See section on End Results of Thyroidectomy, Chapter 14.)

If these figures are broken down further to separate Graves' disease from nodular goiters with hyperthyroidism, it is apparent that the majority of patients with recurrent hyperthyroidism have Graves' disease. In my own experience four-fifths of the operations performed on patients with recurrent hyperthyroidism were done for Graves' disease. Similarly, of the thirteen patients of my own series who developed recurrent hyperthyroidism all but one had Graves' disease. Since most reports on the incidence of recurrent hyperthyroidism do not separate nodular goiters with hyperthyroidism from Graves' disease, since there are few recurrences of hyperthyroidism after removal of nodular goiters, and finally, since the period of time that the reported patients have been followed is not usually more than a few years, the true incidence of recurrent hyperthyroidism in Graves' disease probably is higher than 5 per cent and possibly nearer 15 per cent when the operation is performed by the conventional technic.

Total thyroidectomies are seldom performed in the treatment of hyperthyroidism because of the prohibitive incidence of parathyroid tetany. Studies conducted in relation to total thyroidectomy for heart disease and experiments on animals have shown that unless every vestige of thyroid tissue is removed, regeneration of the thyroid promptly restores its function to normal. This regeneration occurs as a compensatory hypertrophy and hyperplasia stimulated by the pituitary gland in response to a deficiency in circulating thyroid hormone.

Since (1) the normal thyroid is capable of regeneration, (2) a considerable portion of the thyroid is left following subtotal thyroidectomy, and (3) the true causes of hypertrophy, hyperplasia, and hyperfunction of the thyroid in hyperthyroidism are not removed by thyroidectomy, why is it that the remnants of the thyroid do not always enlarge and cause a recurrence of the disease?

On the basis of present knowledge there is no answer to this question unless it is assumed that thyroidectomy merely breaks a link in a vicious circle of nervous or endocrine disorders. It is possible that subtotal thyroidectomy, by accomplishing a reduction in the output of thyroid hormone to normal or subnormal levels, secondarily causes a subsidence of the factors that incited the thyroid gland to hyperfunction. The fact that recurrent hyperthyroidism and postoperative hypothyroidism are most commonly seen after operations for Graves' disease and are seldom seen following operations for nodular goiter is further evidence that some factor other than the amount of thyroid tissue left is responsible for the unpredictable occurrence of postoperative hypothyroidism and recurrent hyperthyroidism. If enough tissue is removed to induce a remission of the symptoms of Graves' disease, it is impossible to predict whether this interruption of the vicious circle will produce myxedema, will stabilize the function of the thyroid at a normal level, or will act but temporarily until the gland is again stimulated, and the disease recurs. The surgical treatment of diffuse goiter with hyperthyroidism is empiric in approach, unpredictable in outcome, and unphysiologic in principle, but from a clinical standpoint is safe, simple, and satisfactory.

Following subtotal thyroidectomy the mechanism of compensatory hypertrophy and hyperplasia and the factors which caused the original hyperfunction of the thyroid would be expected to continue to operate and to produce a recurrence of the goiter and of the hyperthyroidism. Yet this occurs in only a small percentage of cases. An unphysiologic procedure is proved empirically to be a sound clinical treatment. Is the treatment of hyperthyroidism with antithyroid drugs safer, more predictable in its end results, or more physiologic than removal of the gland?

Recurrence Following Use of Antithyroid Drugs. So far as has been determined, the effect of thiouracil derivatives is primarily on the thyroid gland. By blocking formation of active thyroid hormone *thiouracil accomplishes a physiologic instead of an anatomic thyroidectomy.*

The same questions can be asked about the results obtained with thiouracil as were asked about those following thyroidectomy. Why does not the human thyroid invariably enlarge under treatment as it does in animals? The pituitary gland is stimulated by the deficiency of thyroid hormone to pour out its thyroid-stimulating hormone. Hyperplasia of the thyroid results, but the enlargement of the gland usually is negligible. Occasionally there is a case in which the thyroid grows with incredible rapidity, but these cases are the exception and not the rule.

Why does not the hyperthyroidism invariably recur after withdrawal of the drug? Thiouracil, so far as is known, has no effect on the factors which first stimulated the thyroid gland. Prolonged remissions from hyperthyroidism, nevertheless, are obtained following thiouracil therapy in perhaps 50 per cent of the patients who receive adequate treatment. How long these remissions will last is uncertain. It would appear that physiologic thyroidectomy by thiouracil therapy breaks the "vicious circle" just as anatomic thyroidectomy does. When a remission is obtained with thiouracil the end-results are unpredictable, just as they are following thyroidectomy. Recurrence of hyperthyroidism, however, is more common after a course of thiouracil than following an adequate thyroidectomy.

When severe postoperative hypothyroidism or myxedema occurs, the subsequent development of recurrent hyperthyroidism is extremely rare. I have never observed this sequence of events, although I have seen hyperthyroidism recur in patients whose basal metabolic rates after operation were as low as minus 13 per cent. Perhaps the low incidence of recurrent hyperthyroidism in patients who have had hypothyroidism can be explained on the hypothesis that the "vicious circle" is more completely broken by the induction of severe hypothyroidism. I am convinced that postoperative hypothyroidism is not always caused by removing an excessive amount of thyroid tissue and that its persistence is not because there is insufficient thyroid tissue left to regenerate and cause a recurrence if the stimulating mechanism were in operation. In the patients who develop postoperative hypothyroidism some profound alteration has been effected in the mechanism which governs the secretory activity of the thyroid gland. This mechanism is not understood.

Subtotal thyroidectomy and thiouracil therapy accomplish essentially the same end by different means. Both methods of treatment depend upon inducing a temporary remission of the hyperthyroidism. During this remission the "vicious circle" of the pathologic physiology is broken, and in those patients who are to remain well the abnormal stimulation of the thyroid is abolished.

The size of the gland may be a significant factor in determining the duration or permanency of remissions after treatment with antithyroid drugs. To date it appears that longstanding remissions occur most often in patients with small goiters. An analogy can be drawn in this respect to recurrent hyperthyroidism after thyroidectomy where the incidence of recurrence bears a direct relationship to the amount of thyroid tissue left at the time of operation.

Any drug which is as safe as a surgical operation and which can accomplish the same ends without incurring discomfort, morbidity, loss of time from work, and the expense of hospitalization is a better therapeutic measure than surgery. Propylthiouracil fulfills these qualifications. It does not have the disadvantage of serious toxicity. It can safely and apparently in many cases completely break the "vicious circle" of thyroid stimulation. Moreover, it often produces a lasting remission after its withdrawal.

If the remissions obtained after physiologic thyroidectomy induced by propylthiouracil do not prove to be permanent, it will be necessary either to give small maintenance doses of propylthiouracil for an indefinite period of time or at some subsequent date, with the hyperthyroidism completely controlled, to resort to thyroidectomy. For the present, at least, there seem to be few indications for thyroidectomy as the primary treatment of Graves' disease unless the gland is large or enlarges under treatment, unless the patient is uncooperative, the response to the antithyroid drugs is incomplete or slow, or the patient is intolerant of the drug.

When goiters contain adenomas of significant size the situation is different. Tumors are present in the thyroid. These are of cosmetic importance, tend to enlarge, tend to produce symptoms of pressure, and are of possible significance in respect to malignancy. Because tumors of any organ are potentially troublesome, because the risk of operation is slight unless the patient is old or debilitated, and because hyperthyroidism rarely recurs after removal of a nodular goiter thyroidectomy remains the treatment of choice for nodular goiter with hyperthyroidism.

If Lugol's solution is given in doses of 10 or 15 minims three times daily for two weeks before operation, as suggested by Lahey, the technical difficulties of thyroidectomy are not significantly increased by preparation with the antithyroid drugs. An equally acceptable method of effecting and maintaining involution of the thyroid is to give 10 mg. of iodine daily along with the antithyroid drug throughout the entire period of treatment.

Since hyperthyroidism can be controlled safely in patients not intolerant of the antithyroid drugs, it does not seem reasonable to assume the needless risk of operation upon a patient with severe or complicated hyperthyroidism without first completely controlling all signs of toxicity and reducing the basal metabolic rate to normal. It is impossible to predict how long this will take, but in general patients with large nodular goiters and those who have taken iodine before the antithyroid drug was given will react more slowly. Severe hyperthyroidism may respond dramatically in a matter of three or four weeks, and mild hyperthyroidism may take months to control. The simultaneous use of iodine and propylthiouracil does not materially affect the speed of the response, probably because the antithyroid drug blocks the synthesis of iodine into thyroid hormone. The prompt initial response to the iodine is of particular value in the rehabilitation of patients whose hyperthyroidism is severe.

Propylthiouracil in the Treatment of Hyperthyroidism

The medical treatment of hyperthyroidism with the antithyroid drugs is not so simple as it sounds, and considerable knowledge of the physiology of the thyroid and the pharmacology of the drugs is required if the patient is to be managed well. Too often there is a tendency to deviate from the dosage schedule, to interrupt treatment, or to change to some other form of therapy. If the patient is not attended by a physician who is familiar with and sympathetic with the use of the antithyroid drugs, it is important that the patient be cooperative and intelligent and also that she be able to return for periodic observation. If these conditions can be met, medical treatment can be carried out satisfactorily over a period of a year or more, and the chances of obtaining longstanding or permanent remissions are increased. If these conditions cannot be fulfilled it is better to prepare the patient for operation and remove the thyroid.

Propylthiouracil is a weaker antithyroid drug than thiouracil. Astwood has shown that for twenty-four hours after an adequate single dose of thiouracil the thyroid is unable to take up radioactive iodine and presumably is unable to make thyroid hormone. After an effective single dose of prophylthiouracil the uptake of radioactive iodine is blocked for only four hours. This difference may explain the difference in the potency of the two drugs, and the difficulty that has been experienced in depressing the basal metabolism to subnormal levels by administration of propylthiouracil. Because a longstanding or permanent remission probably depends on the completeness and on the duration of the treatment it is important to be cognizant of this inherent weakness of propylthiouracil.

Since the effects of propylthiouracil are of short duration it should be given three times daily and at bedtime. Although it would be desirable to wake the patient at night to give another dose it is impractical to do so. The average dose is 200 to 300 mg. daily, and the dose should be maintained until the basal metabolic rate reaches subnormal levels. If hypothyroidism develops it may be more easily controlled by small doses of thyroid than by readjustment of the dose of propylthiouracil.

For years the internist has criticized the surgeon because hyperthyroidism tended to recur after inadequate thyroidectomies. Recurrent hyperthyroidism after thyroidectomy was not always the fault of the method but often was caused by the lack of thoroughness with which the operation was accomplished. Today the shoe is on the other foot, and the responsibility for thoroughness of treatment rests upon the internist.

Even if the patient is free of symptoms, is gaining weight, and the hyperthyroidism seems well controlled, treatment cannot be considered adequate if the basal metabolic rate remains in the neighborhood of plus 10 per cent. In certain resistant cases the inherent weakness of propylthiouracil renders it difficult to lower the basal metabolic rate below this level. In such cases serious consideration should be given to the use of the more potent methylthiouracil.

The physician who is content to treat hyperthyroidism symptomatically by giving enough propylthiouracil to effect a gratifying improvement in the patient's symptoms, without bringing the basal metabolic rate to 0 or to subnormal levels, will obtain few longstanding remissions. His patients will require perpetual treatment or will have to resort to thyroidectomy or radioactive iodine. The results of inadequate medical treatment are comparable in every respect to those of inadequate thyroidectomy. The internist is therefore confronted today by the same challenge that confronted the surgeons at the turn of the century.

Toxicity of Propylthiouracil. The toxicity of propylthiouracil appears to be between one-fifth and one-tenth that of thiouracil. To my knowledge it has caused no fatalities in several thousand patients who have been treated with it, and in our experience with over 300 cases there has been only one serious reaction, an exfoliative dermatitis. Leukopenia has been so rare that we do not insist on the weekly blood count but merely check the white and differential blood count a week after starting treatment and every three months at the time that the basal metabolic rate is determined. All patients are instructed in the significance of a sore throat, dermatitis, or fever.

Side reactions have been few. In only 3 per cent of over 300 cases was it necessary to discontinue treatment because of toxicity. One patient, a man 64 years of age with auricular fibrillation and arteriosclerotic heart disease, died suddenly after vomiting for a day. No blood counts were made, and there is no record of his having had any fever. He had taken the drug about a month without reaction, and there is little reason to suppose that his death was attributable to the use of propylthiouracil. There has been no case of agranulocytosis and as far as we know only one of granulopenia. This patient had a normal white blood cell count of 4500 but only 25 per cent granulocytes. One patient developed transient hives, two became nauseated, one had transient arthralgia, and one had severe exfoliative dermatitis after recovery from which there was a generalized lichenification of the skin. Interestingly enough, this patient took thiouracil for many months and propylthiouracil for nearly a year before the dermatitis developed. He has not as yet recovered sufficiently to enable us to test him to see if it is in reality the propylthiouracil that is responsible. Certainly, until proved otherwise, it must be assumed that the reaction is due to the drug.

Three patients have complained of numbness of the extremities while under treatment with propylthiouracil. One patient became hysterical after the hyperthyroidism was controlled, and complained incessantly of a sensation of numbness. The emotional disturbances subsided promptly following withdrawal of the drug, but the numbness persisted for several months. There was no alteration of blood chemistry, and no demonstrable sensory or motor changes. Questionable or mild toxic reactions have thus appeared in about 3 per cent of the patients treated, and less than 0.5 per cent have had serious reactions requiring hospital supervision.

Results of Treatment with Propylthiouracil. When in response to treatment with an antithyroid drug the metabolism has fallen to 0 or lower and all objective evidence of hyperthyroidism has been controlled, the disease is as completely and effectively controlled as it is by thyroidectomy. Symptoms referable to hyperthyroidism have been abolished in the patients whose basal metabolic rates have fallen to 0 in response to medical management. On the other hand, there have been a few patients whose basal metabolic rates have not fallen to 0 even after receiving doses of 200 or 300 mg. daily for four or five months, and these patients have clinical evidence of residual hyperthyroidism. If the dosage were further increased or if treatment were continued longer I believe the hyperthyroidism in these patients could be controlled, but we have rarely given more than 400 mg. daily. Most of the refractory patients have had severe hyperthyroidism and large goiters.

From observation of patients who have of their own accord either cut down the dosage of propylthiouracil or stopped taking it after having been well controlled for a short time, it is apparent that there is a very striking tendency for prompt recurrences to take place. On the other hand, seventeen of twenty patients whose hyperthyroidism has been completely controlled for a year by continuous therapy with propylthiouracil have remained well for three months to a year after withdrawal of the drug. It appears, therefore, that the incidence of protracted remissions after withdrawal of the drug is directly proportional to the duration and efficacy of treatment. Judging from our previous experience with thiouracil we can expect that about 50 per cent of the adequately treated patients will remain in remission.

At the present time the mortality and morbidity following treatment of hyperthyroidism with propylthiouracil over a period of one year are probably lower than that of thyroidectomy in the hands of skillful surgeons and are much lower than that of thyroidectomy in the hands of the surgeon who only occasionally performs a thyroidectomy.

From the economic standpoint the patient who is treated medically is far ahead at the end of the first year. He need lose no time from work (provided he was able to work before treatment), he need have no more than four to six determinations of the basal metabolism and white blood counts, nor more than six to twelve visits to a physician, no hospitalization, and no operation. The cost of propylthiouracil is low, not exceeding forty dollars a year, and soon should be less. The only question is whether this will be just the beginning of a lifetime of medical treatment for hyperthyroidism or whether the remissions will be permanent in a high enough percentage of cases to warrant continuation of definitive medical treatment.

It is entirely possible that the treatment of Graves' disease may become comparable to that of duodenal ulcer. The initial treatment may be medical except in certain cases of unusual severity in which experience has taught us that surgery is indicated. Surgical treatment in either ulcer or hyperthyroidism is indicated in those patients who (1) do not respond to medical treatment, (2) do not cooperate, or (3) are subject to recurrences and do not wish to continue indefinitely on medical treatment.

Certain ulcers respond readily to medical treatment, and some are apparently "cured" after a single course of intensive treatment. In most cases, however, the tendency to recurrence is always present and recurrences take place if vigilance is relaxed. The situation regarding hyperthyroidism controlled by antithyroid drugs appears comparable except that the drugs used in the treatment of ulcer are known to be safe and the long-run safety of propylthiouracil is still unknown. Nor have we yet had sufficient experience to evaluate the long-range efforts of the drug on the thyroid itself.

Indications for Treatment

For patients with nodular goiters with hyperthyroidism and for those with large diffuse goiters and severe hyperthyroidism, thyroidectomy after appropriate preparation is the treatment of choice. There is reason to believe that propylthiouracil is not effective in controlling hyperthyroidism associated with nodular goiters, but the cosmetic considerations, the likelihood that the adenoma will enlarge, the remote possibility of carcinoma, and the excellent results of thyroidectomy render operation the treatment of choice in patients who are young and are good surgical risks.

A trial of definitive medical treatment is certainly warranted (1) in patients with Graves' disease with mild or moderate hyperthyroidism when associated with small or medium-sized diffuse goiters, (2) in recurrent hyperthyroidism when the morbidity of thyroidectomy is high, and (3) in patients whose life expectancy is short, regardless of the type of goiter.

One of the most striking features of the effects of the antithyroid drugs is the difference in the speed and completeness of the response in different patients. It is our impression that those patients who are resistant, who require large doses, and whose hyperthyroidism is incompletely controlled, tend to develop exacerbations very promptly upon withdrawal of the drug. The response of the patient to the drug may therefore be of prime importance, and if this is proved to be the case it may be well to defer decision as to the choice of medical versus surgical treatment until this response can be evaluated.

In all cases the problem of medical versus surgical treatment should be explained to the patient frankly so that if she elects medical treatment and it fails to effect a cure, criticism cannot be made that time and money were wasted in medical treatment when the disease could have been corrected in the beginning by operation. Patients who are advised to have thyroidectomy performed should be told of the status of medical treatment, and it should be explained that if they desire to give medicine a trial there are no contraindications. To treat all patients with hyperthyroidism by thyroidectomy or all definitively by propylthiouracil would seem ill-advised. It is quite possible that many of the patients who have been prepared for operation with propylthiouracil and subjected to thyroidectomy would have obtained a longstanding remission if treatment had been continued for a few months longer. Similarly, the attempt to treat all patients medically when the size of the goiter and the severity of the disease are such that little prospect of a permanent cure could be expected would seem to be equally ill advised.

In summary, patients with hyperthyroidism can be divided from the therapeutic standpoint into four main groups:

Fig. 33. Graves' disease with moderate hyperthyroidism and thyroid only slightly enlarged. Suitable for trial on definitive treatment with propylthiouracil.

Fig. 34. Graves' disease with moderate hyperthyroidism and large diffuse goiter. Thyroidectomy recommended because thyroid is large.

Group I. Patients to be treated definitively by antithyroid drugs and the hyperthyroidism completely controlled for one year in the hope of inducing a long-standing remission. This group includes:

(a) Patients with Graves' disease and small to medium-sized goiters (Fig. 33).

(b) Patients with any type of goiter who refuse operation or prefer to try medical treatment.

Group II. Patients to be treated by antithyroid drugs in preparation for operation. This group includes:

(a) Patients with large diffuse goiters (Fig. 34).
(b) Patients whose goiters enlarge under treatment (Fig. 35).
(c) Patients with nodular goiters of significant size (Fig. 36).
(d) Possibly patients who develop hyperthyroidism early in pregnancy.
(e) Old or poor-risk patients who prefer thyroidectomy.

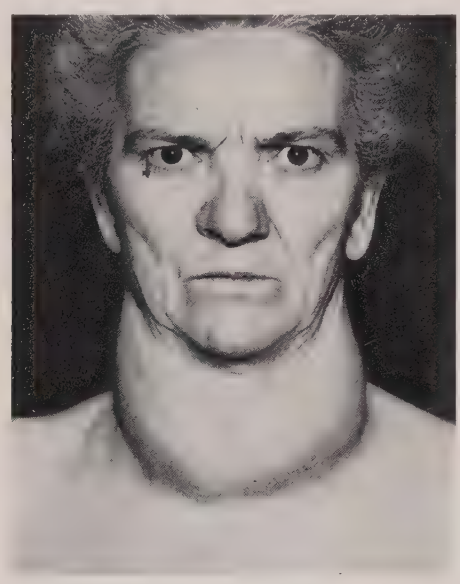


Fig. 35. Patient's thyroid was only slightly enlarged prior to administration of thiouracil. Under treatment it enlarged rapidly and in eleven months attained this size. Hypothyroidism did not develop and the administration of 6 grains of desiccated thyroid daily did not change the rate of growth. Thyroidectomy was performed after preparation with iodine. Gland weighed 542 gm.

Group III. Patients to be prepared for operation with iodine.

(a) Young, good-risk patients with diffuse goiters and mild hyperthyroidism who prefer the greater certainty of surgical cure to the uncertainty of medical cure.
(b) Patients with nodular goiters and mild hyperthyroidism (Fig. 37).
(c) Patients intolerant of antithyroid drugs.

Group IV. Patients in whom operation is contraindicated and who are to be treated indefinitely, if necessary, with antithyroid drugs.

(a) Aged patients.
(b) Patients with short life expectancy.
(c) Patients with recurrent hyperthyroidism when the technical difficulties of operation are increased.

Fig. 36. Solitary adenoma of thyroid with severe hyperthyroidism. No medical treatment will remove the tumor. Preparation with propylthiouracil and thyroidectomy is the preferred treatment.

Methylthiouracil

Methylthiouracil has been used for some time in Europe, but it was given in enormous doses and proved to be nearly as toxic as thiouracil. Methylthiouracil, given in smaller doses of 200 to 300 mg. daily, has not as yet proved toxic, but since agranulocytosis has been reported with the larger doses it is quite likely that this complication occasionally will occur. Its action seems to be more prompt and more complete than that of propylthiouracil, and to date the only toxic effect observed in a series of seventy cases studied by Dr. E. Perry McCullagh at the Cleveland Clinic has been a mild dermatitis in one case.

Summary of Present Status of Treatment with Propylthiouracil

The present status of the treatment of patients with hyperthyroidism can best be visualized by a hypothetical analysis

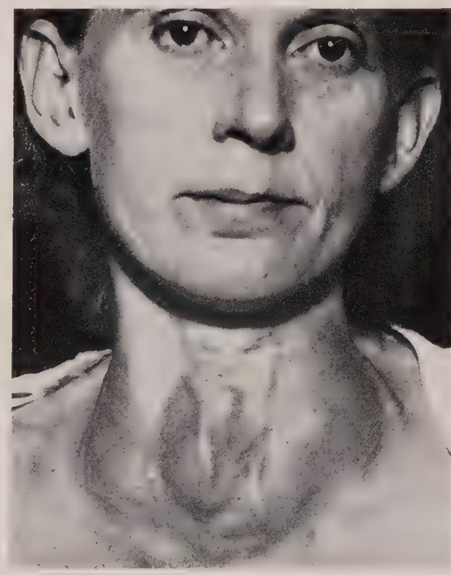


Fig. 37. Large nodular goiter with mild hyperthyroidism. Thyroidectomy after preparation with iodine is the preferred treatment.

of the treatment given to a group of 100 patients with hyperthyroidism.

50 patients had nodular goiters with hyperthyroidism: thyroidectomy after suitable preparation was the preferred treatment except in special cases where radioactive iodine or indefinite treatment with propylthiouracil may have been preferred.

50 patients had diffuse goiters with hyperthyroidism (Graves' disease).

10 of these may have had large goiters with severe hyperthyroidism, and thyroidectomy after suitable preparation was recommended.

5 may have been unwilling or unable to cooperate in prolonged medical treatment so that thyroidectomy after preparation was recommended.

5 may have been intolerant of propylthiouracil in the first four months or the gland so enlarged under treatment that thyroidectomy became the preferred treatment.

In 5 the hyperthyroidism may have been incompletely controlled, the basal metabolic rate not falling to 0, or the hyperthyroidism responded very slowly to treatment indicating that the likelihood of maintaining a longstanding remission after discontinuation of treatment was slight. Within four months it became clear that thyroidectomy was the preferred treatment.

25 remaining patients were suitable for an attempt to effect a longstanding remission by completely controlling the hyperthyroidism for one year.

5 of these may have suffered a prompt relapse as soon as treatment was stopped. Thyroidectomy was performed on some of these patients and others continued medical treatment or were given radioactive iodine.

5 may have suffered relapses at a later date but within a year or two of discontinuing treatment.

15 may remain well and appear cured.

Since it has been possible to induce a remission in only 15 of the original 100 patients with hyperthyroidism, it could be argued that definitive treatment with the antithyroid drugs is hardly worth while and is economically unsound. But the 50 patients with nodular goiters, the 10 with large diffuse goiters, the 5 who could not cooperate, the 5 that were intolerant of the drug or showed enlargement of the thyroid, and the 5 whose response to treatment was unsatisfactory, all were operated upon as soon as they could be prepared for operation and no time or money was wasted. Thus 75 of the 100 patients were operated upon or treated definitively by other means within four months of the time they were first seen. In the remaining 25 patients who responded well to the empiric test of treatment, the incidence of longstanding if not permanent remissions appears to be high enough (at least 60 per cent) to warrant a trial of medical treatment for one year. If such a program is followed the patient who responds well to treatment may avoid thyroidectomy and the patient who does not respond well proceeds with definitive treatment without significant delay.

Bibliography

1. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil. J. A. M. A. *122:* 78–81 (May 8) 1943.
2. Lahey, F. H.: Combination of Lugol's solution with thiouracil in preoperative preparations of patients with toxic goiter. Lahey Clin. Bull. *4:* 2–3 (July) 1944.
3. Idem: Reduction of mortality in hyperthyroidism. New England J. Med. *213:* 475–479 (Sept. 5) 1935.
4. Thompson, W. O., Morris, A. E., and Thompson, P. K.: Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter. Arch. Int. Med. *46:* 946–978 (Dec.) 1930.

Chapter 9

ROENTGENOTHERAPY AND RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM

Roentgenotherapy

Roentgenotherapy, although not recommended for use in the treatment of uncomplicated hyperthyroidism, is of value (1) to prepare patients who are intolerant of the antithyroid drugs for operation, (2) as a palliative form of treatment in senile patients who are inoperable and intolerant of the antithyroid drugs, and (3) in conjunction with iodine or the antithyroid drugs in certain carefully selected cases of recurrent or residual hyperthyroidism. Radioactive iodine is more effective than roentgentherapy and probably will supplant it in the treatment of hyperthyroidism.

Roentgenotherapy is of little value in the treatment of hyperthyroidism associated with large adenomatous goiters. It is effective in about 50 per cent of the patients with diffuse goiters, inducing a partial remission of symptoms and a significant depression of the basal metabolic rate. Our experience in a small series of selected cases corresponds to that of Means and Holmes who found that x-ray therapy alone resulted in the cure of about 30 per cent of fifty-eight patients with hyperthyroidism. Prolonged therapy is not justified if the hyperthyroidism is not controlled within a few months (Fig. 38). In many of the incompletely controlled cases the tachycardia and often the nervousness persist, and eventually thyroidectomy is required. For these reasons, unless strong contraindications are present, thyroidectomy, or the use of the antithyroid drugs or of radioactive iodine, offers a more rapid and certain means of controlling the hyperthyroidism.

Roentgenotherapy, when properly given, does not interfere with healing or increase the technical difficulties of operation. If sufficient fibrosis could be produced, the operation might even be rendered easier because the gland would not be so friable.

Roentgenotherapy for hyperthyroidism should be given with at least a 200 K.V. machine, and at least 2000 r must be given in order to produce satisfactory results. Generally the treatments are given in daily doses of about 200 r each (Portmann).

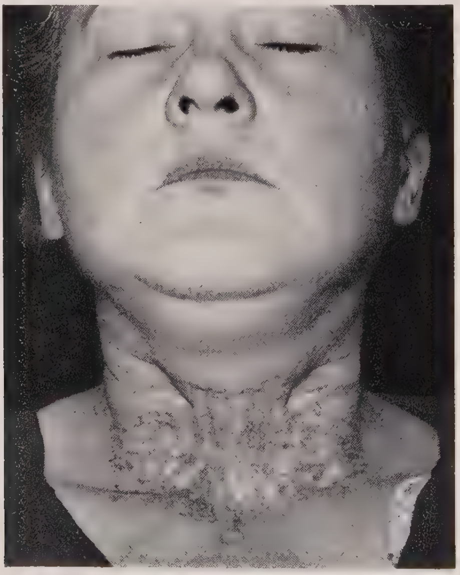


Fig. 38. Skin changes secondary to excessive irradiation of the thyroid in an attempt to cure hyperthyroidism by roentgen therapy. Such changes do not occur when therapy is administered properly.

Therapeutic Use of Radioactive Iodine in Hyperthyroidism

In 1941, Hertz, Roberts, and Chapman in Boston and Hamilton and Soley in San Francisco independently began to use radioactive iodine in the treatment of hyperthyroidism. The radioactive iodine used was a mixture of two isotopes of iodine,

I^{130}, with a half life of 126 hours, and I^{131}, with a half life of eight days. These isotopes were produced in cyclotrons.

Hertz and Roberts used doses varying from 0.7 to 28 millicuries. The average dose given to twenty-nine patients with hyperthyroidism was 14.5 millicuries, the iodine being given orally in aqueous solution. Nineteen patients received only one dose, and ten were given two to four doses. One day to several weeks later 5 minims of a saturated solution of potassium iodide was given twice daily for two to four months. Treatment was followed by no untoward reaction except that when large doses were used some of the patients became nauseated and developed symptoms similar to irradiation sickness. When large doses were used patients often developed transitory pain and tenderness of the thyroid.

In twenty of the twenty-nine cases the hyperthyroidism was completely controlled and has remained so for five years. In one case the dose was too small to have a therapeutic effect. In three cases the hyperthyroidism was not controlled. Five patients later were subjected to thyroidectomy and later developed hypothyroidism.

Chapman and Evans treated twenty-two additional patients with hyperthyroidism, using larger doses averaging 40 to 50 millicuries. The dosage was based on an attempt to give 0.8 millicuries irradiation for each gram of estimated thyroid tissue. Fourteen of the twenty-two patients received one dose, three received two, and five received three doses. In two of the patients mild hyperthyroidism has persisted, and four developed myxedema. Six of the patients developed transitory symptoms of irradiation sickness.

Hamilton has pointed out that iodine in the blood averages less than one part in ten million, whereas it is concentrated in the thyroid to one part in one thousand. The thyroid thus concentrates the iodine in the blood by a factor of 10,000, and receives intensive irradiation while the rest of the body receives very little. Since the iodine is stored in the thyroid until it loses its radioactivity, there is little danger of damage to other organs.

Hamilton and Soley measured the uptake of iodine in patients by giving 24 to 100 microcuries of radioactive iodine and a total of 14 mg. of iodine in the form of sodium iodide, orally. None of the patients had received iodine before. A Geiger counter was placed over the thyroid, and the proportion of the administered dose taken up by the thyroid was calculated. Normal controls and patients with toxic goiter, nontoxic goiter, and hypothyroidism without goiter were studied.

The increased uptake of radioactive iodine in all groups in which smaller doses (6.1 micrograms) of iodine were used emphasizes the importance of avoiding dilution of the radioactive element with the stable form when it is desirable to prevent the physiologic action of flooding the tissues with the administered material. The smaller the dose of iodine that is given the more completely will this dose be taken up by the thyroid. Hamilton concluded: (1) the thyroids of patients with thyrotoxicosis retain a larger proportion of the administered radioactive iodine; (2) the thyroid can be destroyed selectively by radioactive iodine without apparent damage to the other tissues of the body; (3) accumulated iodine is deposited selectively in the most hyperplastic regions of the thyroid tissue.

The ability of the thyroid in thyrotoxicosis to take up iodine is so striking that it has been suggested by Astwood that this ability might be used as a diagnostic test for hyperthyroidism. Unfortunately, it is difficult to control the patient's intake of iodine, and false impressions may be given if the patient has been taking even minute amounts of iodine in any form. From the practical standpoint, therefore, the uptake of radioactive iodine by the thyroids of patients with hyperthyroidism is not consistent enough to be of much aid in diagnosis.

Some adenomas of the thyroid take up radioactive iodine and others do not. Cope gave a tracer dose of radioactive iodine to patients before performing a thyroidectomy and then placed the removed glands on photographic plates. The radio-autograph of these showed that in some cases solitary adenomas took up most of the iodine and that the parenchyma of the gland took up almost none and was physiologically resting. In other cases the reverse was true, and the parenchyma took up nearly all of the radioactive iodine, while the adenoma was inactive and took up none.

Other physiologic studies of the thyroid conducted with radioactive iodine have done little except to confirm the classic studies of Marine, made thirty years ago with the aid of nothing but simple chemical and physiologic methods. It has been shown that thiouracil feeding depresses the ability of the thyroid to concentrate I^{131}, and that the amounts of I^{131} converted in the gland to thyroxin and diiodotyrosine are similarly depressed. Both the iodine-concentrating capacity and the amounts of radioactive thyroxin and radioactive diiodotyrosine formed in the thyroids are restored to normal two weeks after withdrawal of thiouracil. Astwood found that the thyroids of patients under treatment with thiouracil began to regain power to concentrate iodine within twenty-four hours of the last dose of thiouracil.

If sufficient radioactive iodine were given there is little doubt that hyperthyroidism could be controlled in all cases. Since the iodine is taken up so promptly by the thyroid and stored there until most of its radioactivity is gone, there is little reason to suppose that significant damage to kidneys, bone marrow, or other organs can be produced. Yet the thyroid epithelium is not only damaged but destroyed by the intense irradiation.

There has been some apprehension that such intensive irradiation eventually will result in malignant degeneration of the damaged thyroid. X-ray therapy for benign diseases of the thyroid or other glands has not resulted in malignant change, but the dosages used have been much lower. There does not appear to be any tendency for new carcinomas of the uterus to develop in patients treated by intensive irradiation for either benign or malignant disease of the uterus. Experience with radium workers who developed sarcoma of the bone as a result of long exposure to minimal irradiation is not necessarily applicable to the situation in the thyroid when intensive irradiation is given over a short period of time. The irradiation of I^{131}, moreover, is almost all beta irradiation of short penetration, and there is little clinical or experimental evidence that these rays are carcinogenic except in excessive dosages or when given over a long period of time.

Nevertheless, since safe and effective means of treatment for hyperthyroidism are now available, since hyperthyroidism usually occurs in young adults, and since our experience with radioactive iodine extends only over a period of a few years, it seems safer, for the present, to reserve the use of radioactive iodine for the treatment of older patients or of those with special complications. Among these complications are intolerance to the antithyroid drugs, recurrent hyperthyroidism after thyroidectomy, or hyperthyroidism resistant to or recurrent after treatment with the antithyroid drugs. It is quite likely that experience will show that radioactive iodine has no untoward local or systemic effects, but until this is established by the test of time, it may be unwise to recommend its use in the treatment of uncomplicated hyperthyroidism in young adults. Since the uptake of iodine by any given gland is unpredictable, it is probably best to treat the patient according to the method of Soley with small doses, not exceeding 5 millicuries, repeated at monthly intervals until the hyperthyroidism is completely controlled. This method not only allows one to feel his way and treat the disease in accordance with its response, but it minimizes the danger of producing hypothyroidism by overtreatment. The use of small doses, moreover, insures a maximum pick-up and storage of radioactive iodine by the thyroid and to a large extent eliminates the danger of producing untoward effects on tissues other than the thyroid. Since the full effect of a single dose of radioactive iodine may not become apparent for three or four months, it is wise to proceed slowly.

Results of Treatment of Hyperthyroidism with Radioactive Iodine

During the past nine months fifty patients with hyperthyroidism have been treated with I^{131} at the Cleveland Clinic. One patient died of a cerebral accident a few weeks after treatment and one patient has not returned for observation. Twenty-six patients have been treated too recently to allow evaluation of results. The other twenty-two have been followed for from three to ten months.

Graves' Disease. Twelve of the twenty-two followed patients had Graves' disease. One patient is much improved after two small treatments totalling 6 millicuries and has received a third treatment. In the remaining eleven cases the hyperthyroidism is completely controlled after one or two treatments.

In six of the patients with Graves' disease the hyperthyroidism has been completely controlled by one treatment, the average dose in these cases being 5 millicuries. One patient, with a large twice recurrent goiter and moderate hyperthyroidism, was given an initial dose of 8 millicuries. Two months after treatment the basal metabolic rate was minus 4 per cent and the patient was well. Four months after treatment the basal metabolic rate was minus 30 per cent and the patient had symptoms of hypothyroidism. In the other five the basal metabolic rate has fallen to normal, the symptoms are completely controlled and the patients are well. In the one case in which auricular fibrillation was present it reverted to normal rhythm.

In five cases a second dose of I^{131}, making a total dose of 8 millicuries, was required to effect a cure. All of these patients are well and hypothyroidism has not developed. In general the patients who have required a second dose are those whose hyperthyroidism is more severe, the basal metabolic rate in all but one of these patients being above plus 50 per cent. The dosage required to effect a cure has not correlated closely with the size of the gland. Some of the patients who required the largest doses had small glands and vice versa.

In two cases, glands whose estimated weight was 80 to 100 gm. before treatment are no longer palpably enlarged. The consistency and size of the remaining thyroid are normal. In all cases the size of the gland has decreased by at least 30 per cent and in several the thyroid is no longer palpable. There have been no changes to suggest that the thyroid is fibrosed, sclerosed, or fixed by adhesions.

It is apparent that radioactive iodine is a simple and effective treatment of Graves' disease, either primary or recurrent after thyroidectomy. Eleven out of twelve patients have been cured by one or two treatments and the only complication has been the development of hypothyroidism in one case. The twelfth patient is much improved and is still under treatment (Table I).

Nodular Goiter with Hyperthyroidism. Ten patients with nodular goiter with hyperthyroidism have been treated with I^{131} and followed for at least three months. One patient died of a cerebral hemorrhage a few weeks after treatment. In only three of the other nine has the hyperthyroidism been completely controlled by the first one or two treatments. The patients who are well were given doses totalling 12 to 25 millicuries following which the basal metabolic rate fell from plus 40 to normal.

The other six patients are improved and are still under treatment. The average basal metabolic rate of this group has fallen from plus 51 to plus 23. Two have had only one treatment and four have had two. The average total dosage is 10.9 millicuries. Even the patients with small nodular goiters have not all responded well to treatment.

The patients with nodular goiters are now being given much larger doses to see if the hyperthyroidism can be controlled in this way. In two cases, the estimated weight of large nodular goiters has decreased by from one-third to one-half and the patients have commented on the diminution in the size of their goiters. But even in these cases the hyperthyroidism often has persisted. In most cases there is little change in the size of the gland.

It is apparent that hyperthyroidism associated with nodular goiters is more difficult to control than is that of Graves' disease, that much larger doses of radioactive iodine are required, and that the enlargement of the thyroid does not melt away as readily as does the goiter of Graves' disease. From this experience I am not convinced that radioactive iodine will be an effective treatment for all cases of nodular goiter with hyperthyroidism. Unless larger doses prove to be more effective,

Table I. Graves' Disease

Age	B.M.R. before treatment	Size of gland before treatment	Number of treatments	Total dose	Time since first treatment	B.M.R. after treatment	Size of gland after treatment	Comments and clinical result
47	+27	*gm.* 80	1	*mc.* 8	*mo.* 4	−30	Not palpable	Hyperthyroidism recurrent twice after operation. 2 mo. after. treat. B.M.R. + 3. Hypothyroidism in 4 mo. B.M.R. −30.
52	+70	60	1	5	4	+13	40 gm.	Hyperthyroidism recurrent after operation. Clinical cure.
57	+60	30	2	6	4	−8	Not palpable	Clinical cure.
51	+55	55	2	10	10	−1	Not palpable	Clinical cure.
44	+33	60	1	5	3	−12	Not palpable	Hyperthyroidism recurrent after operation. Clinical cure.
33	+28	40	2	6	4	+30	30 gm.	Hyperthyroidism recurrent twice after operation and recurrent after adequate control with propylthiouracil. B.M.R. + 28 before treatment while taking propylthiouracil. Striking clinical improvement but still under treatment.
55	+24	75	1	4	3	+12	Not palpable	Hyperthyroidism recurrent after operation. B.M.R. before treatment + 24 while taking propylthiouracil. Clinical cure.
47	+72	100	2	15	4	+8	Barely palpable	Clinical cure.
45	+48	75	1	5	3	−14	Not palpable	Clinical cure.
55	+79	50	2	8	4	+17	Not palpable	Clinical cure. Auricular fibrillation reverted to normal rhythm.
56	+33	35	2	10	3	+7	35 gm.	No clinical evidence of hyperthyroidism, but hypertension persists.
37	+35	75	1	4	3	+6	50 gm.	Hyperthyroidism recurrent after operation. Clinical cure.
Av. 48	Av. +47	Av. 61	Av. 1.5	Av. 7.2	Av. 4	Av. +2	Av. 28 gm. Not palpable considered 20 gm.	

thyroidectomy after preparation with propylthiouracil will remain the preferred treatment (Table II).

Technic of Treatment with I^{131}. The treatment of hyperthyroidism with radioactive iodine is extraordinarily simple from the standpoint of both patient and physician. After the diagnosis is established the dose is prescribed and the patient is referred to the physicist. The proper dosage is then measured out and administered in a half glass of water. Sometimes the patients say it has a salty taste, sometimes they believe it tastes faintly of iodine, and sometimes no taste is noted.

There has been no reaction to the treatment in the dosages used. In no case has radiation sickness or symptoms of local irritation occurred. There has been no exacerbation of the hyperthyroidism. The beneficial effects are usually noted in about a week, and at the end of two months the full effects usually are apparent.

It is not necessary for the patient to be admitted to the hospital. From two to eight hours after administration of the iodine the amount of radioactive material concentrated in the thyroid is measured with a Geiger counter. In patients with hyperthyroidism this averages about 50 per cent of the administered dose. The patient then goes home and requires no further treatment for two months. The metabolism is rechecked at the end of two months, and if it is still elevated or if there is clinical evidence of residual hyperthyroidism a second dose is given. If the residual hyperthyroidism is mild it is safer to give a very small dose, or to defer treatment for two more months. The amount of the second dose is based on the patient's reaction to the first. If the basal metabolic rate has fallen from plus 60 to plus 30 with 4 millicuries, a second dose of 4 millicuries should suffice to effect a cure. If the basal metabolic rate has fallen only from plus 60 to plus 50 the dose might be increased to 6, or, if the patient's condition demands prompt control of the hyperthyroidism, even to 8 millicuries. If the basal metabolic rate has fallen from plus 60 to plus 20, 2 millicuries should suffice.

The average initial dose for patients with mild to moderate

Table II. Nodular Goiter with Hyperthyroidism

Age	B.M.R. before treatment	Size of gland before treatment	Number of treatments	Total dose	Time since first treatment	B.M.R. after treatment	Size of gland after treatment	Comments and clinical result
76	+30	*gm.* 200	2	*mc.* 25	*mo.* 4	+3	*gm.* 75	Remarkable diminution in size of large nodular recurrent goiter with hyperthyroidism. Clinical cure.
52	+33	100	2	11	6	+18	65	Advanced hydronephrosis with uremia. Blood urea 80. Solitary adenoma with moderate hyperthyroidism well controlled clinically but B.M.R. still + 18 and urea still 80.
61	+50	80	2	5	2	+35	80	Clinical improvement but residual hyperthyroidism persists and is under treatment.
62	+78	60	2	11	4	+42	60	Cardiac decompensation with little clinical evidence of hyperthyroidism. Pulse 60. Hyperthyroidism apparently controlled but decompensation persists.
70	+77	45	2	10	4	+41	25	Clinically improved. Still under treatment.
46	+48	75	1	6	2	+28	50	Clinically improved. Still under treatment.
53	+56	100	2	12	4	+8	100	Clinical cure.
71	+30	350	2	14	4	+24	225	Clinically improved. Still under treatment.
61	+26	30	1	4	4	+16	30	Questionable hyperthyroidism. Advanced arteriosclerosis. No clinical improvement.
Av. 61	Av. +48	Av. 115	Av. 1.8	Av. 10.9	Av. 4	Av. +24	Av. 80	

hyperthyroidism is 3 to 4 millicuries, and that for patients with severe hyperthyroidism 4 to 6. In general we have increased the dose a little in patients with large glands and decreased it a little in those with small ones. The aim of treatment is to give an initial dose small enough to be certain not to induce hypothyroidism. Four millicuries appears to be quite safe in the average patient with Graves' disease.

If the initial dosage is planned so that it provides one-half the total dosage that will be required to effect a cure, approximately one-quarter of the patients treated will be cured by the single dose. The remaining three-quarters can be treated again in doses determined by the patient's reaction to the first dose. The only case in which hypothyroidism was induced occurred early in our experience when we were attempting to effect a cure in one treatment.

This method of treatment is empiric, but safe, effective, and simple. It avoids the expense and delay involved in giving tracer doses and in studying the urinary excretion of iodine. If the patients are informed in the beginning that two treatments probably will be required, they do not anticipate an immediate cure and cooperate well in returning for observation.

Evaluation of Results. From the economic standpoint radioactive iodine has advantages over both thyroidectomy and prolonged treatment with propylthiouracil. Hospitalization, prolonged medication, and frequent observation are not required. The actual cost of the I^{131} used in the average treatment is less than ten dollars if the handling charge and costs of measuring and administering it are disregarded.

Since the radiation given by this empiric method of treatment is so controlled that only as much as is necessary to control the hyperthyroidism is given, there would seem to be little danger of late ill effects. Radioactive iodine therefore bids fair to become the preferred treatment for all patients with Graves' disease and may be of value also in selected cases of nodular goiter with hyperthyroidism.

Bibliography

1. Astwood, E. B., and Stanley, M. M.: Use of radioactive iodine in study of thyroid function in man. West. J. Surg. *55:* 625–639 (Dec.) 1947.
2. Chapman, E. M., and Evans, R. D.: Treatment of hyperthyroidism with radioactive iodine. J. A. M. A. *131:* 86–91 (May 11) 1946.
3. Cope, O., Rawson, R. W., and McArthur, J. W.: Hyperfunctioning single adenoma of thyroid. Tr. Am. A. Study Goiter, 1942–1946, 156–174, 1946.
4. Franklin, A. L., Lerner, S. R., and Chaikoff, I. L.: Effect of thiouracil on formation of thyroxine and diiodotyrosine by thyroid gland of rat with radioactive iodine as indicator. Endocrinology *34:* 265–268 (April) 1944.
5. Hamilton, J. G., and Soley, M. H.: Studies in iodine metabolism of thyroid gland in situ by use of radio-iodine in normal subjects and in patients with various types of goiter. Am. J. Physiol. *131:* 135-143 (Nov.) 1940.
6. Hamilton, J. G.: Use of radioactive tracers in biology and medicine. Radiology *39:* 541–572 (Nov.) 1942.
7. Hertz, S., and Roberts, A.: Radioactive iodine as indicator in thyroid physiology; iodine collection as criterion of thyroid function in rabbits injected with thyrotropic hormone. Endocrinology *29:* 82–88 (July) 1941.
8. Keston, A. S., Ball, R. P., Frantz, V. K., and Palmer, W. W.: Storage of radioactive iodine in metastasis from thyroid carcinoma. Science *95:* 362–363 (April 3) 1942.
9. Leiter, L., Seidlin, S. M., Marinelli, L. D., and Baumann, E. J.: Adenocarcinoma of thyroid with hyperthyroidism and functional metastases; studies with thiouracil and radio-iodine. J. Clin. Endocrinol. *6:* 247–261 (Mar.) 1946.
10. Marine, D.: Etiology and prevention of simple goiter. Medicine *3:* 453–479 (Nov.) 1924.
11. Means, J. H.: The Thyroid and Its Diseases. Being an Account Based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital. Philadelphia: J. B. Lippincott Co., 1937.
12. Portmann, U. V.: Personal communication.
13. Seidlin, S. M., Marinelli, L. D., and Oshry, E.: Radioactive iodine therapy; effect of functioning metastases of adenocarcinoma of thyroid. J. A. M. A. *132:* 838–847 (Dec. 7) 1946.
14. Soley, M. H., and Mayo, C. W.: Personal communication.

Chapter 10

PREOPERATIVE MANAGEMENT OF PATIENTS WITH HYPERTHYROIDISM

The complications of hyperthyroidism, such as thyroid crises and cardiac decompensation, are difficult to treat but easy to avoid. Although the risk of thyroidectomy for hyperthyroidism may be slight, this risk can be still further reduced and almost eliminated if the operation is deferred until the hyperthyroidism is completely controlled.

The chief factors influencing the risk of thyroidectomy are: (1) the condition of the heart, (2) the age of the patient, (3) the response of the pulse curve to preoperative treatment, and (4) the degree of extension of the goiter into the thorax.

Of lesser importance are the presence of a rapid pulse rate at the time of the patient's entry into the hospital, a history of great loss of weight, or the finding of a high basal metabolic rate. Except in special instances, the prognosis is not materially altered by the duration of the disease.

Factors Influencing Operative Risk

Heart Disease. The presence of cardiac decompensation, auricular fibrillation, valvular heart disease, or severe myocarditis increases the risk of thyroidectomy in a patient with hyperthyroidism. Over a period of twenty years the mortality rate in patients with auricular fibrillation was nearly seven times as high as when this complication was not present.

Age. Next in importance to the condition of the heart is the age of the patient. In patients over 60 years of age, not only is the myocardium apt to be damaged by the vascular changes, but the margin of safety in liver function is diminished. Pneumonia is a constant threat to the feeble patient in advanced years. Hence it is not surprising to find that the postoperative mortality rate in patients over 60 years of age in our series was more than four times as high as in patients under 60. Penicillin has reduced this risk by reducing the danger of pneumonia.

Pulse Curve. Although the pulse rate at the time of entry to the hospital does not bear any striking relationship to the postoperative mortality rate, the response of the pulse curve to preoperative treatment has a definite bearing upon the operative risk. Thus the prognosis of a patient who enters the hospital with a pulse rate of 160 is good, provided the pulse curve falls satisfactorily before the operation. But a patient whose pulse rate is 120 at the time of entry and ten days later is still 120 may not be a good operative risk. This type of pulse curve was more than five times as common in the group of patients who died after operation as in those who survived. The physiologic indications of a remission of hyperthyroidism are a falling pulse curve and a gain in weight. When the disease is entering a remission, severe thyroid reactions are not apt to occur, but when, in spite of iodine and bed rest, the hyperthyroidism remains stationary or increases in severity, a thyroid crisis may follow. (Fig. 30.)

Intrathoracic Goiter. When hyperthyroidism was associated with an intrathoracic goiter, the risk of operation was nearly four times as great as in patients in whom the goiter did not extend into the thorax. Since the average age of the patients with intrathoracic goiter in this series was 50, it is quite possible that age as well as the mechanical factors involved in the removal of an intrathoracic goiter may be a potent factor in increasing the risk.

Duration of Hyperthyroidism. The relation of operative risk to duration of symptoms has not been striking. The mortality rate in patients having hyperthyroidism longer than two years was only one and one-half times as great as in the patients having hyperthyroidism for less than two years. The severity of the postoperative reaction of the pulse and temperature depends to a large extent on the severity of the hyperthyroidism at the time of operation. It is true that longstanding, severe hyperthyroidism can result in great loss of weight, in impairment of liver function, and in a serious depletion of the patient's resistance to intercurrent infection, especially pneumonia. There is, however, little evidence to indicate that the myocardium suffers any specific damage (Friedberg and Sohval) as a result of longstanding hyperthyroidism or that the heart is less able to cope with a postoperative thyroid crisis of a given severity, whether the disease is of short or of long duration. The majority of patients with hyperthyroidism of long duration suffer from a relatively mild form of the disease and can withstand the minimal postoperative reaction which occurs in patients with mild hyperthyroidism.

Loss of Weight. In older patients, a history of loss of considerable weight may be an indication of an unfavorable prognosis, but in younger patients, the risk of operation does not seem to be materially increased by loss of weight up to one-fourth of the total body weight. The mortality rate was approximately three times as high in those patients who had lost over twenty-five pounds of weight as in those who had lost less than this amount, the greatest mortality occurring in the oldest patients.

Basal Metabolic Rate. The highest operative mortality rate occurs in elderly patients. This group, consisting largely of patients with nodular goiters and cardiac manifestations of hyperthyroidism, do not, as a rule, have as high basal metabolic rates as the younger patients with diffuse goiters and relatively acute hyperthyroidism. The risk of thyroidectomy is dependent not so much upon the severity of the hyperthyroidism as upon the ability of the myocardium and of the individual as a whole to cope with the postoperative reaction. For example, statistically the risk of operation on patients with basal metabolic rates above plus 50 per cent is only three times as great as on those whose basal metabolic rates are between plus 15 and plus 50 per cent. If, however, the basal metabolic rate, along with the pulse curve, fails to fall in response to preoperative treatment and remains excessively high (above plus 80 per cent) the operative risk is still considerably increased.

Special Types of Patients. There are several types of patients who present special risks. The first type is the uncooperative, high-strung individual, who is especially difficult to manage if she does not understand English. When hyperthyroidism develops in such a patient, her innate emotionalism is tremendously exaggerated and makes her apprehensive, uncooperative, and apt to develop a postoperative thyroid crisis.

The second type is the patient with "burned-out" hyperthyroidism, so aptly described by Lahey as the patient with "apathetic" hyperthyroidism. This type of patient is generally over 40 years of age, does not appear to be actively stimulated, and often has only a mildly elevated basal metabolic rate. As a rule the hyperthyroidism is of long duration, and it is in this rare type of patient that a history of longstanding hyperthyroidism increases the risk of operation. In the patient shown in Fig. 28 a mild thyroid crisis was precipitated by the patient falling out of bed.

When a patient with hyperthyroidism becomes delirious, it is unwise to attempt any surgical procedure.

Preoperative Treatment

Diet. When a patient with hyperthyroidism has a basal metabolic rate of plus 100 per cent the basal caloric requirement is increased by 100 per cent over the requirement of a person of equal weight with a normal metabolism. When a sufficient caloric intake is not provided, such a patient must find fuel for the demands of metabolism and in so doing will oxidize her own body. The glycogen of the liver is depleted, fat disappears rapidly, and weight is lost with amazing rapidity.

Unless a concentrated high caloric diet is given, it is often impossible for a patient with a high basal metabolic rate to eat the bulk of food necessary to maintain her weight. The diet should contain large amounts of carbohydrate in order to replenish the depleted glycogen reserves of the liver. In addition, since the serum proteins tend to be lowered in severe hyperthyroidism, the diet should be relatively high in protein.

States of mental confusion may follow restriction of diet.

The superior thyroid artery of a patient with severe hyperthyroidism and a basal metabolic rate of plus 96 per cent had been ligated. Through a misunderstanding of orders, he was put on a limited diet such as is given to patients after abdominal operations. There was no immediate reaction to the surgical procedure, but six days later the patient became delirious, refused food, exhibited a rising pulse rate and temperature, and for ten days was critically ill. The usual treatment with iodine and the continuous intravenous administration of a 5 per cent solution of glucose was given, but the symptoms did not subside until a daily intake of 6000 calories was given by feeding through a nasal tube.

Sedation. Sedatives are valuable during the preoperative period. Bromides or codeine is of more value than barbiturates. Occasionally, especially in older patients or in cases of extreme hyperthyroidism, barbiturates will excite the patient or may even precipitate a maniacal state. The barbiturates and bromides are contraindicated in the presence of mental confusion because the deliriums may have been due to the prolonged use of these drugs before the patient entered the hospital.

Physiologic Considerations. Fear may induce a thyroid crisis. I have seen a fatal thyroid crisis initiated by draping a patient for operation and administering the lightest gas oxygen analgesia, although the operation was cancelled because of the patient's emotional reaction (Fig. 31, page 74).

Morphine is a useful adjunct to operations performed under local anesthesia. The tolerance to morphine, as well as to basal anesthetics and to the majority of depressant drugs, varies in direct proportion to the basal metabolic rate of the patient. When the metabolism is high, the drugs are metabolized quickly without exerting their full pharmacologic effects. The amount given should be based on the basal metabolic rate, the weight, and the age of the patient. It varies in adults from $\frac{1}{6}$ to $\frac{1}{2}$ grain.

Digitalis. Before operation, it is advisable to digitalize patients in whom there is evidence of cardiac decompensation, patients with auricular fibrillation, and patients with valvular or myocardial heart disease. In addition, digitalis may be given to elderly patients with vascular disease, in whom the incidence of postoperative auricular fibrillation is relatively high.

Bibliography

1. Friedberg, C. K., and Sohval, A. R.: Occurrence and pathogenesis of cardiac hypertrophy in Graves' disease. Am. Heart J. *13:* 599–618 (May) 1937.

Chapter 11

ANESTHESIA FOR THYROIDECTOMY

Choice of Anesthesia

Before the advent of the antithyroid drugs, it was necessary to operate on patients handicapped by active hyperthyroidism. At this time the surgeon was concerned chiefly with the physiologic effects of anesthesia, emotional stimuli, and surgical trauma. Today these considerations, except in the case of the aged or the infirm, are of less importance. The organism is no longer handicapped by the presence of uncontrolled hyperthyroidism. The risk of thyroid crisis or of a fatality incident to the exacerbations of hyperthyroidism need no longer be considered. Emphasis can now be placed upon the comfort of the patient and the convenience of the surgeon.

The ideal anesthesia from the standpoint of the basic physiology of the handicapped patient is *local infiltration* or *cervical block* following premedication with morphine, ¼ grain, and one of the quick-acting barbiturates, such as seconal, 1½ to 3 grains. However, from the standpoint of the patient's wants and comfort, local or regional block anesthesia leaves much to be desired. A cervical block cannot be accomplished without multiple needle pricks and some discomfort, and even after a satisfactory block there may be sensations of pressure or of pulling and occasionally even of dull, deep pain. Local anesthesia has the same disadvantages and probably affords less complete anesthesia than the block. A combination of the two, with local infiltration of the deeper structures, still may leave the conscious patient tense, nervous, and aware of uncomfortable sensations, sometimes interpreted as pain.

If a basal anesthesia such as *avertin* is added to the local or regional block, a satisfactory amnesia may be obtained, but a certain number of these patients, although subsequently remembering nothing, will struggle and squirm and render the operation difficult from the standpoint of the surgeon. If deeper basal anesthesia is used the patient may be unduly depressed, and anxiety regarding respiration may be aroused. The zone of deep basal anesthesia is too narrowly separated from the zone of dangerous depression to render it entirely safe.

Pentothal has been used in conjunction with regional anesthesia and is often satisfactory in that its level can be controlled, amnesia is obtained, and recovery is prompt. But pentothal predisposes to the development of laryngospasm. Laryngospasm is not serious when the operation is one which cannot jeopardize the respiratory exchange, but when there is a possibility of a mechanical distortion of the larynx or trachea, or when one or both recurrent laryngeal nerves may be temporarily paralyzed, it may be impossible to decide whether the obstruction to respiration is the result of uncomplicated laryngospasm or of mechanical factors that demand tracheotomy. If under these circumstances tracheotomy is done early it may have been done unnecessarily for laryngospasm. If done late, it may be too late to resuscitate a patient with mechanical obstruction of the larynx or trachea. Pentothal anesthesia is therefore not devoid of danger.

A general anesthetic with *nitrous oxide*, *oxygen*, and *ether*, or with *cyclopropane* is satisfactory in most cases but again raises the problem of respiratory obstruction. The crowing respiration of a patient in the early stages of ether anesthesia and the cyanosis that occasionally occurs at this stage are accepted, in most general surgical operations, as undesirable but not serious complications. When this type of respiration occurs during an operation on the thyroid, it is difficult to decide whether it is caused by spasm or by mechanical obstruction.

Under general anesthesia there is usually hyperventilation and, unless open drop ether is used, there is a tendency for the pressure of the gas machine to raise the venous pressure and cause increased bleeding from the vessels of the neck. This can be avoided to a large degree by tracheal intubation.

Intratracheal nitrous oxide oxygen anesthesia, induced and supplemented by pentothal or intratracheal cyclopropane, gives a quiet controlled anesthesia, satisfactory to both patient and surgeon, and results in little increase in bleeding. If an anatomic technic of thyroidectomy is followed there is little to be gained by having the patient cough or speak after removal of the first lobe. The surgeon knows where the recurrent nerve is and knows that it either is intact or has been sacrificed. The test of speaking was never accurate, because many patients with a fresh injury of the nerves maintain a satisfactory voice. My preference in patients under 55 years of age who present no special surgical risk is intratracheal anesthesia.

Intubation of the trachea probably increases the amount of postoperative mucus and increases any tendency to edema of the larynx. This may predispose either to postoperative pulmonary complications or, in the event of an injury to the recurrent nerve, to the development of stridor and respiratory obstruction. These disadvantages and the increased depression incident to a general anesthetic are outweighed by the greater comfort afforded the patient and the increased ease of operation. Yet when the patient is old or is a poor surgical risk, the physiologic considerations cannot be disregarded, and in this group cervical block is the anesthesia of choice. Fortunately most older patients are aware of their infirmities, are afraid of general anesthesia, and welcome the suggestion of a local or regional block.

The main advantage of a good cervical block over local infiltration is that the block is performed first. The patient is informed that the blocking will cause discomfort but that after that there will be no pain. He regards the block, not as a part of the dreaded ordeal of operation, but as a preliminary inconvenience that he must accept. After the block there is a rest period in which the patient can relax and then, to his gratification, when the operation begins he feels nothing.

When the surgeon injects novocain locally during the course of an operation, it is hard for the patient to believe that it is not the operation itself that he is feeling. He interprets the needle pricks and the sensations of the novocain distending the subcutaneous tissue as part of the removal of the thyroid, and it is difficult to convince him that the surgeon has not started to operate before the anesthetic has had its effect. He may become panicky and uncooperative and interpret all sensations as pain. These considerations, the fact that anesthesia in a good block is more complete than with local infiltration, and the advantage of not having cleavage planes obscured by the edema of the anesthetic solution, give a margin of superiority to the deep cervical block.

Basal Anesthesia. In elderly patients pneumonia is the most common cause of death after thyroidectomy. General anesthetics and basal anesthesia tend to depress respiration, to abolish the cough reflex, and to lower the patient's resistance to pneumonia. In the aged, the depression incident to a basal or general anesthesia may be the deciding factor as to whether or not a fatal pneumonia will develop. Basal anesthesia is therefore contraindicated in patients over 45 years of age.

A patient with a low or with a normal basal metabolic rate will be analgesic (although generally not completely unconscious) after the administration of avertin in a dosage of 50 or 60 mg. per kilogram of body weight. One with a basal metabolic rate of plus 40 per cent will require 70 mg. per kilogram for a similar effect, while patients with higher metabolic rates may require even larger doses. If a middle ground is to be reached between absence of analgesic effect on the one hand and undue depression on the other, the amount of anesthetic to be given should be varied in accordance with the basal metabolic rate.

In a strong young individual the margin of safety is so great that the depression induced by a basal anesthetic can be disregarded. But even in young patients profound narcosis is undesirable whether it be induced by inhalation anesthesia or by any of the various drugs used as basal anesthetics. Occasionally in the course of a thyroidectomy, particularly when it is necessary to deliver a retrotracheal extension of the gland, a stridor may develop even in the absence of injury to the recurrent laryngeal nerves. When this occurs, a patient who is conscious is better able to maintain respiratory exchange than is a patient who is under deep anesthesia. The same principle applies as in the surgical treatment of a deep abscess or cellulitis of the neck, in which case it is widely recognized that a general anesthetic may result in fatal respiratory obstruction. Tracheotomies will be avoided by performing thyroidectomies under intratracheal, regional, or local anesthesia. In recurrent goiters in which one of the laryngeal nerves is paralyzed before operation, local or block anesthesia is safer than intratracheal because it does not traumatize the larynx or increase postoperative laryngeal edema.

Technic of Anesthesia

Local Anesthesia. If the neck is pinched hard before the insertion of the first small hypodermic needle and if the first injection is carried out slowly, the procaine can be infiltrated practically without sensation. The anesthetist is always careful to warn the patient to expect this initial pinch. A 0.75 per cent solution of procaine is used, and epinephrine is never added when hyperthyroidism is present.

The first wheal is placed in the midline halfway between the cricoid cartilage and the suprasternal notch (Fig. 39). From this point the anesthetic is infiltrated into the subcutaneous tissue along the line of the proposed incision. The injection is carried out slowly and care is taken not to allow the point of the needle to come through again to the sensitive skin. Painful intracutaneous infiltration is avoided, the solution being injected well beneath the skin. Sufficient time is allowed for the procaine to anesthetize each area before a second needle is inserted. When the line of the proposed incision has been infiltrated thoroughly, the injection is carried upward and downward at the extremities of the transverse area of infiltration. In this way the nerves traversing the neck from the lateral to the medial aspects are anesthetized. The central portion can then be infiltrated quickly and without pain because the greater part of the innervation of this area has already been anesthetized.

After the skin incision has been made and the flaps elevated, the muscles are infiltrated with procaine so that the patient will not be conscious of pressure sensations when the muscles

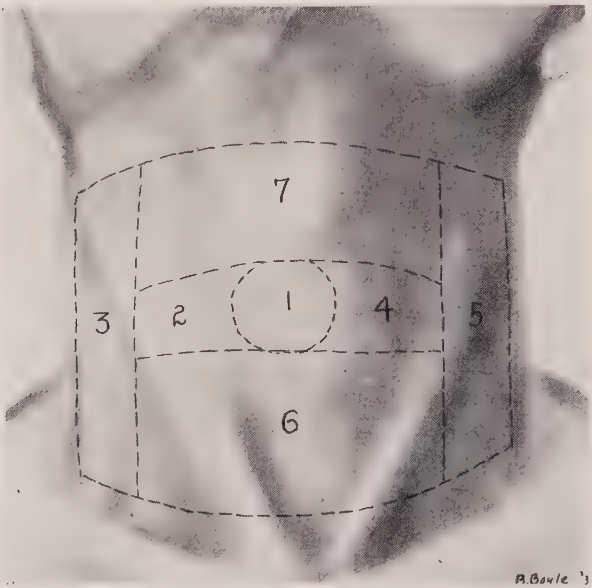


Fig. 39. The numbered areas are infiltrated in sequence.

are retracted to expose the gland. Manipulations of the thyroid gland usually cause little sensation, and the injection of a small amount of procaine around the capsule, especially at the superior pole, is all that is necessary during the actual resection of the gland. Subanesthetic doses of pentothal may be used judiciously, if necessary, to produce analgesia.

When the procedure is carried out in this manner, the patient is awake and talking with the anesthetist during the entire operation. When the patient is conscious, she is better able to adjust herself to distortion of the larynx and trachea and can maintain an adequate respiratory exchange with greater ease than can a patient who is relaxed under a general anesthesia. Following operation the patient is conscious and free of depression.

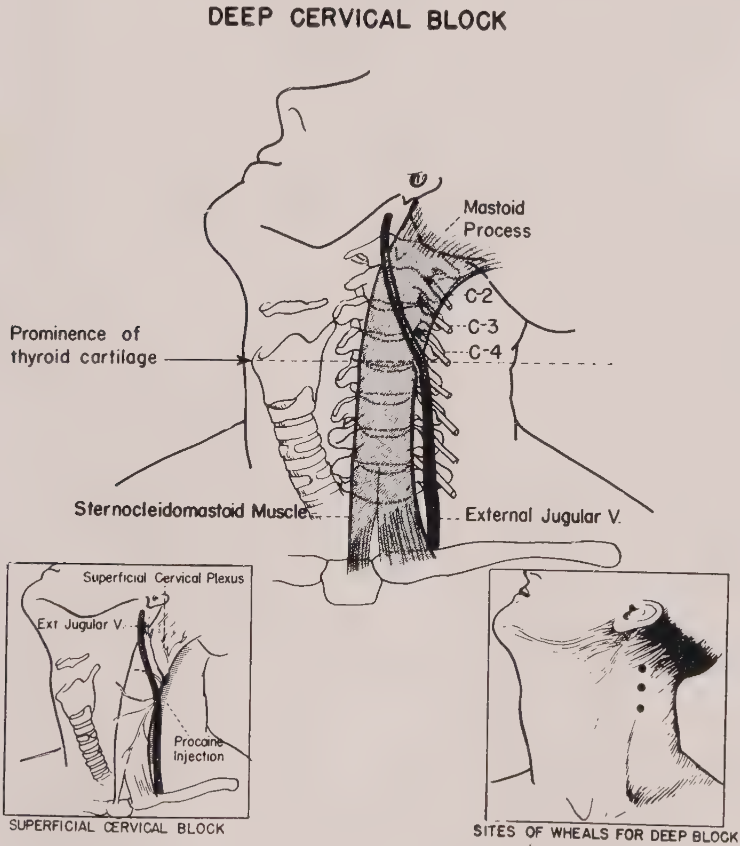


Fig. 40.

*Cervical Block Anesthesia for Thyroidectomy.** Both deep and superficial cervical blocks are needed to provide anesthesia for thyroidectomy. The deep block is done by injecting the second,

* Courtesy of Donald E. Hale, M.D., Department of Anesthesiology, Cleveland Clinic Hospital.

third, and fourth cervical nerves, and is followed by injection of the superficial cervical plexus (Fig. 40).

Equipment

1. Towels for draping field
2. Towel clip
3. Sponge forceps
4. Skin antiseptic
5. Needles
   (a) Two 24 gauge ¾ inch hypodermic
   (b) Four 22 gauge 2 inch hypodermic
   (c) Two 22 gauge 2½ inch hypodermic
6. Syringe, 10 cc. Luer lock control
7. Beaker, 100 cc.
8. Medicine glass
9. Metycaine solution 5 cc. of 20 per cent
10. Physiologic saline solution

The anesthetic solution is prepared by mixing, in the beaker, the contents of the ampule of metycaine (5 cc. 20 per cent) with 95 cc. of physiologic saline solution. Twenty cubic centimeters of this solution are added to an equal quantity of physiologic saline solution in the medicine glass to make a ½ per cent solution of metycaine.

After preparation of the field, the face is turned away from the side to be blocked, and wheals are raised along the posterior border of the sternocleidomastoid muscle. The uppermost of these wheals is placed 1 finger's breadth below the mastoid process. The second wheal is a finger's breadth below this, and the third, another finger's breadth below. The third wheal is on a perpendicular line dropped from the tip of the thyroid cartilage and is approximately at the junction of the external jugular vein with the posterior margin of the sternocleidomastoid muscle. Through the upper wheal is passed one of the 2½-inch needles. It is directed downward, and its point is made to come in contact with the tip of the transverse process of the second cervical vertebra. This is the most superficial bone point in the region, and is reached ordinarily at a depth of about 1 inch beneath the skin. When properly placed, this needle is left in position and a 2-inch needle is passed through the second wheal. This needle passes parallel to the first and extends also slightly downward in order to make contact with the transverse process of the third cervical vertebra. Through the third wheal is passed another 2-inch needle, which comes to rest in contact with the transverse process of the fourth cervical vertebra. Through each needle is then injected 7 cc. of 1 per cent metycaine solution. During the injection the point of the needle is kept in contact with the bone and aspiration is carried out before and during the injection in order to avoid intravascular infusion of the solution. Each needle is withdrawn as the injection is completed. Following the deep cervical block, the superficial plexus is blocked with ½ per cent metycaine solution infiltrated into the subcutaneous tissue in the middle third of the area along the posterior border of the sternocleidomastoid muscle. The procedure is completed by turning the patient's head to the opposite side and repeating these injections on the other side of the neck.

This block ordinarily affords satisfactory anesthesia for thyroidectomy. It may have to be supplemented by local anesthesia infiltrated in the region of the upper pole. If necessary, the block may be supplemented by light pentothal analgesia.

Chapter 12

ANATOMY OF THE THYROID*

The normal thyroid gland is composed of numerous acini lined with low cuboidal epithelial cells, and filled with an iodine-containing colloidal substance. The gland has a rich blood supply and a large number of lymphatic vessels drain the acini.

The weight of a normal thyroid is usually given as 30 gm., but this weight is variable and may be slightly greater in regions of endemic goiter, even in the absence of gross or histologic evidence of goiter.

The thyroid is composed of two lateral lobes and a connecting isthmus. A small pyramidal lobe extending upward from the isthmus into the thyroglossal tract is also commonly present.

The isthmus lies on the trachea just below the cricoid cartilage of the larynx, and the lateral lobes lie on each side of the trachea extending upward and downward from the isthmus. Anteriorly, the thyroid is covered by the sternothyroid and sternohyoid muscles, the former lying directly upon the loose fibromuscular capsule which surrounds the gland itself. The thyroid has little or no true fibrous capsule other than that furnished by the cervical fascia and muscles.

The lobes of the thyroid, on their posterolateral surfaces, are in close proximity to the carotid sheath. Medially, these lobes are firmly attached to the trachea. Two parathyroid glands (the number varies) lie on the posterior surface of each lobe. The parathyroid at the upper pole is inconstant in its location, but that at the lower pole can quite regularly be found along one of the branches of the inferior thyroid artery. The parathyroids may lie in the substance of the thyroid itself in the areolar tissue along the branches of the inferior thyroid artery,

---

* See illustrations under Technic of Thyroidectomy, Chapter 13.

or even in the mediastinum, but are located in the fibrous tissue of the capsule in close relationship to the small branches of the inferior arteries.

Innervation of the Thyroid

The recurrent laryngeal nerves bear an important relationship to the posteromedial aspect of the lateral lobes. Originating from the vagus, these nerves pass downward, looping around the subclavian artery on the right and the arch of the aorta on the left, and then rise in the tracheo-esophageal groove well behind the lower pole of the thyroid. As they rise higher in the neck, their location becomes more superficial, and they assume a closer relationship to the posteromedial aspect of the thyroid lobes. Their relationship to the inferior thyroid artery is variable. In about 75 per cent of the cases, the nerves pass beneath the artery. In some instances they lie in a position superficial to one branch of the artery and beneath another, or they may pass anterior to the entire artery. The nerves always lie beneath the lateral thyroid vein. I have never seen the recurrent nerve traverse the substance of the thyroid gland although it may be densely adherent to its capsule.

The recurrent nerve is closest to the thyroid and is therefore most vulnerable to injury at the point where it comes forward to enter the larynx. The ascending branch of the inferior thyroid artery lies close to the nerve at this point, and the nerve may be injured during an attempt to clamp branches of this vessel (Lahey).

The superior laryngeal nerve descends from above and divides into two branches, the external and the internal. The internal branch enters under the upper aspect of the thyroid cartilage, providing sensory innervation to the larynx, and is located so high that it is not vulnerable during a thyroidectomy.

The external branch is a small filament that descends near the superior pole of the thyroid and is distributed as a motor nerve to the cricothyroid muscle and the pharyngeal musculature. This filament lies close to the larynx but can be injured if the plane of dissection of the superior pole is carried too close to the larynx (Fig. 57, page 169). Injury of this nerve causes no demonstrable change in the function of the vocal cords but results in a lowering of the pitch of the voice and in a tendency to hoarseness. These changes may be permanent.

Blood Supply of the Thyroid

Each lateral lobe of the thyroid is supplied by two main arteries, the superior and the inferior thyroid artery. The superior thyroid artery, which is the first branch of the external carotid, leaves its parent vessel at the level of the cricoid cartilage, passes upward and medially, and then loops downward to enter the medial aspect of the superior pole of the thyroid gland. Here it gives off two main branches. The smaller is variable but often continues downward along the posterior border of the thyroid. The larger courses medially along the medial and anterior aspect of the lobe and enters the thyroid near the junction of the isthmus and later lobe. The blood supply of the pyramidal lobe is from the laryngeal artery. This vessel is a branch of the superior thyroid artery and is given off at a point well above the superior pole of the thyroid gland.

The inferior thyroid artery, arising from the subclavian, courses upward, passes beneath the carotid artery, and then descends to enter the posterolateral aspect of the gland at about the junction of the lower and middle thirds. The artery divides into an ascending branch which rises along the posterior surface of the gland, and a descending branch, which, after reaching the inferior pole, wraps around this pole and comes forward onto its anterior surface. The inferior artery is variable in size and course and is sometimes absent. Usually it is larger than the superior vessel. When absent, it may be replaced by the thyroid ima vessel.

Veins accompany the superior thyroid artery and drain into the internal jugular. The lateral thyroid vein is variable but usually is formed on the posterolateral surface of the thyroid. After traversing the gland's entire posterior surface nearly as far as the trachea, it courses laterally to the jugular vein. The thyroid ima veins are variable and descend from the region of the isthmus into the mediastinum.

Bibliography

1. Lahey. L. H.: Routine dissection and demonstration of recurrent laryngeal nerve in subtotal thyroidectomy. Surg., Gynec. & Obst. *66:* 775–777 (April) 1938.
2. Reinhoff. W. F., Jr.: New conception of some marked changes in diseases of thyroid gland. Tr. Am. A. Study Goiter 167–189, 1930.

Chapter 13

TECHNIC OF THYROIDECTOMY*

The essentials of a satisfactory technic for thyroidectomy include:

(1) Placement and closure of the incision for the best cosmetic effect.

(2) Adequate exposure of the gland.

(3) Protection of the parathyroid bodies.

(4) Protection of the recurrent laryngeal nerve.

(5) Protection of the external branch of the superior laryngeal nerve.

(6) Removal of sufficient thyroid tissue to effect a cure.

(7) Preservation of sufficient thyroid tissue to maintain normal function.

(8) Adequate hemostasis.

Position

A sand bag or pillow is placed under the shoulders, and the neck is hyperextended. The head of the table is elevated at about a 15-degree angle to decrease venous bleeding. The head should be held straight so that the scar will be symmetrical.

Incision (Fig. 41)

The incision is slightly elliptical and is placed midway between the cricoid cartilage and the sternal notch. It should be parallel to the natural wrinkles of the neck.

The neck is hyperextended during the operation causing the skin to be pulled upward. For this reason the surgeon tends to place the incision too low. When the incision is placed too

* All illustrations of thyroid technic in this chapter were modified from the original drawings by Miss Beatrice Boyle.

low it results in a conspicuous and ugly scar on or below the clavicles. If the incision is placed high the scar looks like a wrinkle, is inconspicuous, and may be almost invisible.

The incision must be symmetrical and particular care should be taken to avoid having one end higher than the other. Symmetry can be assured by marking the neck with a piece of thread held taut on the skin about 2 fingers' breadth above the clavicle on each side. The center of the proposed incision is then scratched with the scalpel to aid in accurate closure.

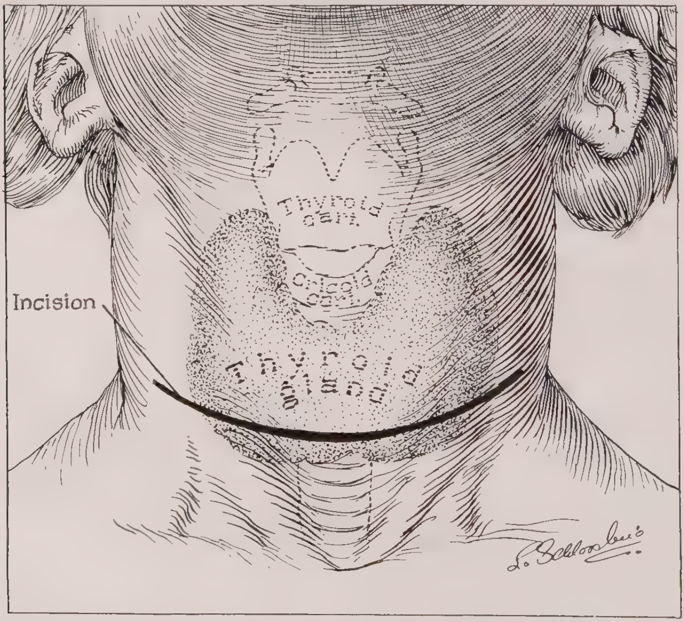


Fig. 41. Elliptical incision midway between cricoid cartilage and sternal notch and parallel to wrinkles.

After the removal of a very large goiter the skin is redundant and tends to hang down in elliptical folds which exaggerate the ellipse of the incision. A transverse incision is therefore better for large goiters. The incision should be placed relatively higher in these cases or the scar will sag down over the clavicles and be conspicuous.

Elevation of the Flaps (Fig. 42)

The skin and subcutaneous fat are divided down to the platysma and significant arterial bleeding is controlled with ligatures of No. 60 cotton. Small vessels directly under the skin may be disregarded as they stop bleeding spontaneously or are controlled by the closure. The skin of the upper flap is

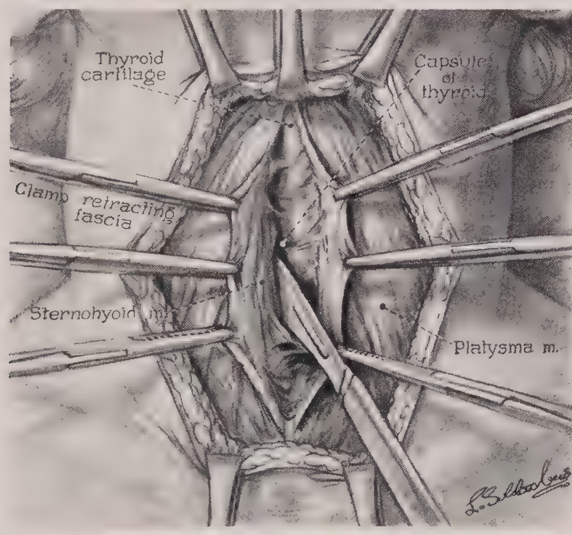


Fig. 42. Flap raised superficial to platysma upward as high as the thyroid cartilage and downward to jugular notch. The muscles are divided exactly in the midline.

then grasped with three Lahey clamps and held upward under tension. Countertraction exerted downward by an assistant facilitates the dissection.

The plane immediately superficial to the platysma muscle is avascular if an accurate sharp dissection is made. If the muscle is damaged or if the dissection is carried too close to the skin, bleeding will occur. High on each side a single vessel frequently perforates through the platysma muscle to the subcutaneous fat and to the skin. Often this is the only vessel that requires ligation. Dissection is carried up to the lower end of the thyroid cartilage. If the plane of cleavage superficial to the platysma is followed, the necessity of cutting this muscle transversely and ligating a number of vessels is avoided.

The Lahey clamps are next transferred to the lower flap and dissection is carried downward to the jugular notch. It is helpful to have the second assistant support the platysma by traction upward with a square of gauze so that the plane of cleavage is better defined and more easily followed. There is no reason to carry the dissection either above the thyroid cartilage of the larynx or below the jugular notch because the muscles of the neck insert on these structures and further dissection does not increase exposure. Nor is it desirable to raise the lateral portion of the flap any higher or lower than necessary to allow exposure of the central portion. The purpose of raising the flaps is only to enable the muscles to be separated in the midline from larynx to sternum, and the amount of skin raised should be no more than necessary for this.

Separation of Muscles (Fig. 42)

Three hemostats are placed on each side of the midline to pick up the fascia and facilitate finding the avascular midline cleavage plane between the muscles. Dissection is carried down to the capsule of the thyroid. Scissors are then inserted beneath the muscles which are separated from the underlying structures as far as the thyroid cartilage, and the fascia is cut in the midline between the muscles. If the dissection is exactly in the midline bleeding does not often occur, although sometimes there are transverse communicating branches of the anterior jugular veins which cannot be avoided. When these are present, they should be isolated and ligated without including fascia or muscle in the ligatures.

Dissection is next carried downward, still exactly in the midline, towards the sternum. Just above the sternum the veins often give off transverse branches which cause troublesome bleeding. If only the fascia is incised in the lower 1 or 2 cm. of the incision, the muscles and areolar tissues containing the branches of the veins can be separated by traction and blunt dissection, and bleeding is avoided.

In most instances, longitudinal division of the pretracheal muscles from the midpoint of the larynx down to the sternal notch will suffice to give adequate exposure. In dealing with carcinomas, intrathoracic goiters, goiters with large retrotracheal extensions, goiters with extremely high upper poles, recurrent goiters, adherent goiters, and very vascular glands on which traction cannot be exerted without risk of tearing the gland, it may be advisable to divide the muscles transversely as well. Although this may increase the pain of convalescence and may be attended by an increased tendency to the formation of serum, they should be divided without hesitation when it will facilitate exposure. Transverse division of the muscles should not be necessary in over 10 per cent of the cases.

Cleaning the Capsule

Before the lobe of the thyroid can be delivered it is necessary to remove the overlying fibers of the so-called "muscular capsule." In most cases this can be accomplished by blunt dissection, taking care to avoid the branches of the lateral thyroid vein which course over the surface of the gland. Since there are no veins in the muscle tissue it is certain that whenever the dissection enters a plane beneath veins, the wrong plane has been entered. There is an exception to this rule. Near the insertion of the sternothyroid muscle a tiny muscular branch of the superior thyroid artery leaves the main artery and, sometimes accompanied by a vein, enters the substance of the muscle. This vessel can be avoided by division of the muscle below it or it can be ligated.

After the anterior surface of the gland is cleaned of its overlying muscles and areolar tissue, attention is directed to the superior pole. Hemostats are inserted into the substance of the gland tangential to the capsule and the pole is drawn downward. If several hemostats are used simultaneously for this purpose the pull is divided and the capsule is less apt to be torn than if only a single hemostat is used. While the pole is pulled downward the ribbon muscles are retracted laterally and upward with small right angle retractors. As the muscle and areolar tissue are dissected free of the thyroid more hemostats are placed in the gland, so that by serial steps of dissection and traction the anterior and lateral surfaces of the superior pole are cleaned.

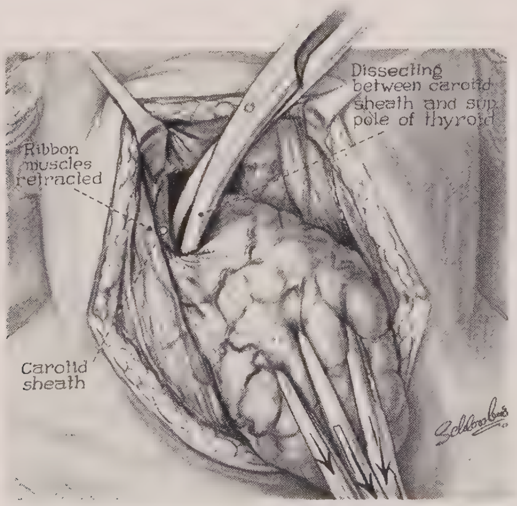


Fig. 43. Mobilization of superior pole by carrying dissection between carotid sheath and thyroid down to vertebral column.

Many types of clamps for holding the thyroid have been devised. All will hold most thyroids but none will hold all thyroids without tearing. Hemostats of the "Crile" type, as made by Stille, have the advantage of being easily inserted and of holding securely. One blade is inserted parallel to the capsule and the clamp is closed on the capsule, care being taken to exert traction exactly in the longitudinal axis of the clamp. The hemostats can be used simultaneously for controlling oozing from the capsule and exerting traction. If they tear out, a Lahey clamp may control the resultant oozing and hold well enough to allow traction. If this pulls out a large bleeding defect remains, and it is necessary to control the hemorrhage with pressure.

Mobilization of the Superior Pole (Fig. 43)

Dissection is carried laterally at the upper pole to expose the carotid sheath which lies just lateral to the thyroid. Dissection is carried down between the sheath and the superior pole of the thyroid, keeping as close as possible to the gland, until the bodies of the cervical vertebrae can be palpated. Unless this space between the carotid sheath and the superior pole is estab-

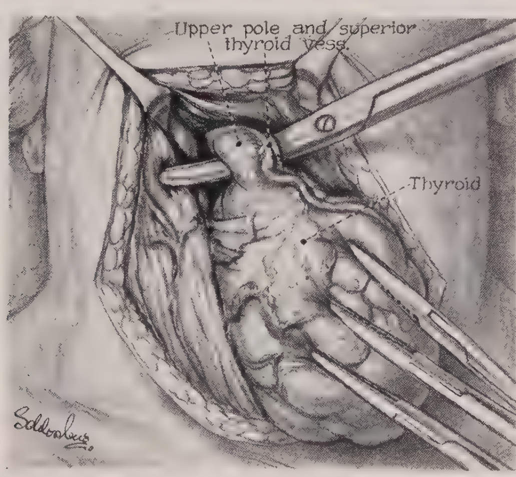


Fig. 44. Isolation of superior pole over scissor inserted from tracheal side into previously prepared space. Note vessels on medial side of pole. Top of pole is avascular.

lished and opened down to the vertebral column it is not possible to mobilize completely the superior pole.

When the pole has been mobilized, scissors are inserted beneath it from the medial side, through its posterior fibrous attachments, and into the previously prepared lateral space. In order to avoid injury to the external branch of the superior laryngeal nerve, the dissection should be made close to the thyroid or to the superior pole vessels and the dissection should not be carried close to the larynx. The point of the scissors is then elevated so that it lies on the ribbon muscles, and the superior pole is delivered forward into the wound (Fig. 44). The pole is then triply clamped and severed distal to the second clamp (Figs. 45 and 46). This results in complete mobilization of the superior pole and in turn allows complete rotation of the remainder of the gland and delivery of any retrotracheal extensions.

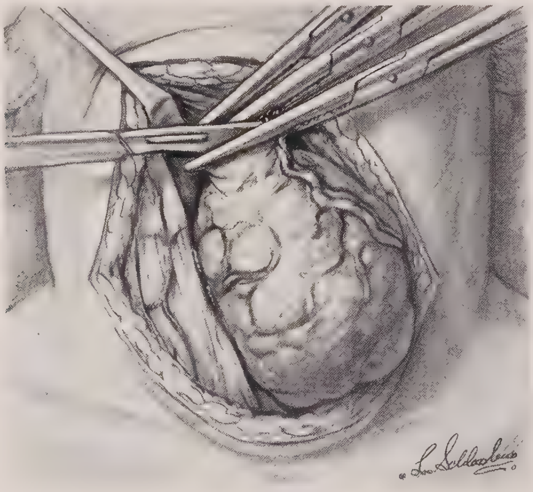


Fig. 45. Clamping and dividing superior pole.

The superior thyroid artery courses down along the medial side of the superior pole and enters the substance of the gland slightly above the junction of the lobe and isthmus. Occasionally, when the superior pole is large and lies high it is easier to isolate and divide the superior vessels low in their course along the side of the pole. Following this procedure, the avascular superior pole can be drawn downward and delivered without danger of bleeding.

Division of the Suspensory Ligament

The suspensory ligament of the thyroid runs from the isthmus to the cricoid cartilage. It transmits branches of the laryngeal vessels. Although these vessels are branches of the superior thyroid artery, they are given off above the point at which the superior thyroid is ligated and hence still carry blood to the thyroid. The cricothyroid ligament also may impede complete rotation of the gland unless it is clamped and divided (Fig. 47), care being taken to avoid clamping any structure deep along the side of the larynx where the recurrent nerve is vulnerable.

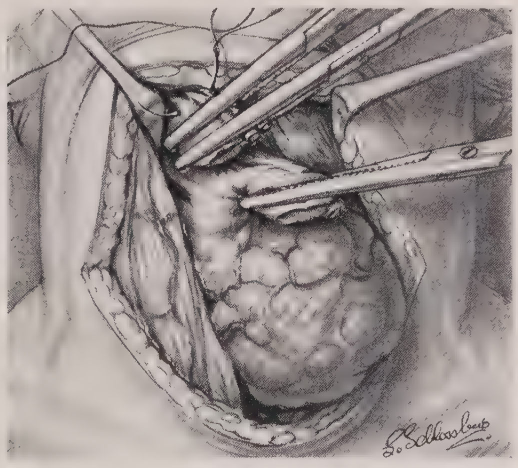


Fig. 46. Ligating superior thyroid vessels.

Ligation of the Lateral Thyroid Vein

The lateral thyroid vein leaves the posterior or lateral surface of the thyroid to cross the areolar tissues and enter the jugular vein. Sometimes it is given off so far posteriorly that it can be disregarded, and sometimes it is absent, the inferior thyroid veins replacing it. In many cases, however, the gland cannot be rotated completely from its bed until the lateral thyroid vein is divided. If the vein is not divided it may be torn when the gland is rotated (Fig. 48). It should be isolated and ligated after it has formed a single trunk and has left the surface of the thyroid.

Ligation of the Inferior Thyroid Artery

Although hemorrhage during the course of a thyroidectomy is rarely significant in respect to loss of blood, attempts to control this bleeding commonly result in injury to vital structures, notably the recurrent laryngeal nerve. Usually the offending vessel in these cases is a branch of the inferior thyroid artery.

Prior to the adoption of a technic in which the inferior thyroid artery was isolated and ligated, persistent unilateral recurrent laryngeal nerve paralysis was observed following

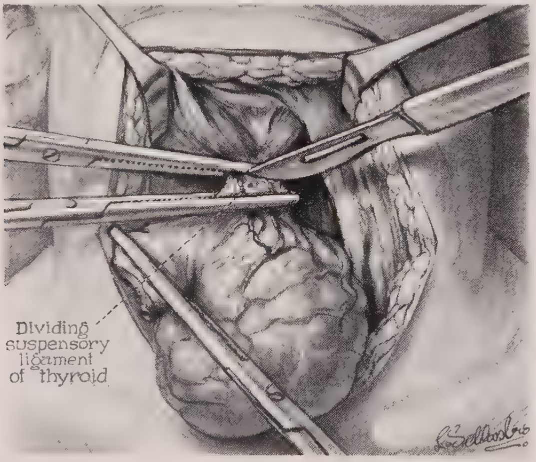


Fig. 47. Division of suspensory ligament of thyroid. This structure may transmit branches of laryngeal artery. Complete rotation of gland from its bed cannot always be obtained until it is divided.

nearly 4 per cent of all thyroidectomies. In the last 539 cases, including recurrent goiters, intrathoracic goiters and all types of cases exclusive of malignancies (in which one nerve was occasionally purposefully sacrificed) there have been only two (0.37 per cent) persistent recurrent laryngeal nerve paralyses. The vocal cords have been examined routinely after operation. I believe, therefore, that the extracapsular ligation of the inferior thyroid artery is valuable in diminishing the morbidity of thyroid surgery.

*Anomalies of the Inferior Thyroid Artery.** The inferior thyroid artery is more inconstant and irregular than the superior vessel, and occasionally is entirely absent. In 6 per cent of the cases, careful dissection failed to reveal the inferior thyroid artery in its normal position.

There are wide variations not only in the location at which the artery enters the gland, but also in the direction from which

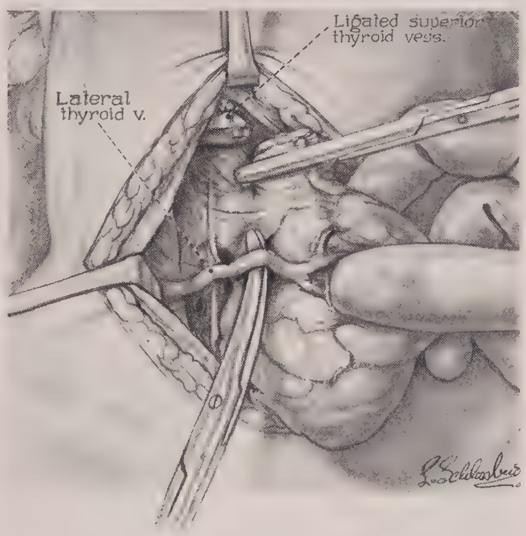


Fig. 48. Isolation of lateral thyroid vein where it leaves the thyroid to cross areolar space and enter the jugular vein. Often the gland cannot be rotated until this vessel is divided.

it enters. Occasionally the vessel crosses beneath the carotids at the level of the upper pole of the gland and descends almost vertically to enter the lower pole. Sometimes it will cross beneath the carotid at the level of the lower pole and ascend nearly vertically to enter the gland near its upper pole. On one occasion, I observed an anomalous inferior thyroid artery arising from the carotid.

* For Anatomy of the Inferior Thyroid Artery see Chapter 12, p. 131.

The site of bifurcation of the inferior thyroid artery is variable. In the majority of cases the main trunk extends to a point within a centimeter of the gland, and then divides. The inferior thyroid artery may bifurcate 4 cm. from the gland, just beyond the point at which it passes beneath the carotid sheath

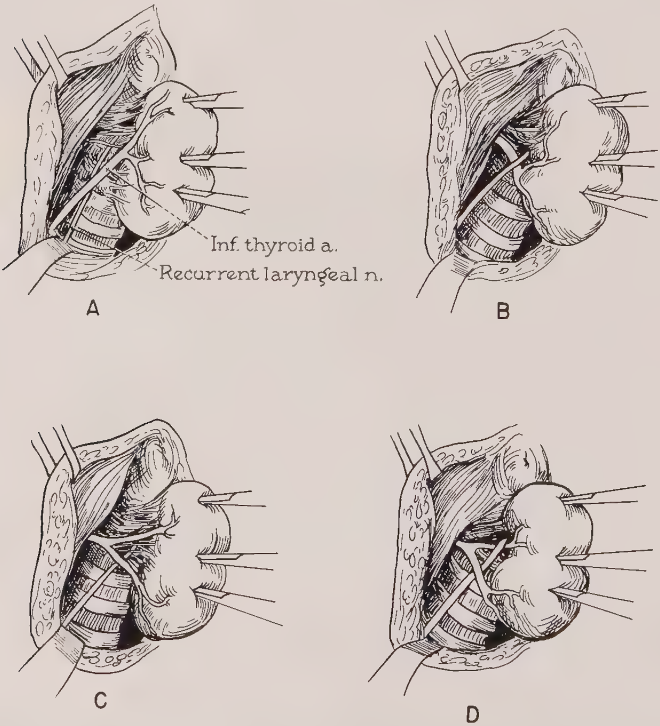


Fig. 49. Variations in relationship of inferior thyroid artery and recurrent laryngeal nerve. A, Artery ascending parallel to nerve. B, Nerve passing anterior to artery. C, Artery bifurcating far lateral to the thyroid. D, Nerve passing between branches of artery.

(Fig. 49). This anomaly is important, because it may result in ligation of only one branch when the operator intended to ligate the main trunk.

Technical Aspects of Ligation of the Inferior Thyroid Artery. Anomalies may cause difficulties in locating the inferior thyroid artery. In cases in which exposure of the inferior thyroid artery is complicated by anomalous ramifications of the lateral thyroid vein and in the rare cases in which the gland is unusually friable, adherent, or hard to deliver, complete lateral exposure of the lobe may be difficult. Under these circumstances, or when the operation is for the removal of a midline adenoma, it may be simpler to proceed with a conventional thyroidectomy without preliminary ligation of the inferior thyroid artery. Since the artery is sometimes absent, it is unwise to spend too much time searching for it.

Since there is such wide variation in the gross pathology of the thyroid, it is not wise to attempt to standardize the operation to too high a degree. Certain types of goiters can best be dealt with by one technic, other types by another. In one instance it may be desirable to divide the pretracheal muscles transversely; in another this procedure may be totally unnecessary and undesirable. It should be understood that when ligation of the inferior thyroid artery is recommended, it is with the reservation that this procedure will not be applicable in some cases. In about 6 per cent of the cases I do not ligate either of the inferior thyroid arteries.

After the lobe is elevated from its bed, the inferior thyroid artery is usually seen coursing upward from the junction of the lower and middle third of the lobe. If the artery is not visible, it may be easily palpable. After it is located it is a simple matter to expose it and isolate the main trunk by blunt dissection. A curved Moynihan forceps is inserted beneath the vessel, and a ligature is grasped and pulled through (Fig. 50). Before this ligature is tied the vessel is completely isolated in order to make certain that the recurrent nerve is not included in the ligature.

Identification of the Recurrent Laryngeal Nerve

By the time the artery has been isolated and ligated the course of the recurrent nerve usually has been visualized. Although the entire cervical portion of the nerve sometimes can be dissected out and handled with impunity, stretching or a minimal amount of trauma occasionally will result in an unpleasant temporary paresis. In about 90 per cent of the cases, one or both nerves are easily identified.

As Lahey has pointed out, the nerve is often easily palpable against the trachea. If after ligation of the artery the nerve has not been identified, a careful search for the nerve is made in the structures lying anterior to the artery. If the nerve is

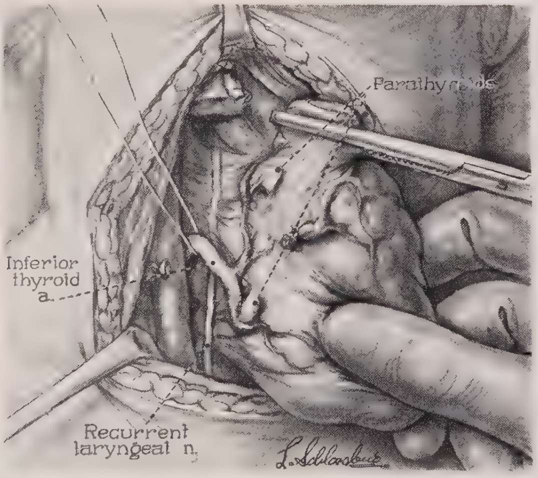


Fig. 50. Ligation of inferior thyroid artery. Note recurrent nerve crossing at right angles beneath artery.

not found here or along the lateral surface of the lobe, it is assumed that its position is well posterior, where it will not be injured during the course of thyroidectomy.

Actual isolation and dissection of the nerve is indicated in cases of possible malignancy when a total lobectomy is to be performed or when, as in thyroiditis or recurrent goiters, the posterior capsule of the gland may be adherent to the nerve. The nerve is found most easily just below the point where it crosses the inferior thyroid artery (Fig. 50).

Preservation of the Parathyroid Bodies

The parathyroid bodies are variable in their location and are difficult to identify as they often lie on the posterior aspect of the superior pole. The inferior parathyroids usually can be identified lying along the branches of the inferior thyroid artery close to the junction of the lower and middle third of the gland on its posterior or posterolateral surface (Fig. 50). If adenomas are present the parathyroids may be displaced or may be so flattened out on the capsule of the adenoma that it is difficult to recognize them. Often they are found in the areolar tissue along the inferior thyroid vessels, and occasionally it is said that they are found in the substance of the thyroid. Their color is a characteristic brownish yellow, and their vascularity and color distinguish them from lymph tissue, thyroid nodules, and deposits of fat. In most, but not in all cases, at least the inferior parathyroids can be identified.

Resection of the Thyroid

After definite orientation in respect to the nerve and the parathyroid glands has been obtained, a line of hemostats is inserted along the posterolateral surface of the gland, and a groove is cut in the gland above the hemostats (Fig. 51). This groove marks off the portion of the gland to be preserved. Hemostats are then applied to the central portion of the isthmus and the isthmus is divided between closed hemostats down to the trachea. Hemostats thus applied will not pick up the trachea; and if the hemostats are not overcut, there is no possibility of tracheal injury.

Care must be taken at this stage not to carry the dissection too far down the side of the trachea into the tracheo-esophageal groove, because at the upper portion of the gland the nerve curves forward to enter the larynx and lies close to the capsule of the thyroid. If the points of the hemostats are kept within the substance of the thyroid itself, the nerve will not be injured, as the nerve does not enter the capsule of the gland. A pedicle of thyroid tissue is now formed between the lateral groove and the exposed trachea. It is a simple matter to cut this pedicle, leaving the desired amount of thyroid tissue. It is not necessary to clamp the thyroid tissue before cutting it as there is no brisk bleeding. All of the isthmus and the pyramidal lobe are removed (Fig. 52).

When a thyroidectomy has been performed by this technic, a shell of thyroid remains consisting of the major portion of the

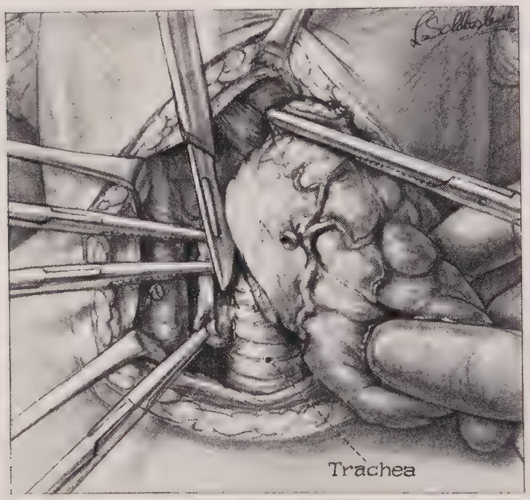


Fig. 51. Resection of thyroid started just above line of 3 pilot hemostats. Gland can now be cut without encountering significant bleeding and it is not necessary to carry out resection over multiple hemostats.

posterior capsule of each lobe. Removal of the maximum amount of thyroid is insured and yet, by preserving the posterior capsule, maximum protection for the parathyroid bodies is afforded. The blood supply of the thyroid remnants and parathyroids is adequate to maintain the normal function of these organs.

Amount of Thyroid to Leave. The amount of thyroid that should be resected is an individual problem, different in each case. Occasionally a solitary adenoma is solely responsible for hyperthyroidism, but this situation is rare. Subtotal thyroidectomy is the treatment of choice in most cases of hyperthyroidism.

In large goiters more gland can be left than in small ones without running the risk of residual or recurrent hyperthyroidism. Hypothyroidism rarely occurs following removal of nodular goiters with or without hyperthyroidism and is much more common following operation for Graves' disease. The development of postoperative hypothyroidism does not correlate closely with the amount of tissue left. This represents a

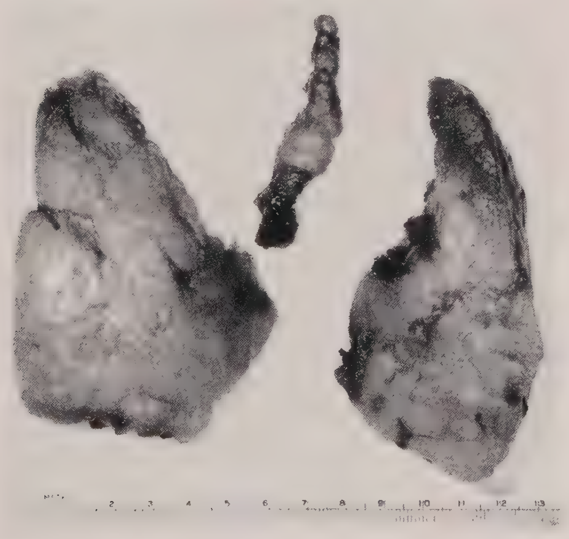


Fig. 52. Large hyperplastic goiter of Graves' disease. Note hypertrophy of pyramidal lobe.

remission of the disease and is more often due to a failure of function of the thyroid remnants than to removal of too much thyroid. Hertzler expressed this lack of correlation in his statement that total thyroidectomy could be performed without causing hypothyroidism, but it is questionable whether the thyroidectomies to which he referred were indeed total. It was the experience of those who performed ablations of the thyroid for heart disease that hypothyroidism was but transitory unless an absolutely total thyroidectomy was done. If not, the remnants of the normal thyroid would regenerate and the basal metabolic rate would soon rise to normal.

On several occasions I have done nearly total ablations of all thyroid tissue for carcinoma of the thyroid or for bilateral adenomas suspected of being carcinomas and have noted that hypothyroidism did not ensue. It is probable that the normal thyroid or the thyroids of patients with endemic goiter have

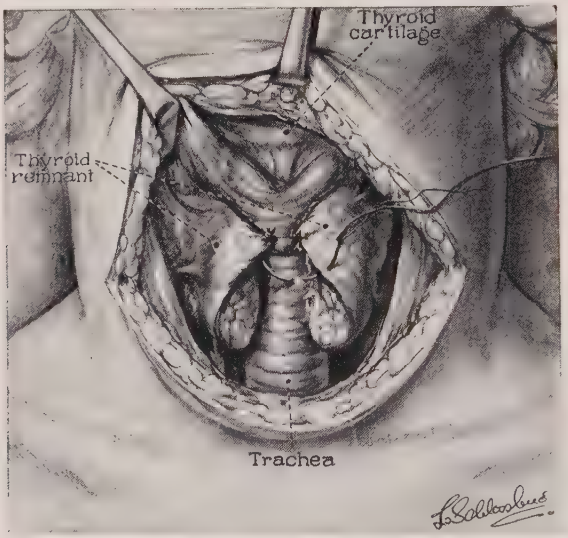


Fig. 53. Hemostasis secured by suture of remnant of glands to pretracheal fascia with interrupted sutures of no. 60 cotton. Fine cotton used throughout operation for both sutures and ligatures. Note that the thyroid remnant is a thin shell of posterior capsule.

remarkable regenerative powers and undergo compensatory hyperplasia after even the most radical subtotal thyroidectomies. In Graves' disease, on the other hand, severe hypothyroidism may follow a conservative thyroidectomy in which a relatively large amount of thyroid tissue is left.

Since recurrent hyperthyroidism is a much more distressing complication than transitory postoperative hypothyroidism and since permanent hypothyroidism can be completely and economically controlled by feeding desiccated thyroid, it is better to err on the side of removing too much rather than too little. In the hyperplastic glands of Graves' disease, as much of the parenchyma of the gland as possible, including all of the superior pole, all of the pyramidal lobe, and the isthmus, should be removed leaving only the shell of the posterior capsule to

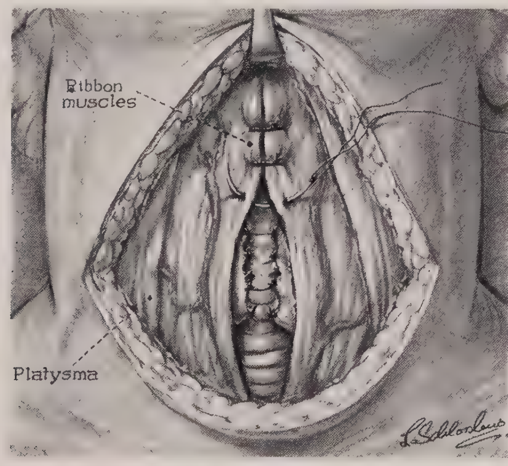


Fig. 54. Closure of muscles.

protect the parathyroid glands and maintain thyroid function. If this type of thyroidectomy is performed, residual hyperthyroidism will not occur. Recurrences in 144 patients followed for five years or longer have, in my experience, been 2 per cent of the followed cases and only 1 per cent of the total number operated upon. The recurrences took place from three to six years after operation.

Hemostasis

Reconstruction of the thyroid lobe controls the oozing from the cut surface of the gland. The lateral margin of the cut surface of the thyroid is sutured to the tracheal fascia with interrupted No. 60 cotton sutures, thus closing the thyroid bed and obtaining hemostasis by pressure (Fig. 53). Occasionally, if a radical lobectomy has been performed, there is so little tissue remaining that closure of the thyroid bed would be both difficult and unnecessary.

Before starting the closure, it is important to make certain that hemostasis is complete. When the head is elevated, as

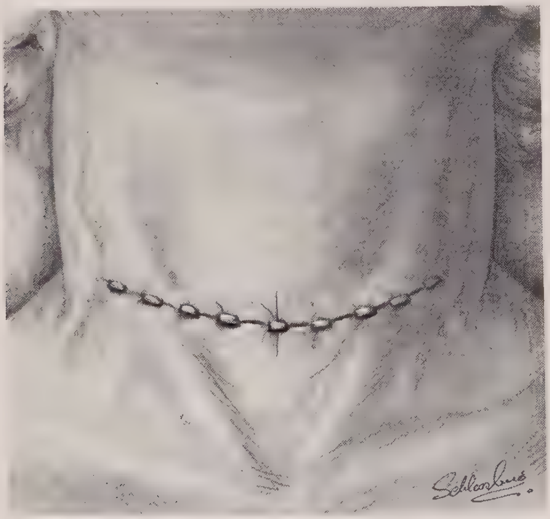


Fig. 55. Closure of neck with skin clips and without drainage.

is the case during the operation, the venous pressure in the neck often is so low that the cardiac end of a severed vein will not bleed even when it is wide open. To insure against subsequent bleeding from these veins, the venous pressure should be raised either by having the patient cough or, if the patient is unconscious, by applying positive pressure through the gas machine. The open vein will then spurt blood and can be caught and tied.

Closure

There is little tendency for the muscles to separate. Four or five small interrupted sutures of No. 60 cotton suffice to approximate the muscles and fascia, care being taken to include all layers so that a thick layer of muscle and fascia lies between the trachea and the skin (Fig. 54). No subcutaneous sutures are necessary. Before closing the skin, accurate hemostasis should be obtained. A little bleeding from the skin flaps may cause an extravasation of blood with discoloration extending down to the nipples. The skin is closed with clips starting at the mark in the midline so that the approximation will be perfect. Before the last clip is inserted the air and blood are expressed by rolling the flap with a piece of gauze. Drains are not inserted (Fig. 55).

Bibliography

1. Dinsmore, R. S., and Crile, G., Jr.: Thyroid problems and end-results of operations on thyroid gland. S. Clin. North America *15:* 859–884 (Aug.) 1935.
2. Hertzler, A. E.: Surgical Pathology of the Thyroid Gland. Philadelphia: J. B. Lippincott Co., 1936.
3. Lahey, L. H.: Routine dissection and demonstration of recurrent laryngeal nerve in subtotal thyroidectomy. Surg., Gynec. & Obst. *66:* 775–777 (April) 1938.

Chapter 14

RESULTS OF THYROIDECTOMY AND EVALUATION OF TECHNIC

Two important considerations in making a final judgment as to the value of any surgical technic are (1) the mortality rate, and (2) the incidence of complications and morbidity.

Mortality

I have performed 540 consecutive thyroidectomies by this technic and have had no postoperative deaths. One hundred fifty-eight of these patients had Graves' disease, 157 had nodular goiters with hyperthyroidism, 201 had simple goiter, and 24 had carcinoma of the thyroid. Since the mortality rate following thyroidectomy has been below 1 per cent for the past ten years, this small group of cases is of little statistical value. It is apparent, however, that the mortality rate has not been increased by extracapsular ligation of the inferior thyroid artery.

Complications

Injuries to the Recurrent Laryngeal Nerve. Extracapsular ligation of the inferior thyroid artery has lowered the incidence of accidental injuries to the recurrent nerve. The incidence of accidental injuries has fallen from 3.2 per cent in the earlier cases to 0.37 per cent in the last 540 cases. These statistics refer to permanent paralysis as proved by routine postoperative examination of the vocal cords and are not based merely on return of normal phonation. In about 3 per cent of the cases, transitory pareses have occurred and cleared within a few days or at most within a month. In no case has a tracheotomy been performed, and significant stridor has not occurred.

Postoperative Hemorrhage. There has been only one case in which hemorrhage has been a problem either at the time of operation or during convalescence. This patient had an anomalous arterial supply of the thyroid and no inferior artery could be found. Except in this case, incisions have not had to be reopened to control postoperative bleeding, and there have been no hematomas other than those due to venous oozing from the skin flaps. These have required no treatment other than aspiration. Hemostasis has been much more complete and much easier to attain than in the earlier cases.

Serum. Fine silk or cotton has been used for sutures and ligatures, and the quality of wound healing has been far superior to anything observed even with 0000 chromic catgut. In only one of the cases in which silk or cotton was used has serum accumulated to the extent that more than two aspirations of the neck with a needle and syringe were required. The average hospital stay following operation has been reduced by several days, and the necessity for subsequent dressings has been avoided (Fig. 56).

Infection. On four occasions infection developed in the wounds. Once the offending organism was a type III pneumococcus which presumably metastasized to the neck from a pneumonia which had developed on the second postoperative day. The wound healed promptly when sulfadiazine was given and there was no drainage. Once, before the introduction of penicillin, a low-grade Staphylococcus albus infection appeared ten days after thyroidectomy and was followed by drainage and the necessity of reoperation for removal of silk ligatures. Since cotton has been used, in the last 200 cases, there have been two wound infections and these resolved at once after aspiration of the pus and injection of 100,000 units of penicillin into the wound. Penicillin was given systemically as well and the wounds healed promptly without requiring drainage.

Tetany. Greater care in leaving more of the posterior capsule has resulted in a decrease in the incidence of postoperative tetany.

Hypocalcemia, often without any other symptoms than transitory sensations of numbness, has occurred in 1.5 per cent of the patients operated on by the technic in which the inferior thyroid arteries were ligated as compared with 2.0 per cent of the patients operated on by the conventional technic. In many of these cases the symptoms were so mild and transitory that they easily could have escaped recognition.

In three of the patients who developed tetany after operations in which the artery was ligated, the operation was per-

Fig. 56. Typical appearance of thyroid wound on fifth postoperative day.

formed for a recurrent goiter. In one of these only a single lobe was removed, but this was removed completely because the preoperative diagnosis was carcinoma. In four of the eight cases one parathyroid was found on the specimen, and in two cases two parathyroids were identified. The tetany must therefore be attributed as much to removal of the parathyroids as to interference with their blood supply by ligation of the inferior thyroid artery.

In only one of the eight cases operated upon by the anatomic technic was the tetany permanent. In six cases it cleared spontaneously in a few days or weeks, and the blood calcium returned to normal and has remained within normal limits without treatment. In one other case, we know that the patient is taking no treatment and that she has no symptoms of tetany, but we have not been able to persuade her to return to have the level of blood calcium and phosphorus determined. Although we can assume that she is well, we cannot be certain that she does not have a latent tetany which might result in the production of cataracts.

In two of the seven patients operated upon by the earlier technic, the tetany is permanent, in three it cleared spontaneously, and in two the patients are taking no treatment and have no symptoms, but we do not know what their blood calcium level is.

The incidence of permanent symptoms of tetany or of asymptomatic latent tetany following the anatomic operation is 0.18 per cent as compared to 0.58 per cent following the conventional operation. Transitory tetany may occur but clears promptly and completely in the majority of the cases (Table III).

TABLE III
Incidence of Tetany Following Anatomic as Compared to Conventional Type of Thyroidectomy

Anatomic Technic	540 Cases	Conventional Technic	344 Cases
Permanent tetany	0.18%	Permanent tetany	0.58%
Transitory tetany	1.12%	Transitory tetany	0.87%
Calcium not followed		Calcium not followed	
no symptoms	0.18%	no symptoms	0.58%
no treatment		no treatment	

The low incidence of persistent tetany discounts any objection to extracapsular ligation of the inferior thyroid artery on the grounds that it might interfere with the blood supply of the parathyroids. When better hemostasis is obtained the glandules can more readily be identified and preserved, the danger of injuring them with clamps and ligatures is avoided, and the incidence of tetany is lowered. The thyroid remnants have a collateral blood supply adequate to preserve normal thyroid and parathyroid function, provided no direct injury is done to the parathyroids or to their immediate vessels of supply. If parathyroids have not been definitely identified and preserved, it is a wise precaution to leave a large amount of the posterior capsule at least on one side.

Residual and Recurrent Hyperthyroidism

We have been able to follow, for a five to ten-year period, approximately 50 per cent of the patients operated upon. In a series of 144 patients with hyperthyroidism upon whom operations were performed by an anatomic technic and who were followed longer than five years, there have been two recurrences of hyperthyroidism. In a third case, there was recurrence of a goiter associated with questionable hyperthyroidism and a normal basal metabolic rate. The incidence of recurrent hyperthyroidism in this group was 2.1 per cent.

In a series of 117 cases operated upon by the earlier less anatomic technic, a comparable follow-up study revealed two cases of residual and eight cases of recurrent hyperthyroidism, an incidence of 8.6 per cent. Since all but one of the ten followed patients who developed recurrences returned to the Cleveland Clinic for further treatment, we can assume that we know of most of the recurrences which have taken place. Although it is impossible, without a longer period of observation, to state an accurate figure for recurrences, I believe that we are correct in assuming that the incidence of recurrent hyperthyroidism over a five to ten-year period for the first technic is in the neighborhood of 4 per cent and for the anatomic technic is about 1 per cent (Table IV).

All but four of the thirteen patients who developed recurrent or residual hyperthyroidism had very mild hyperthyroidism that was easily controlled by nonsurgical measures; three were cured by iodine alone, two by x-ray, and one by a combination

TABLE IV

RELATION OF RECURRENT AND RESIDUAL HYPERTHYROIDISM TO TYPE OF GOITER AND TECHNIC OF OPERATION

	Technic I* Incidence of Recurrences	Technic II* Incidence of Recurrences
Graves' disease		
Total patients operated upon Followed and unfollowed—291	6.3% known recurrences	1.3% known recurrences
Nodular goiter with hyperthyroidism		
Total patients operated upon Followed and unfollowed—248	0% known recurrences	0.6% known recurrences
Hyperthyroidism, all types		
Total patients operated upon Followed and unfollowed—539	4.3% known recurrences	1% known recurrences
Graves' disease—162 cases	15%	2.1%
Patients followed 5 to 10 years	(of 66 cases)	(of 96 cases)
Nodular goiter with hyperthyroidism	0%	2.1%
Patients followed 5 to 8 years—99 cases	(of 51 cases)	(of 48 cases)
Hyperthyroidism, all types	8.6%	2.1%
Patients followed 5 to 10 years—261 cases	(of 117 cases)	(of 144 cases)

* Technic I is conventional thyroidectomy.

Technic II is anatomic thyroidectomy with ligation of inferior thyroid artery and identification of recurrent nerves.

of x-ray and iodine. Three of the four patients that were operated on again did not return to me. If they had, I believe that conservative treatment might have proved effective.

Recurrent Goiter without Hyperthyroidism

There have been two recurrences of goiters without any associated hyperthyroidism. In one of these cases, hyperthyroidism was present before the first operation but did not recur. In the other, there was never any hyperthyroidism. This is the only recurrence in 114 patients having nodular goiters without hyperthyroidism who have been followed from five to ten years.

Postoperative Hypothyroidism

The incidence of postoperative hypothyroidism is inversely proportional to the incidence of recurrent hyperthyroidism. In the first group of 117 cases in which a less complete thyroidectomy was performed, only 3.4 per cent of the patients developed a significant and persistent degree of postoperative hypothyroidism, whereas 16 per cent of the second group of 144 patients developed this complication (Table V). But postoperative hypothyroidism is easy to treat and does not constitute a disability. Its appearance should be welcomed because it signifies that there will be no recurrence of the hyperthyroidism.

TABLE V

Incidence of Postoperative Hypothyroidism as Related to Type of Goiter and Type of Operation

	Operation Type I* % Hypothyroid	Operation Type II* % Hypothyroid
Graves' disease		
Total patients operated upon—162	4.5% (of 66 cases)	21% (of 96 cases)
Nodular goiter with hyperthyroidism		
Total patients operated upon—99	2% (mild) (of 51 cases)	4.3% (mild) (of 48 cases)

* Same as Table II.

Other Considerations

With recent improvements in the preparation of the patient for operation, and with the development of better methods of anesthesia, the factor of speed is of less importance than the development of a careful anatomic technic. Accurate hemostasis, the use of nonirritating, nonabsorbable suture material, and anatomic dissection result in a smooth convalescence. Speed is too often attained at the expense of accuracy.

One of the chief reasons for performing a thyroidectomy for a nontoxic nodular goiter is the possibility that the adenoma is malignant. For this reason, it is imperative that the adenoma be removed in its entirety. A complete lobectomy often is necessary.

Adenomas cannot be removed completely without incurring a significant incidence of injuries to the recurrent nerves unless these nerves are identified and preserved. If the nerve has not been identified, there is always a temptation to leave that part of the adenoma which impinges on the area traversed by the nerve. If the nerve is identified this temptation is removed, and a cleaner and more complete operation for these potentially malignant tumors is performed.

Chapter 15

COMPLICATIONS DURING THYROIDECTOMY

There is no longer any need for dividing thyroidectomy into stages unless technical difficulties are encountered during the removal of the first lobe. In this eventuality, the second lobe can be removed the following day or whenever the patient's condition becomes satisfactory. Packing the wound open between stages introduces infection and is not recommended.

Hemorrhage

The most common complication at the time of operation is hemorrhage, which is of less consequence than the damage done in attempting to control it. I have never seen a fatality resulting from hemorrhage at the time of thyroidectomy.

The most difficult hemorrhage to control is that originating from a severed superior thyroid artery that has retracted high in the neck. This artery is a branch of the carotid, and pressure on the carotid usually will diminish the bleeding. As a rule, it is simpler and more effective to place the finger directly on the bleeding point and control the hemorrhage by pressure or packing until satisfactory exposure can be obtained.

As soon as the initial hemorrhage is controlled by pressure, the muscles should be divided so that the bleeding vessel can be clamped and tied under direct vision. If blind attempts are made to grasp a bleeding superior thyroid artery, the jugular vein may be injured, causing further increase of the hemorrhage or damage to the superior laryngeal nerve. Hemorrhage from a superior thyroid artery may appear alarming but is dangerous only when the surgeon becomes excited and overhasty in his attempts to control it.

Hemorrhage from the branches of the inferior thyroid artery is apt to be less brisk but more dangerous than that from the superior pole vessels. Again, the danger is not from the loss of blood, but from the proximity of important structures, notably the recurrent laryngeal nerve, that may be damaged by blind attempts to control the bleeding. The inferior thyroid artery enters the gland on its posterolateral surface, and if the finger is inserted behind the gland and the gland remnants are compressed against the trachea, bleeding can be controlled. After the field has been sponged dry, release of the pressure will reveal the spurting vessel and it can be caught and tied. Care must be taken to include in this ligature only the bleeding point, because the ascending branch of the inferior thyroid artery, lying on the posterior capsule of the gland, is in close proximity to the recurrent nerve. Often it is simpler to ligate the main inferior thyroid trunk well away from the bleeding point. The inferior thyroid artery is a branch of the subclavian, and bleeding from this vessel cannot be controlled by compression of the carotid.

In large goiters, when there is obstruction of the deep veins, injury of the anterior jugular veins may result in brisk bleeding. Attempts to control this by merely grasping the opening of the vein in a hemostat and ligating it often result in the ligatures being thrown off later in the operation when retraction stretches the vein. It is better to doubly clamp, divide, and ligate these veins. The same technic should be applied to injuries of the internal jugular.

Injury to the Trachea

The trachea may be injured during the course of a difficult thyroidectomy. This accident is serious because of the danger of aspirating blood and because of the probability of contamination and wound infection. If the trachea is injured, the opening should be covered with a damp sponge, accurate hemostasis obtained, and the trachea closed again with fine interrupted catgut sutures. Under these circumstances, penicillin should be given and the wound drained for at least three days because wound infection, often of a foul nature due to contamination with Vincent's organisms and other flora of the upper respiratory tract, may result.

Stridor

Stridor may complicate thyroidectomy even in the absence of injury to the recurrent laryngeal nerves. This is most apt to occur when the patient is under a general anesthesia and may be the result of mechanical distortion of the trachea or of reflex laryngospasm. Pentothal predisposes to this complication. If the technic is gentle, laryngospasm is rarely seen. If respiratory exchange is impaired to the point that the patient becomes cyanotic, an emergency tracheotomy may be necessary. This complication is extremely rare and usually denotes an injury to the recurrent nerves. If there is no possibility that the nerve has been injured, the laryngospasm almost certainly will subside without necessitating tracheotomy. If there is any question of injury to the nerve, recovery may not take place, and it is safer to perform a tracheotomy. If the stridor does not recur when the opening in the trachea is closed, it is safe to close the trachea in the manner described above.

Injury to the Recurrent Laryngeal Nerves

Occasionally a recurrent laryngeal nerve is injured, as indicated by a change in voice or by visualization of the injury. In my experience, the most common cause of injury is stretching of the nerve when the nerve runs anterior to the artery and is tensed by rotation of the gland. Although this accident occurs in only about 1 per cent of the cases, and although the function of the nerve is impaired for only one to three weeks, it is a satisfaction to have visualized the nerve and to be able to assure the patient that its function will return. If the function does not return in two months, it is unlikely that it will return at all. Bertelsen states that he has not seen recovery take place after six months.

When a nerve is permanently injured by cutting or tying, it will not recover. I have never seen any return of function even if the ends of the nerve have been sutured immediately, nor have I seen a report of such a case. On the other hand, I once placed a ligature on the recurrent nerve, recognized my mistake, and removed it at once. The paralysis in this case cleared after three weeks.

If thyroidectomy is performed without visualization of the nerve, and if after operation it is recognized that the nerve has been injured, exploration may be indicated in the hopes that a constricting suture can be removed. But if the nerve has been severed there is no hope of restoring its function.

Transitory paralysis of a recurrent nerve may appear, for the first time, as long as twenty-four hours after operation. A nurse, subjected to thyroidectomy, noted no symptoms of injury of the larynx until twenty-four hours after operation, at which time she became suddenly hoarse, noticed that she could not swallow without choking, and lost her ability to cough normally. The symptoms cleared in eight days, and the function of the paralyzed cord returned to normal. Edema of the larynx compressing the nerve at its point of entry into the larynx may play a part in the production of these temporary paralyses which usually occur in association with visible ecchymosis and edema of the larynx.

Obstruction of the Trachea

Obstruction to respiratory exchange may be caused by faulty reconstruction of the thyroid remnants over the trachea. In an operation on a 14-year-old child, whose trachea was exceedingly soft and small, the thyroid remnants were reconstructed in the usual way. When the intratracheal tube was removed, the patient had difficulty in breathing. It seemed certain that the recurrent nerves were intact. Bronchoscopy showed obstruction below the larynx. The sutures reconstructing the thyroid remnants and suturing them to the trachea were loosened and normal respiratory exchange was restored. The appearance of collapse of the trachea probably is due to obstruction in the larynx and to the negative pressure that occurs in the trachea when strong respiratory efforts are made.

Injury to the External Branch of the Superior Laryngeal Nerve

This small filament, too tiny to be identified at operation, descends between the superior thyroid vessels and the larynx to innervate the cricothyroid muscle and to send a branch to the pharyngeal musculature. Its injury results in no immediate ill effects but may cause a transitory and sometimes permanent

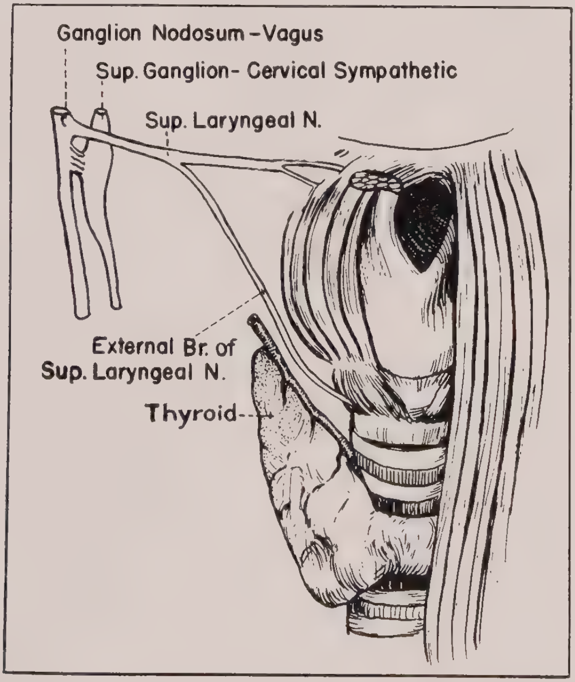


Fig. 57. Note proximity of external branch of superior laryngeal nerve to superior pole of the thyroid.

lowering in the pitch of the voice (Cope, quoted by Means). Injury to this nerve can be avoided by incorporating no more tissue than is necessary on the laryngeal side of the superior thyroid vessels when these vessels are ligated. (Fig. 57.)

Air Embolism

When the head of the table is elevated in the usual position for thyroidectomy there is a negative pressure in the great veins of the neck. If a slit is made in the anterior wall of one of these veins, usually an anterior jugular, the elasticity of the vein holds this slit open and air may rush in. Usually there is an audible sucking noise which gives warning in time to allow the surgeon to cover the opening with a finger. Occasionally enough air is admitted to cause a fatal air embolism (Guthrie).

Minor air embolisms may cause no symptoms or may give rise to an audible churning sound when the air reaches the heart. This persists for about fifteen seconds until the air is absorbed. There is no specific treatment except administration of 100 per cent oxygen to facilitate absorption of the nitrogen. I have never seen a fatality from this cause although several have been reported.

Convulsions from Procaine

When a large amount of ¾ per cent procaine solution is infiltrated into the vascular region of the neck, a convulsion occasionally may occur. This complication may be the result of injection of the solution into a vein, and in theory could be prevented either by aspiration of the syringe before injection of the solution or by keeping the tip of the needle in constant motion so that no significant amount of the procaine could be injected into any one vein. The convulsions do not last long, and I have never seen them end fatally or produce any residual symptoms.

Removal of Parathyroid Glands

Before the specimen is sent to the pathologist and while it is still sterile, it should be examined carefully to see if any parathyroid glands are attached. The superior pole parathyroids are easily overlooked as they may lie on the posterior surface of the upper pole and may not be visible until the gland is removed.

If a parathyroid is identified, it should be removed and reimplanted either into the remnants of the thyroid or into muscle. Little is known of the efficacy of this procedure as there is no way of determining with certainty whether the transplants survive. It would appear that the best chance of survival would be given by cutting the parathyroid into thin slices and grafting it into the remnants of the thyroid. Such an autotransplant should survive, but homografts, even when cultured in the patient's own serum, have not appeared to be of any permanent value in controlling tetany.

Bibliography

1. Bertelsen, A., Christensen, E., Bruun, E., and Becker-Christensen, P.: Mortality, operative complications and recurrence frequency in surgical treatment of thyrotoxicosis. Acta chir. Scandinav. *96:* 1–86 (supplement 133), 1947.
2. Cope, O., quoted by Means, J. H. in The Thyroid and Its Diseases. Being an Account Based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital. P. 443. Philadelphia: J. B. Lippincott Co., 1937.
3. Guthrie, D., and Hughes, F. A., Jr.: Dangers of avertin anesthesia; report of fatality. Tr. South S. A. (1936) *49:* 430–434, 1937.

Chapter 16

POSTOPERATIVE CARE

Immediate Postoperative Care

After operation, the patient is placed in a semi-Fowler's position which diminishes the venous pressure and so prevents oozing. Morphine or its derivatives are given as needed for analgesia and sedation. Fluids can be taken as soon as they can be retained and as much carbohydrate as possible is added to the fluids. The diet is increased as rapidly as can be tolerated. The patient is allowed to be up from the first. The period of hospitalization rarely exceeds three or four days after operation.

Postoperative Treatment of the Handicapped Patient

The postoperative thyroid reaction is directly or indirectly responsible for the majority of deaths following operations for hyperthyroidism. Even though pneumonia, cardiac failure, and the thyroid crisis, in this order, have been the commonest causes of death, in the majority of cases the thyroid reaction is the indirect cause of the fatal complication. For this reason all patients with significant hyperthyroidism, all elderly patients with hyperthyroidism, and all patients having complications which increase the operative risk should be thoroughly prepared with an antithyroid drug until their basal metabolic rate has fallen to normal and the hyperthyroidism is completely controlled.

Before the use of thiouracil, we recognized an unclassifiable type of fatality in which an old and feeble patient appeared to "fade away" as though from a profound metabolic exhaustion. This "metabolic exhaustion" is perhaps a modification of the thyroid reaction dependent on the inability of feeble and aged patients to muster sufficient strength to give the appearance of thyroid stimulation or even to produce a marked elevation of the temperature. Although a classical thyroid crisis was the immediate cause of death in less than one-fourth of all fatal cases, it is clear that thyroid reactions of lesser intensity predisposed not only to the reaction just described but also to cardiac failure and to pneumonia.

Special Aspects of Postoperative Treatment

Administration of Iodine after Operation. The action of iodine is not on the tissues of the body or on the thyroid hormone circulating in the blood, but is on the secretory activity of the thyroid gland (Kunde). Large doses of iodine cannot be expected to produce any further effect on the postoperative reaction of a fully iodized patient. One cubic centimeter of Lugol's solution can be given for a day or two after operation so that at least there will be no exacerbation of symptoms incident to its withdrawal. It is questionable if the effect of withdrawal would manifest itself in less than a week.

Blood Transfusion. If anemia is present, the heart is handicapped by the inability of the blood to carry its full quota of oxygen. Although a blood transfusion given during or immediately after operation may be a valuable therapeutic measure in the treatment of aged or debilitated patients or in those who are anemic or have lost significant amounts of blood, it is not advisable to give a transfusion during the height of a thyroid crisis when the slightest reaction to transfusion would tend to elevate a temperature that is already dangerously high.

Oxygen Tent. All bad risk patients should be placed in the oxygen tent immediately after operation. The oxygen tent is not used for pulmonary complications only, but has been found effective in the treatment of cardiac failure and of uncomplicated thyroid crisis. The temperature often falls from 1 to 3 degrees within three hours of the time the patient is placed in an oxygen tent. It is not clear whether this effect is the result of the oxygen, of the refrigerated air of the tent, or of a combination of the two factors. That the temperature of the air undoubtedly plays a part in the control of the thyroid crises is indicated by the fact that before oxygen tents were used, fatal thyroid crises were 2.4 times more frequent in the hot summer months.

Sedation. Morphine is the most valuable drug for the control of discomfort and restlessness in patients convalescing from thyroidectomy. The tolerance of the patient to morphine varies in direct proportion to the degree of elevation of the basal metabolic rate. Patients with high basal metabolic rates, especially when in the height of a thyroid crisis, should be given large doses of morphine (up to ½ grain) at frequent intervals.

Continuous Intravenous Glucose. Patients with severe hyperthyroidism exhaust the reserves of glycogen that are normally present in the liver (Frazier and Brown). The increased metabolism demands fuel for oxidation. After operation it is painful to swallow, nausea and vomiting may be present, and the patient takes little nourishment. Thus, at the time when the caloric demand is highest, the liver is depleted of glycogen and food is not taken. Unless an adequate caloric intake is restored, the organism must literally oxidize itself in order to provide fuel for the increased metabolism. In patients with severe hyperthyroidism, the continuous administration of glucose solution into a vein will prevent this crisis of catabolic processes, and minimize the postoperative elevation of pulse rate and temperature.

Forced Feeding. It is usually impossible to give intravenously more than 2000 calories a day in the form of glucose, without losing much of the glucose through the kidneys. This is a small part of the total caloric requirement of a patient in thyroid crisis and should be supplemented, when the patient is able to eat, with high caloric, high carbohydrate feedings. If the patient refuses food, feedings can be given through a nasal tube.

Postoperative Treatment of Patients with Severe Hyperthyroidism

In the younger patients who have a flat pulse curve and an excessively high basal metabolic rate, or in those who are or have been disoriented, the greatest danger is from thyroid crisis. Therapeutic measures against thyroid crisis are continuous intravenous drip of glucose solution, oxygen tent, and morphine in doses sufficient to ensure comfort and rest. Such measures should be used *immediately following the operation.* Patients with severe hyperthyroidism lose enormous quantities of water through the skin (Coller), and it is advisable to give from 4000 to 6000 cc. of 5 per cent glucose solution a day until the patient is eating and drinking well.

A thyroid crisis is a vicious circle of hyperthermia and hypermetabolism in which each Fahrenheit degree of elevation of the temperature results in a 7.2 per cent increase in the metabolism and in the production of heat. Unless the mechanism for the dispersion of heat is accelerated, a further rise of body temperature will ensue. The oxygen tent and ice bags placed on the patient's extremities and about the side of the body usually will control any tendency to hyperthermia. If, in spite of these measures, the temperature should rise to critical levels, the patient, with the skin protected, can be literally packed in cracked ice so that more heat is abstracted than can be created. Fortunately, this type of reaction is now extremely rare, and in the majority of cases 10 grains of aspirin will result in a defervescence of from 1 to 3 degrees in two hours.

Occasionally during the postoperative reaction and especially when there has been damage to a recurrent laryngeal nerve, an elderly patient becomes so feeble that she is unable to raise the mucus which has accumulated in the trachea and bronchi. When this occurs the patient becomes cyanotic and dyspneic, the temperature rises, she becomes more feeble, the attempts to cough become progressively weaker and a fatal bronchopneumonia may develop. Atropine and the various expectorant mixtures have not given satisfactory results. In such cases an effective treatment is to give the patient 7½ grains of caffeine sodium benzoate, withhold sedation, periodically elevate the foot of the bed on high shock blocks, and urge the patient to cough while lying prone with the head down at an angle of approximately 30 degrees. In a few minutes of postural drainage an astonishing amount of mucus will pour out, cyanosis may clear, and the temperature may fall. Aspiration of the trachea with a catheter or through a bronchoscope may be necessary if other methods fail.

Hyperthyroidism with Cardiac Complications

Preoperative digitalization is of value in those patients who show evidence of severe myocarditis or who have auricular fibrillation or cardiac decompensation. Oxygen therapy is of value in the presence of cardiac complications, as is morphine in doses adequate to insure rest. The failing myocardium is strengthened by the digitalis, the efficiency of the oxygen-distributing function of the heart is increased by the oxygen tent, and the metabolic demands of the organism as a whole are decreased by the morphine to the point where a balance between oxygen supply and demand is struck and cardiac compensation is restored.

Blood transfusion is contraindicated in the presence of acute cardiac decompensation. Not over 3000 cc. of fluid should be given per day and the fluid should be given slowly, preferably by the continuous drip method.

Quinidine should not be used to correct auricular fibrillation associated with hyperthyroidism until after the postoperative reaction has subsided. Since the heart often reverts spontaneously to normal rhythm, quinidine is not used before the fifth postoperative day. When fibrillation has been present for a long time, quinidine should not be given lest reversion to normal rhythm dislodge an auricular thrombus and cause a fatal embolism.

Bibliography

1. Coller, F. A., and Maddock, W. G.: Water balance in patients with hyperthyroidism. West. J. Surg. *41:* 438–452 (Aug.) 1933.
2. Frazier, C. H., and Brown, R. B.: Thyroid and the liver. West. J. Surg. *43:* 636–646 (Nov.) 1935.
3. Kunde, M. M.: Studies on metabolism; experimental hyperthyroidism. Am. J. Physiol. *82:* 195–215 (Sept.) 1927.

Chapter 17

POSTOPERATIVE COMPLICATIONS

Postoperative Hemorrhage

Occasionally, after what appears to be a perfectly dry closure, secondary bleeding will take place from a subcutaneous vessel. Usually the bleeding is from a vein and causes a soft hematoma under the skin flap or extravasation of blood into the subcutaneous tissues, but is of no serious importance.

If the hematoma is small and not progressive, and if it is producing no pressure symptoms, it is of venous origin and will require no operative intervention. The patient should sit upright and should be given enough morphine to prevent coughing with its attendant liability to raise the venous pressure and produce further bleeding. Sometimes some of the blood can be aspirated with a needle and syringe. No attempts to evacuate the blood clot should be made for at least a week. At the end of a week the clot begins to liquefy, and is no longer adherent. By this time the skin edges are fairly well agglutinated. The midportion of the incision can be opened, the sides reinforced with adhesive tape to prevent spreading of the incision, and the clot can be expressed by firm pressure over the sides of the neck. Earlier attempts to remove the clot will result in failure because of the clot's adherence. In addition, if the clot is extruded before it is soft and before the incision is healed, there is risk of splitting the incision open through its entire length.

Hemorrhage may occur from a deep vessel, usually a branch of the inferior thyroid artery. The first symptom is a sense of tightness in the neck. This is soon followed by difficulty in breathing or even by the development of stridor. The patient holds his head in a peculiar fixed position, and finds it quite impossible to move his head without exaggerating the symptoms of pressure.

This complication is commonly overlooked in its earliest stages, owing to the lack of external bleeding and the failure of the attendants to look under the dressings. The diagnosis is established by observation of a hard swelling of the neck caused by a tense submuscular hematoma. Often there is a bluish discoloration of the skin flap, or even a visible subcutaneous extravasation of blood.

If the hemorrhage is arterial and progressive, or if it is producing pressure symptoms, preparation as for a thyroidectomy should be made in the operating room. The control of a secondary hemorrhage may be more difficult than the primary operation, and should not be undertaken without an instrument nurse, an anesthetist, and a full operating team.

Secondary hemorrhage usually appears within the first four hours after operation but may be delayed. In one case, a severe secondary hemorrhage occurred from the ascending branch of the inferior thyroid artery in a perfectly clean wound nine days after thyroidectomy.

Serum

If catgut is used as a suture material, there will be a small collection of serum beneath the flaps in from 30 to 60 per cent of the cases, depending on the amount and size of the catgut used. Chromic catgut is absorbed more slowly than plain catgut, and hence gives less tissue reaction and less serum. The smaller the caliber of the gut, the less serum will form.

Serum tends to appear from the fifth to the tenth day. Prior to its appearance, there is a moderate amount of induration of the wound, noticeable chiefly in the lower flap. During this preliminary period, heat applied to the neck in the form of hot packs or by means of an electric light bulb shaded to fit the contour of the neck will aid in resolving the induration.

When fluctuation is detected, the serum can be aspirated by inserting an 18 gauge needle through the midpoint of the incision. In uncomplicated cases, the serum does not reaccumulate after the seventh or eighth day. If serum persists in accumulating, or if it becomes cloudy, it is likely that unabsorbed catgut, hematoma, or slough is present in the wound and is acting as a foreign body. Under these circumstances, time will be saved if the midportion of the incision is opened for a distance of about 1 cm. Firm pressure will often result in the discharge of foreign material. If this fails, exploration of the wound with a hemostat may reveal slough, knots, or small clots that can be grasped and withdrawn. This type of reaction rarely occurs when nonabsorbable suture material is used. If serum or blood accumulates when nonabsorbable material has been used, it can be aspirated through a needle or left to absorb spontaneously.

Infection

Occasionally, in spite of every precaution, clean thyroid wounds will become infected. This complication occurs in about 1 per cent of the cases when cotton or silk is used and is much more common with catgut. A culture should be taken at the earliest possible moment. If nonabsorbable suture material is used, the wound should not be opened. Penicillin in doses of 50,000 units every three hours should be given intramuscularly, and each day 100,000 units should be injected into the wound after aspiration of the pus. The common staphylococcus and streptococcus are sensitive to penicillin and the infection resolves spontaneously without necessitating drainage or removal of cotton sutures. If the wound were opened, saprophytic organisms would be introduced and since these organisms are resistant to penicillin, prolonged suppuration would ensue. The two infections encountered in the six years that I have used fine cotton resolved spontaneously without drainage in response to closed treatment with penicillin. If aspiration of pus and injection of penicillin fail the incision should be opened for a distance of 1 or 2 cm., a soft rubber catheter inserted, and the wound irrigated. Occasionally an infection deep in the thyroid bed will fail to show itself by fluctuation, and the neck must be probed deeply before the pus is found. In cases in which nonabsorbable suture material has been used, persistent drainage may necessitate removal of sutures.

Injuries of the Recurrent Laryngeal Nerve

An injury to one recurrent nerve usually, but not always, shows itself at once by a striking change in the quality of the voice or by a total loss of voice. The most reliable sign of injury is noted when the patient attempts to cough. The cough has no explosive quality, but has a sound of rapid exhalation as if the patient were trying to clear the throat. A slight stridor may be present at first but invariably clears up. Difficulty may be experienced in swallowing liquids, as the defense mechanism of the glottis is disturbed, and the fluid tends to enter the larynx where it produces paroxysms of coughing.

The patient may be unable to talk above a whisper for a few days, but the spoken voice invariably returns. When a vocal cord is paralyzed by injury to the recurrent nerve, it falls toward the midline and assumes the "cadaveric" position. At first the muscles of the larynx are flaccid, and the cord hangs loosely or may be bowed outward. Thus the two cords do not approximate, and speaking is impossible. Later, atrophy, fibrosis, and contraction of the muscles occur and the cord becomes tense and rigid in the midline. Bowing is absent and it is always possible for the other cord to meet it and so effect a satisfactory speaking voice. Singing may be impaired, and prolonged use of the voice may be tiresome. The voice may never be as strong as it was before the operation, but a speaking voice always returns. Persistent aphonia is a sign of hysteria, not of injury to the recurrent nerves. The end results of a single cord paralysis, although undesirable, are not of as grave significance as one might suppose.

If both nerves are injured, a serious disability follows. At first there is complete loss of voice, both cords lying atonic in the midline in the cadaveric position. Later, as atrophy and contraction of the muscles occur, the cords become tense and the voice returns. Unfortunately with the return of the voice, there is a narrowing of the glottis to such an extent that an inspiratory stridor develops. More often than not, this stridor eventually becomes so marked that tracheotomy is necessary (Fig. 58).

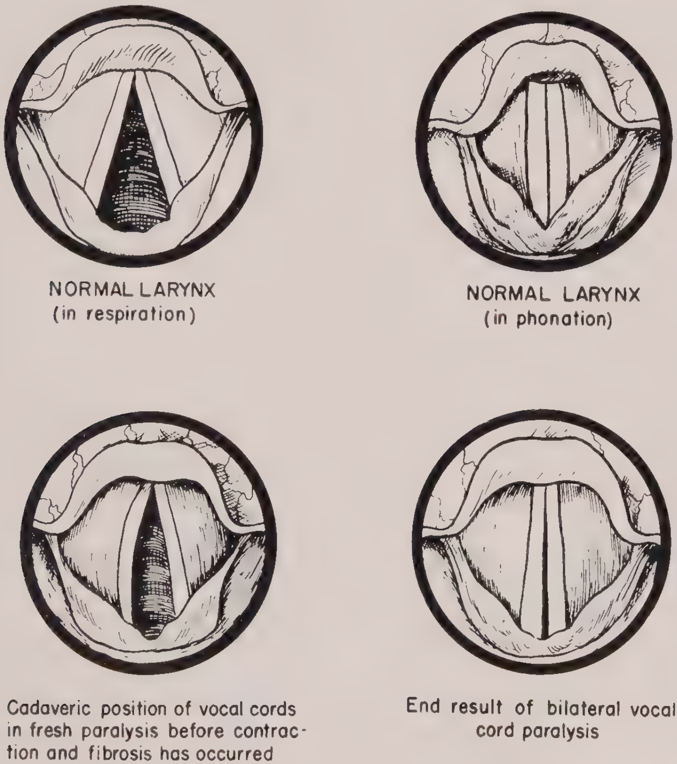


Fig. 58.

Often the first sign of a bilateral injury is the development of stridor. This stridor may necessitate performing a tracheotomy during the course of the thyroidectomy. Frequently the stridor is not observed until after the operation. It may increase in severity during the first few days as the result of edema of the vocal cords. In such cases, the greatest judgment must be exercised as to whether or not tracheotomy should be performed. If the patient is *cyanotic, or has a stridor while awake, or complains persistently of dyspnea, or cannot sleep, or appears afraid, it is best to do a tracheotomy at once.* Although tracheotomy predisposes to the development of pneumonia and should not be undertaken lightly, it is better to err on the side of performing the tracheotomy than to allow the patient to die of asphyxia.

When the end comes, it comes with surprising rapidity. If the patient's respiratory exchange ceases, it is often impossible to resuscitate him even if the trachea is opened at once. This is more apt to occur if the respiratory depressants have been given. Morphine should never be given to a patient in respiratory distress from obstruction of the airway. Neither should any type of general anesthetic be used for the tracheotomy nor should the patient be forced to lie flat or extend the head. The tracheotomy must be done under local anesthesia without preliminary medication and with the head in the position in which it is easiest for the patient to breathe.

The best operation for the correction of bilateral paralysis of the vocal cords is a modification of the operation devised by King. One of the arytenoids is rotated outward or removed, and the vocal cord is fixed in such a way as to widen the gap between the cords. If the glottic chink is widened to exactly the right degree (6 mm. is considered ideal) both an adequate airway and a satisfactory voice are obtained. If this fails the most satisfactory method of dealing with these cases is to insert a permanent valved tracheotomy tube. A gold flutter valve allows inspiration through the tube, but closes on expiration, so that the speaking voice is normal. When covered with a necklace, such an apparatus is both efficient and inconspicuous.

Tetany

Tetany results from the injury or removal of the parathyroid glands. In about one-half of the cases, parathyroids are found on the specimen removed. In the other half, it must be assumed that the parathyroids or their blood supply were damaged. Removal of two parathyroids does not necessarily produce tetany if the other two are intact. Tetany usually appears from one to five days after operation but occasionally may not be recognized for several weeks. The earlier it appears, the more severe it is apt to be.

The first symptom of tetany may be a sensation of numbness or tingling of the extremities or around the mouth. A peculiar circumoral pallor may be present. Tapping of the face over the course of the facial nerve will cause the facial muscles to twitch (Chvostek's sign). Applying the manometer cuff to the arm and raising the pressure to 200 mm. of mercury in case of arterial hypertension to a level well over that of the systolic blood pressure will induce a typical spasm of the muscles of the hand and arm (Trousseau's sign). This usually appears within three minutes. The fingers are extended except at the metacarpophalangeal joints, and all the fingers and the thumb are adducted to produce the picture of the "obstetrical hand." Various other carpal postures such as the "fist" or the claw hand may occur, but a strong adduction of the thumb, so that it crosses over to touch the middle, ring, or little finger, is almost always present.

In severe tetany, painful cramps of the hands, feet, and of all muscles of the body occur. The feet are extended, and this, with the pictures already described in the hands, constitutes the so-called "carpopedal spasm." Occasionally spasm of the muscles of respiration results in severe dyspnea, so that the patient is not only in great pain, but is also in desperate fear of suffocation. Blurring of vision due to spasm of the intraocular muscles is also common.

The intravenous administration of 10 to 20 cc. of 10 per cent calcium chloride or calcium gluconate usually results in immediate relaxation of the spasm. The effect of this medication is short lived, and it should be accompanied by the oral administration of large doses (2 heaping teaspoons, two to four times daily) of calcium lactate. The administration of calcium lactate should be continued either indefinitely or until the blood calcium and phosphorus levels return spontaneously to normal.

Equivalent doses of a mixture of equal parts of calcium lactate and calcium carbonate can be used if diarrhea is troublesome. The chemically pure form of calcium carbonate is more finely divided and is preferable because it is absorbed more readily. Laxatives should not be given to patients with tetany because catharsis causes loss of calcium and an exacerbation of the tetany.

Fortunately, in over half of the cases, the tetany disappears spontaneously, the blood calcium and phosphorus levels return to normal, and the patients experience no further difficulty. If the tetany persists longer than a month, it is apt to be permanent, but complete recovery may take place after longer periods of time.

Even if symptoms are absent or very mild, cataracts are common late complications of the disease. Since this change is irreversible it is important to avoid it by adequate treatment of latent tetany even if the patient is free of symptoms. Vitamin D in doses of from 50,000 to 300,000 units daily is effective in relieving chronic parathyroid tetany (McCullagh). This drug has little cumulative action, and, when the proper dosage has been determined, does not tend to produce a dangerous hypercalcemia.

The combination of calcium lactate and vitamin D given by mouth appears to be the most effective means of controlling chronic tetany. Care should be taken to avoid raising the blood calcium level too high lest calcification, renal damage, or symptoms of toxicity ensue. In the absence of hypercalcemia no toxic effects are observed. Dihydrotachysterol (AT 10) is a potent vitamin A derivative which has a dangerous cumulative effect and easily raises the blood calcium to toxic or even to fatal levels. In cases which prove resistant to large doses of Vitamin D, AT 10 may still have a place, but it should be used with extreme caution and with frequent determination of the level of blood calcium.

Parathyroid extract is expensive and inconvenient because it must be given parenterally. Its effect is slow, compared with that of calcium gluconate given intravenously, as it requires one-half hour or more to raise the level of calcium. Nevertheless this extract may be helpful in maintaining normal calcium levels in the first few hours of an acute tetany and in tiding over the period required for the vitamin D compounds to become effective. One cubic centimeter (100 units) of the extract usually suffices to relieve the symptoms.

Confusion, Delirium, or Coma

Confusion or delirium may complicate hyperthyroidism or convalescence from thyroidectomy. These symptoms are of serious significance and no patient should be operated upon if they are present preoperatively.

Confusion, delirium, or coma following operation denotes an overwhelmingly severe postoperative reaction. Often, but not always, the icteric index is elevated and even clinical jaundice may occur. This finding suggests that at least a part of this reaction may be due to liver failure. The increased retention of bromsulfalein observed in severe hyperthyroidism and especially in elderly patients, and the occasional findings of focal necrosis of the liver in patients dying in thyroid crisis, lend support to the belief that failure of liver function plays a significant part in the production of the reaction.

Forced feeding of high carbohydrate-high protein diets, liver extract, vitamins, and withdrawal of bromides and barbiturates may be helpful in the treatment of postoperative delirium. Glucose given continuously by intravenous drip may also be of value.

Hypothyroidism

Hypothyroidism is a late complication of thyroidectomy, rarely appearing before the second or third month after operation. It does not appear to be related in any precise way to the amount of thyroid that was left at the time of operation. It occurs six times as often following operations for Graves' disease than following operations for nodular goiter with hyperthyroidism. The more radical the thyroidectomy the higher will be the incidence of hypothyroidism and the lower the incidence of recurrent or persistent hyperthyroidism. The development of postoperative hypothyroidism seems to be dependent more on the activity than on the amount of the remaining thyroid tissue.

About two-thirds of the cases of hypothyroidism are mild or transitory. Severe and persistent hypothyroidism developed following 4.2 per cent of 261 operations performed for hyperthyroidism. I have never seen hypothyroidism develop after operations for simple goiter.

Hypothyroidism is characterized by gain of weight, loss of energy, drowsiness, dryness of skin, sallowness of color, puffiness of the eyelids, and by muscle pains and stiffness. The skin on the dorsum of the hand and on the back of the wrists becomes thick, dry, and scaly, so that it resembles the skin of a lizard. The eyes are narrowed, the skin dull, thick, and yellowish, and the body temperature is low. There is a puffy, slit-eyed, almost reptilian expression which is easily recognized. The presence of hypothyroidism is confirmed by the finding of a low basal metabolic rate and a high cholesterol content. It is specifically corrected by taking 1 to 4 grains of United States Pharmacopeia desiccated thyroid daily. If Burroughs Wellcome thyroid is used, the dose must be trebled as the standards are different for the English product.

Even following the most radical removal of almost all thyroid tissue in patients with normal thyroids or with multinodular goiters hypothyroidism either does not occur or is mild and transitory. The thyroid remnants are apparently able to regenerate and maintain normal function unless the underlying disorder is Graves' disease. In Graves' disease the remnants of the thyroid may either regenerate excessively and cause a recurrence of the hyperthyroidism or unpredictably, even when a considerable amount of thyroid tissue is left, may cease function altogether with the result that the patient develops myxedema.

Exophthalmos

One of the rarest, yet one of the most distressing, of all complications of thyroidectomy is progressive postoperative exophthalmos. This condition, sometimes known as "malignant exophthalmos," may be associated with postoperative hypothyroidism, with a recurrence of the original hyperthyroidism, or with no demonstrable abnormality of thyroid function. Occasionally it develops many years after an operation for hyperthyroidism performed on a patient who had no exophthalmos prior to his operation. It may occur in patients who have never had clinical or laboratory evidence of hyperthy-

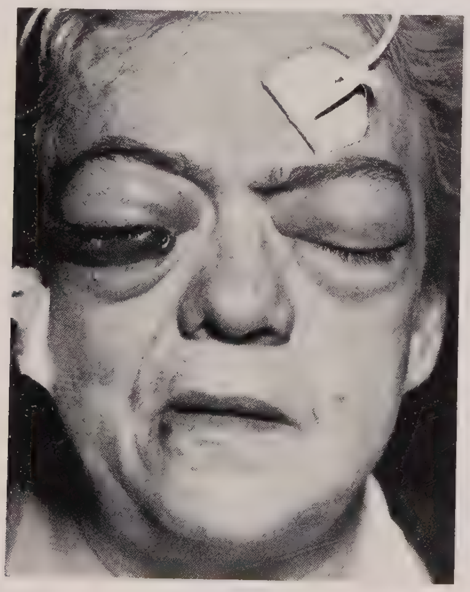


Fig. 59. Exophthalmos showing edema of conjunctiva

roidism and whose thyroid glands are normal in size and in histologic structure. In these cases there is often marked edema of the conjunctiva (Fig. 59) as well as protrusion of the eyeball and ophthalmoplegia.

The cause of exophthalmos is not known, although some believe that the pituitary gland is responsible for its development. Certainly it is not related in any direct manner to the presence of hyperthyroidism but is rather a manifestation of the systemic disorder of Graves' disease and is totally independent of its hyperthyroid manifestations.

The exophthalmos is produced to a large degree by a deposit of fat in the ocular muscles. These muscles may also undergo varying degrees of weakness or paralysis (Fig. 60). In extreme cases edema causes a further protrusion of the eyeball.

Fig. 60. Exophthalmos showing paralysis of extraocular muscles.

The antithyroid drugs have the same effect on the course of malignant exophthalmos as other methods of controlling the hyperthyroidism. Since the exophthalmos is not related to the function of the thyroid there is no reason to advocate thyroidectomy or antithyroid drugs in its treatment unless hyperthyroidism is present. Cervical sympathectomy has not been beneficial.

McCullagh believes that control of hyperthyroidism, whether it be by thyroidectomy or by the antithyroid drugs, helps to control the extrathyroid manifestations of Graves' disease.

He believes that control of the hyperthyroidism is important not because the hyperthyroidism of itself causes the exophthalmos but because the exophthalmos-producing factor of Graves' disease tends to subside after the hyperthyroidism is controlled. Unlike Means, who believes that hypothyroidism causes an exacerbation of the exophthalmos, McCullagh has been unable to find any correlation between hypothyroidism and progression of the exophthalmos and is not afraid of inducing mild hypothyroidism in patients with exophthalmos.

Treatment is directed first at the correction of any hyperthyroidism that may be present. If the condition still fails to improve, roentgen therapy to the pituitary may be tried, but its value is questionable. Correction of hypothyroidism may cause absorption of myxedematous deposits in the orbit, but this does not have any specific effect on the underlying cause of exophthalmos which is a deposit of fat in the retrobulbar tissues. Finally, if all other methods of treatment fail, it may be necessary to decompress the orbit by the Naffziger operation. This operation is not without danger because the edema which follows the operation may result in an immediate (although temporary) exacerbation of the exophthalmos, during which period the eye may become infected, resulting in its ultimate loss. McCullagh has reported apparent improvement in a small group of cases in which the anterior lobe of the pituitary or the stalk was cauterized.

The patient should sleep with his head elevated to minimize orbital edema, should wear shields over the eyes if the lids do not close, and should be under the care of a competent ophthalmologist who can follow the progress of the exophthalmos by measurements with the exophthalmometer and advise orbital decompression in cases in which the exophthalmos passes beyond the limits of safety. The usual upper limit of normal is considered to be 22 mm., and the danger limit is approximately 26 mm.

Exophthalmos rarely recedes more than a millimeter or two after thyroidectomy or treatment with the antithyroid drugs. After thyroidectomy it tends to increase a little and then remains constant, but the widening of the palpebral fissures that produces the stare and the appearance of exophthalmos usually is controlled by any measure that controls the hyperthyroidism.

Bibliography

1. McCullagh, E. P.: Personal communication.
2. Means, J. H., and Aub, J. C.: Basal metabolism in hypothyroidism. Arch. Int. Med. *24:* 404 (Oct.) 1919.
3. Rundle, F. F., and Pochin, E. E.: Orbital tissues in thyrotoxicosis; quantitative analysis relating to exophthalmos. Clin. Sc. *5:* 51–74 (Aug.) 1944.

Chapter 18

RECURRENT HYPERTHYROIDISM

Incidence

The literature on the incidence of recurrence of hyperthyroidism following thyroidectomy recently has been summarized by Bertelsen. The figures given range from 2.2 per cent to 27.9 per cent and depend on many factors, including the criteria for establishing the diagnosis of hyperthyroidism, the relative number of patients with Graves' disease as compared with nodular goiter, and the duration and completeness of the follow-up data. For these reasons, comparison of statistics is impossible. The average reported rate of recurrence is about 5 per cent (Table VI) (Bertelsen).

Bertelsen, in an accurate and detailed study of his own cases over a ten-year period, found that 6.3 per cent of the patients with Graves' disease developed a recurrence of their hyperthyroidism as compared with 2.8 per cent of those with nodular goiter. The average recurrence rate of hyperthyroidism in his patients was 4.9 per cent.

Etiology

The factors influencing the recurrence of hyperthyroidism are as little understood as are the initial causes of the disease. Focal infection, emotional or physical overactivity, pregnancy, dietary deficiencies, the use of stimulants, and numerous other factors often have been incriminated on scant evidence. Although all of these factors are worthy of consideration, it is questionable whether any one of them plays a large part in the production of recurrences. I believe that most recurrences are the result of removal of insufficient thyroid tissue at the time of the first operation.

TABLE VI

PAPERS ON RECURRENCE FREQUENCY IN THYROTOXICOSIS PUBLISHED SINCE 1930*

	Year	Number of reexamined cases	Recurrence frequency %
Clarke and Black	1930	76	10
Crile, G. W.	1930	17120	4.4
Pemberton, J. deJ.	1930	1683	2.9
Richter. H. M.	1930	1096	9
Thompson, Morris and Thompson	1930	190	19.5
Coller and Potter	1931	540	2.4
Troell, A.	1931	453	6
Clute and Veal	1932	97	6.2
Engel, A.	1932	36	27.9
Pool and Garlock	1934	171	9.3
Frazier and Johnson	1935	630	2.7
Tebroke, R.	1935	73	5.5
Strom, R.	1936	271	5
Gilette, N. W.	1937	102	6.5
McQuillan and Breidenbach	1937	803	5.6
Rasmussen, H.	1937	34	20.6
McGraw, A. B.	1938	189	11.5
Berlin and Gargill	1939	237	2.2
Cattell and Morgan	1939	306	3.7
Tinker and Tinker	1939	182	10
Windfeld, P.	1940	340	6.2
Hertz, J.	1943	90	3.3
Bruun, E.	1947	recurrences in 4.9% of 647 thyrotoxicosis patients treated in a medical department	

* Courtesy of Bertelsen, *et al.*

Hyperthyroidism, persistent or residual after thyroidectomy, is clearly the result of an inadequate thyroidectomy. If sufficient thyroid tissue is removed hyperthyroidism is controlled. But the late recurrences, occurring from two to five or more years after operation, cannot be so definitely attributed to an incomplete operation.

I have never seen hyperthyroidism recur in a patient who developed a pronounced hypothyroidism following thyroidectomy. Although this sequence of events has been reported (Pemberton), it is rare. If hyperthyroidism rarely recurs after an operation complete enough to cause hypothyroidism, and if incomplete thyroidectomy, followed by residual low-grade hyperthyroidism, usually is followed in turn by a true recurrence of the hyperthyroidism, the implication is that recurrent hyperthyroidism is caused by failure to remove enough thyroid tissue.

The results of 539 operations performed for hyperthyroidism support this hypothesis. In 261 cases the patients were followed from five to ten years after operation.

In the first 117 followed cases, the operation was performed by resection of the gland over hemostats. The gland was not rotated from its bed, and the inferior thyroid artery was not ligated. Consequently, it was impossible to estimate the exact amount of thyroid tissue that was left. Tongues of thyroid tissue extending behind the trachea could have been overlooked. Disregarding three cases of residual hyperthyroidism in which the operation obviously was inadequate, there were seven recurrences that occurred from one to seven years after operation, a recurrence rate of 6 per cent.

In the second group of 144 followed cases, an anatomic technic was employed. All the thyroid except enough of the posterior capsule to insure protection of the parathyroid glands was removed. All of the patients were followed longer than five years. In this group there was no case of residual hyperthyroidism and there were only three cases of recurrent hyperthyroidism (2.1 per cent). The conclusion based on this small group of cases is inescapable. The chief cause of recurrent hyperthyroidism is failure to remove an adequate amount of thyroid tissue, even when the hyperthyroidism recurs a year or more after operation (Table IV, page 162).

Hyperthyroidism may recur after operations for nodular goiter with hyperthyroidism, but this is rare. In a group of thirty-six cases of recurrent hyperthyroidism five-sixths of the patients appeared to have true Graves' disease.

Prevention of Recurrent Goiters and of Recurrent Hyperthyroidism

Slight recurrences of nontoxic nodular goiters following thyroidectomy are not uncommon if the patients are followed for many years. Here again the etiology is not clearly understood, although compensatory hyperplasia of the thyroid remnants and the subsequent development of additional nodules or enlargement of preexisting ones probably are responsible. Small doses of iodine, such as 10 mg. daily, or sufficient desiccated thyroid to correct hypometabolism might tend to prevent this type of recurrence. Iodine also may be of value in involuting and preventing enlargement of the remnants of a hyperplastic thyroid that was prepared for operation by administration of an antithyroid drug.

After thyroidectomy for a diffuse hyperplastic goiter, the remnants of the gland may be so small that they are put to a physiologic strain to maintain the thyroid balance of the body. If this is the case, a further hyperplasia of a compensatory nature may take place and may result in the enlargement of the thyroid remnants. One minim of Lugol's solution given daily for a period of six months to patients having unusually hyperplastic glands may aid in preventing this enlargement and the subsequent recurrence of hyperthyroidism. During this time the patient should be observed at regular intervals. Postoperative hypothyroidism seems to occur more frequently when iodine is given and the incidence of recurrent hyperthyroidism appears to be reduced. Since iodine was given only in selected cases, this conclusion is based on a clinical impression rather than on statistical facts.

Treatment of Recurrent Hyperthyroidism

Small doses of iodine (3 minims daily of Lugol's solution) given over a long period of time often will result in the permanent control of low-grade recurrent or residual hyperthyroidism associated with small goiters. Haines estimates that 25 per cent of these cases can be controlled satisfactorily and eventually cured by this treatment.

Thirteen patients upon whom I did the initial thyroidectomies have developed recurrent hyperthyroidism. In three of these, the hyperthyroidism manifested itself within a few months and is classified as residual. In the others, the recurrence took place after the patients had been entirely well from one to seven years.

One of the three cases with residual hyperthyroidism was controlled and finally cured by iodine alone, one by x-ray alone, and one by excising a recurrence the size of a cherry located in the thyroglossal tract just below the hyoid bone.

I did not find it necessary to operate again on any of the ten patients who developed recurrent hyperthyroidism. Propylthiouracil controlled the hyperthyroidism in two cases but the patients are still under treatment. One patient is well over a year after the thiouracil was stopped. X-ray cured one, iodine cured one, and a combination of x-ray and iodine cured one. One patient cannot be followed. Three patients went elsewhere and thyroidectomies were performed. In one of these the basal metabolic rate was normal, and it was questionable whether hyperthyroidism was present, but an operation was performed because the eyes were becoming more prominent.

In view of the excellent results obtained by conservative treatment of recurrent hyperthyroidism, especially when the thyroid remnants are small and hyperthyroidism is not severe, every patient with mild residual or recurrent hyperthyroidism should be given the benefit of a trial on conservative treatment. The antithyroid drugs enable us to control the hyperthyroidism indefinitely, and unless the patient is intolerant of them or the gland enlarges rapidly, I believe that this is the treatment of choice. Radioactive iodine should be effective in those cases that prove resistant to the thiouracil derivatives. When safe and effective means are at our disposal for controlling indefinitely or for curing recurrent hyperthyroidism, I do not believe that we are justified, except in special circumstances, in subjecting the patients to the risk of morbidity that is involved in the removal of a recurrent goiter.

Technical Aspects of Operations for Recurrent Goiter. There is perhaps no operation which can be so difficult as the adequate removal of a brittle, hyperplastic, and vascular recurrent goiter. The recurrent nerve is often drawn into the capsule of the gland by the inflammation following the previous operation. The jugular vein becomes adherent to the lateral border of the gland

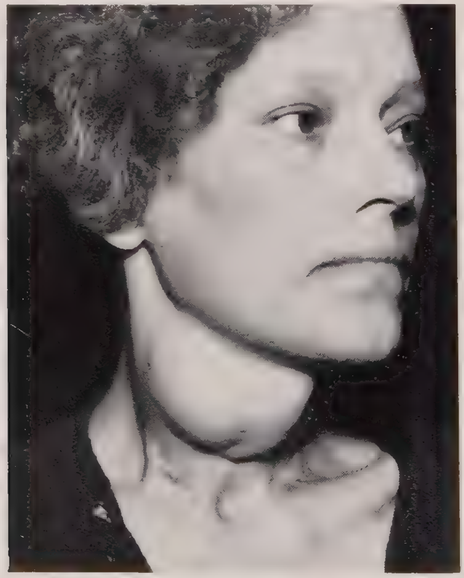


Fig. 61. Twice recurrent hyperthyroidism. Both recurrent laryngeal nerves had been damaged at previous operations, necessitating a tracheotomy before the recurrent thyroid tissue could be removed.

and the parathyroids are hidden by scar tissue. Several of the parathyroids may have been destroyed by the previous operation, and the location of the remaining glands may be atypical. Technical accidents, therefore, are certain to be increased in any large series of operations for recurrent hyperthyroidism (Fig. 61).

If recurrent goiters are removed by the conventional type of thyroidectomy, the incidence of tetany and of injury to the recurrent laryngeal nerves is high. If these important structures are to be protected, they must be demonstrated or avoided completely. In easy operations they can be identified and preserved, but in the more difficult cases it is safer to use a technic by which an adequate amount of thyroid tissue can be removed without disturbing the posterior capsule of the thyroid.

Exposure may be difficult to obtain without transverse division of the pretracheal muscles. As the gland is rotated up into the field of operation, care must be taken to avoid injury to the internal jugular vein which is often densely adherent to its lateral surface. Extracapsular ligation of the inferior thyroid artery just medial to the point at which it passes underneath the carotid is of value in effecting hemostasis. Isolation and preservation of the recurrent laryngeal nerve are desirable but may be difficult. A careful dissection often assures preservation of this important structure which may be hidden and distorted by scar tissue. The recurrent laryngeal nerves can be demonstrated in their relation to the inferior thyroid artery. If the nerve is not seen coursing under the artery, it should be searched for on the posterolateral surface of the gland where it may lie buried in the scar of the previous operation. Despite the greatest care, technical accidents will occur occasionally.

In difficult operations, when the remnants are either small or adherent or when the nerves and the parathyroids cannot be identified, there is only one safe and satisfactory way of removing an adequate amount of thyroid tissue and still preserving the important structures. The capsule of the gland is left intact laterally and posteriorly, and after ligation of the inferior thyroid artery and of the superior, when it is present, the soft parenchyma of the thyroid is scooped and cut out leaving only a shell of capsule. Oozing is controlled by sewing over the capsule after its contents have been removed.

Results of Surgical Treatment of Recurrent Hyperthyroidism. If the recurrent hyperthyroidism is associated with a large recurrence of thyroid tissue, if the hyperthyroidism is severe, or if the conservative methods of treatment fail, the surgeon may advise a second operation. The chances of relieving the hyperthyroidism by the second operation are excellent, the percentage of second recurrences being little if any higher than the recurrence rate following primary operations. In a series of forty-three operations for recurrent hyperthyroidism, I have seen no recurrences of the hyperthyroidism. The average basal metabolic rate of this group of patients was plus 31 per cent.

The morbidity is increased in secondary operations. The incidence of technical accidents such as tetany and injury to the recurrent laryngeal nerve is nearly four times as high as in primary operations (Cattell). In fifty-nine operations that I have performed for recurrent goiter, with or without hyperthyroidism, the incidence of permanent tetany was 1.7 per cent but 6.8 per cent had transitory hypocalcemia. (One of these patients had no symptoms and the hypocalcemia, which was found accidentally, probably had been present ever since the first operation.) There was only one case of persistent tetany requiring treatment.

In eight of the fifty-nine cases (13.6 per cent), there was preoperative paralysis of one recurrent laryngeal nerve. Twenty-nine patients were operated upon by the conventional technic without ligation of the inferior thyroid artery or an attempt to identify the nerve. In four of these (14 per cent) one recurrent nerve was injured (in one there was probable bilateral injury). Thirty patients were operated upon by the anatomic technic previously described, and in this group there were no injuries to the recurrent nerves. The incidence of injury in the entire group of fifty-nine cases was 6.8 per cent.

In one case a nontoxic adenoma has recurred five years after two previous removals of a similar goiter. There is no evidence of malignancy or of hyperthyroidism.

Four patients (7 per cent) have developed permanent and severe hypothyroidism.

Two patients, operated upon before the introduction of thiouracil, died after operation. One had a goiter that had recurred three times, wore a tracheotomy tube, and died as a result of infection and septicemia. The other died as a result of thyroid crisis and pneumonia which followed a tracheotomy performed for laryngeal paralysis and edema. Both patients were operated upon by the conventional nonanatomic technic.

Treatment of Choice of Recurrent Hyperthyroidism. I prefer to treat most patients with recurrent hyperthyroidism by prolonged or even indefinite use of propylthiouracil or with radioactive iodine unless the bulk of recurrent tissue be exceptionally large. The morbidity of secondary thyroidectomy, even in the hands of experienced surgeons, is high enough to raise the question of whether surgery is indicated when the disease can be controlled by other means. If the remnants of thyroid tissue are small and if the hyperthyroidism is refractory to control by antithyroid drugs, or if the patients are elderly, radioactive iodine appears to be the treatment of choice. Thyroidectomy should be reserved for cases in which the recurrent goiters are large or there are contraindications to other methods of treatment.

Bibliography

1. Bertelsen, A., Christensen, E., Bruun, E., and Becker-Christensen, P.: Mortality, operative complications and recurrence frequency in surgical treatment of thyrotoxicosis. Acta chir. Scandinav. *96:* 1–86 (supp. 133) 1947.
2. Cattell, R. B., and Morgan, E. S.: Recurrent hyperthyroidism; report of 306 cases operated upon from 1928–1937. Surg., Gynec. & Obst. *68:* 347–351 (Feb.) (No. 2A) 1939.
3. Haines, S. F.: Use of iodine in recurrent exophthalmic goiter. West. J. Surg. *42:* 449–455 (Aug.) 1934.
4. Pemberton, J. deJ.: Recurring exophthalmic goiter; its relation to amount of tissue preserved in operation on thyroid gland. J. A. M. A. *94:* 1483–1489 (May 10) 1930.

Chapter 19

HYPERTHYROIDISM IN EXTREMES OF LIFE

Hyperthyroidism is rarely encountered in patients in the extremes of life. In a series of 13,200 consecutive cases of hyperthyroidism seen at the Cleveland Clinic, there were only forty-two thyroidectomies performed for hyperthyroidism in children under 14 years of age and only forty-five in patients beyond the age of 70. The youngest child undergoing thyroidectomy for hyperthyroidism was a boy of 2½ years and the oldest patient was a man of 81 years of age.

Symptoms

Hyperthyroidism in children is almost always associated with a diffuse enlargement of the thyroid. On the other hand, nodules were present in the thyroids of 96 per cent of the patients over 70 years of age, even when the glands were diffusely hyperplastic and true Graves' disease was present.

In the aged, the clinical picture of hyperthyroidism is distorted by the myocardial, vascular, and cerebral changes of senility. Striking differences in the clinical expression of hyperthyroidism in children and in the aged are found.

The eye signs of hyperthyroidism occurred in 76 per cent of the children in this series (Fig. 62). In 14 per cent of the cases exophthalmos appeared so early and was so marked that it was considered the leading symptom. In the aged, exophthalmos rarely was seen.

In the aged, the predominating symptoms are nervousness, weakness, exhaustion, and loss of weight. In 20 per cent of these patients, the leading symptoms were attributable to cardiac decompensation. In the children, no instance of cardiac decompensation occurred and auricular fibrillation was not observed.

Hyperthyroidism in the aged expresses itself as exhaustion. The myocardial reserve, the nutrition of the body, and the energy of the organism are depleted by the constant demands of hypermetabolism. It is in children and in young adults that the stimulation of exophthalmic goiter in its typical form is seen.

Children with hyperthyroidism do not lose much weight and remain fairly well nourished. Nervousness, ceaseless activity,

Fig. 62. Graves' disease in a child. Exophthalmos and widening of the palpebral fissures usually are present.

emotional disturbances, tachycardia, and exophthalmos are the predominating symptoms. The nervousness and hyperactivity may even be so marked as to result in choreiform twitchings. In two cases in this series chorea was suspected when the child was first seen. Hyperthyroidism in children is almost never "masked" and rapidly assumes the clear-cut state of stimulation characteristic of exophthalmic goiter.

TABLE VII

Incidence of Auricular Fibrillation as Related to Age of Patient and Type of Goiter

Age	−10 yrs.	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80+ yrs.
No. of cases	4	12	49	76	62	35	18*	0	
Incidence of auricular fibrillation in patients with diffuse goiter	0.0%	0.0%	8.0%	3.9%	4.8%	20.0%	42.0%		
No. of cases		2	17	54	114	124	146	8	1
Incidence of auricular fibrillation in patients with adenomatous goiters		0.0%	0.0%	3.7%	9.6%	21.7%	35.0%	25.0%	0.0%

Diffuse: 258 cases: 8.1 per cent showed auricular fibrillation
Adenomatous: 466 cases: 16.6 per cent showed auricular fibrillation

* Because only seven cases of diffuse goiter with hyperthyroidism occurred in patients over 60 years of age in the period covered by this analysis, this group was enlarged by including all cases of hyperthyroidism in patients from 60 to 70 years of age over a period of several years.

It is chiefly in the aged that hyperthyroidism, masked as organic heart disease, is unsuspected until examination of the thyroid reveals the presence of an adenoma. In these patients, nervousness, cardiac symptoms, and weakness are the chief complaints.

Diagnosis

Although complications may obscure the diagnosis, the basal metabolic rate is reliable in the aged. Except in the presence of cardiac decompensation, a consistent elevation of the metabolic rate is strong evidence for the diagnosis of hyperthyroidism. The basal metabolic rate in twenty-seven patients over 70 years of age varied from plus 9 to plus 70 per cent, and averaged plus 27 per cent. In only two instances was it above plus 45 per cent.

Many of these patients had had large amounts of iodine for a long period of time, and this treatment had produced hard nodular glands that were of a consistency suggestive of malignancy. Since in the presence of hyperthyroidism malignant tumors of the thyroid are rare, it is well to consider any goiter associated with hyperthyroidism as benign unless definite signs of malignancy are present.

The basal metabolic rate is of less diagnostic value in children than in adults. The standards are not so accurately determined, and wide variations occur as a result of failure of the child to cooperate. The highest basal metabolic rate in this series was plus 87 per cent, the average being plus 36 per cent. In the twenty cases in which the basal metabolic rate was determined, the reading was below plus 5 per cent in only one instance, and this patient had been treated with iodine before the test was made.

Although clinical findings are of much more value than laboratory tests in establishing the diagnosis of hyperthyroidism in children, the determination of the level of the blood cholesterol is a valuable aid. The cholesterol varied in our series from 110 to 160 mg. per 100 cc. of blood. Roentgen examination of the epiphyses will often show development in advance of that normal for the patient's bone age.

Treatment of Hyperthyroidism in Children

The treatment of hyperthyroidism in children is the same as that in the adult. Prolonged attempts at conservative management are undesirable if the hyperthyroidism cannot be completely and easily controlled.

The remission of hyperthyroidism in children in response to bed rest and iodine usually is satisfactory and the operation is, therefore, safe. There were no deaths among thirty-seven patients on whom operation was performed before the introduction of thiouracil.

If the hyperthyroidism is not controlled by an antithyroid drug, the postoperative reactions of the pulse and temperature of children are often severe. In seven instances the pulse rose above 170 and the average temperature reaction was more severe than in an adult. Although the patients often looked quite sick on the first day after operation, the reaction always subsided quickly. In no instance was the patient's condition considered critical. Preparation with propylthiouracil has facilitated operations for hyperthyroidism in children.

The end results of thyroidectomy for hyperthyroidism in children have been excellent. Thirty-two of the thirty-six traced patients have remained free of symptoms and have developed normally. In one case a psychosis resembling an early schizophrenia appeared about four years after operation, and in one patient a troublesome neurocirculatory asthenia developed.

Hyperthyroidism recurred in two instances, both patients being young children whose hyperthyroidism was severe. It was formerly believed that a little more gland should be left in children than in adults in order to guard against the development of hypothyroidism during the years of the child's development. This complication has rarely occurred, and I now believe that the operation should be as complete in a child as in an adult with an exophthalmic goiter. A second operation has effected a permanent cure in both cases in which there was a recurrence.

The fomulation of keloids in the thyroidectomy scar of children is a common occurrence which can best be controlled by irradiation of the skin soon after, or both before and after, operation.

We have not as yet had sufficient experience with the treatment of hyperthyroidism with antithyroid drugs in children to know whether or not the incidence of longstanding or permanent remissions will be high enough to justify definitive medical treatment of these cases. Some of the children treated have required large doses of propylthiouracil and have not been easily controlled. It would appear that hyperthyroidism in children is often of a severe and resistant type.

Treatment of Hyperthyroidism in the Aged

Thyroidectomy should not be undertaken lightly in the aged patient with uncontrolled hyperthyroidism. Prior to the use of thiouracil, operation was performed on twenty-four patients over 70 years of age with five postoperative deaths, a mortality rate of 21 per cent. In addition, one patient on whom merely a ligation was performed became delirious and died at home a few weeks after operation without ever having fully regained his reason. For these reasons radioactive iodine or prolonged or indefinite treatment with an antithyroid drug is the treatment of choice for aged patients with hyperthyroidism.

Roentgenotherapy is not of much benefit in the control of hyperthyroidism associated with large nodular goiters. Satisfactory remissions were obtained with iodine alone in several instances, but many of the patients remained chronic invalids or soon expired. In justice to the conservative form of management, it must be remembered that the majority of the patients not subjected to operation were hopeless risks, in whom good results could not be expected from any form of therapy.

In spite of this conservatism, the postoperative reactions were alarming. Approximately one-half of the patients became delirious after operation, and many were critically ill. Pneumonia was the cause of death in three instances, cardiac failure accounted for one death, and "metabolic exhaustion" for the fifth. By "metabolic exhaustion" is meant the unclassifiable "fading away" which occasionally is seen following thyroidectomy in feeble and in elderly patients (p. 209). Without any particular elevation of the temperature and often without alarming elevation of the pulse rate, the patient will become confused, enter a state of muttering delirium, and will succumb without any obvious cause of death either clinically or on postmortem examination (Fig. 63).

Pulmonary complications, often intervening in the course of the reaction described above, are the greatest threat to the aged patient. Beyond the age of 60, pneumonia is the most common cause of death following thyroidectomy for hyperthyroidism. Starting with apathy or mental confusion, the aged patient will become progressively weaker. Pulmonary congestion may occur as a result of a failing myocardium.

Fig. 63. "Metabolic exhaustion" associated with confusion and delirium in an aged patient following thyroidectomy.

Mucus from tracheal irritation accumulates and the delirious patient will be too weak or too uncooperative to attempt to cough it up.

The bromsulfalein test of liver function shows dye retention in a high percentage of the older patients with hyperthyroidism and clinical jaundice may occur. Failure of liver function can best be corrected by the administration of a high protein-high carbohydrate diet.

In the aged, depression, whether induced by inhalation anesthesia or by basal anesthetic agents, must be avoided. Any depression of respiration, of the cough reflex, or of the internal metabolism of the body may lower the vital reserve below the threshold of resistance to a terminal pneumonia. The operation should be performed under local or cervical block anesthesia.

In children and young adults, morphine should be given in doses sufficient to obtain complete relaxation and analgesia. In the aged, undue depression may result if the usual doses are given. Confusion, delirium, and depression are minimized if the dosage of morphine is limited to ⅛ grain or if only codeine is given. As Dr. Crile, Sr., has stated, "Old age is its own analgesia."

In the child or young adult with severe hyperthyroidism, we must do everything in our power to combat hyperthyroidism and depress the stimulation and the emotional drive of the thyroid crisis. Sedation with large doses of morphine is of value.

Table VIII summarizes the manifestations of hyperthyroidism in the extremes of life.

TABLE VIII

Hyperthyroidism in the Extremes of Life

Children under 14	*Patients over 70*
Hyperthyroidism expresses itself as stimulation	Hyperthyroidism expresses itself as exhaustion
Exophthalmos is the rule	Exophthalmos is rare
Goiter is diffuse	Goiter is adenomatous
Cardiac complications absent	40 per cent of patients have auricular fibrillation or cardiac decompensation
Diagnosis usually clear	Complications may obscure diagnosis
Basal metabolic rate unreliable	Basal metabolic rate reliable
Reaction of pulse and temperature to operation tends to be severe, but patients do well	Reaction to operation tends to be mild but complications are common
No deaths following 37 operations	Mortality rate 21 per cent for 24 operations before thiouracil

Treatment of choice: Subtotal thyroidectomy after preparation with propylthiouracil or possibly Propylthiouracil as definitive treatment	Treatment of choice: Propylthiouracil indefinitely if necessary or Radioactive iodine
General anesthesia	Local anesthesia
Keep patient relaxed and analgesic with sedation	Avoid excessive sedation and attempt to build up resistance of patient
Postoperative complications very rare	Delirium occurs in 50 per cent of cases, and pulmonary complications are common.

Bibliography

1. Cole, W. H., Slaughter, D. P., and Rossiter, L. J.: Potential dangers of nontoxic nodular goiter. J. A. M. A. *127:* 883–888 (April 7) 1945.
2. Goetsch, E.: New concept regarding origin of so-called primary carcinoma of hyperplastic thyroid. Ann. Surg. *118:* 843–858 (Nov.) 1943.
3. Graham, A.: Personal communication.
4. Hinton, J. W., and Lord, J. W., Jr.: Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? J. A. M. A. *129:* 605–606 (Oct. 27) 1945.

Chapter 20

DISEASES ASSOCIATED WITH HYPERTHYROIDISM

Cardiac Complications

Auricular fibrillation is rarely seen in young people with normal hearts. But in the presence of organic heart disease, whether it be arteriosclerotic or rheumatic, auricular fibrillation and cardiac decompensation are common complications of hyperthyroidism.

There is little evidence that hyperthyroidism of itself causes any permanent or irreversible damage to the heart. If the underlying heart disease is negligible or mild, reversion to normal rhythm and restoration of cardiac compensation will follow correction of the hyperthyroidism. If, on the other hand, there is serious sclerosis of the coronary vessels, irreversible changes have taken place. Although the patient may be much improved following thyroidectomy, the heart disease will not be cured.

Hyperthyroidism predisposes to the development of auricular fibrillation. Sometimes the fibrillation is intermittent but more often it continues until the hyperthyroidism is completely controlled either by one of the antithyroid drugs or by thyroidectomy. Provided that the control is complete and the basal metabolic rate has fallen to 0 or to subnormal levels, there is little reason to believe that the heart is benefited more by thyroidectomy than by the antithyroid drugs. A possible consideration in large goiters is the increased burden on the circulation incident to the presence of the large vascular bed of thyroid. If the hyperthyroidism is to be treated medically, it may be wise to control the excessive vascularity of the thyroid by administration of iodine along with an antithyroid drug.

The heart often reverts spontaneously to normal rhythm within a few days or weeks of the time that the hyperthyroidism is completely controlled. Spontaneous reversion is more commonly seen in patients whose underlying cardiac disease is mild and whose fibrillation has not been of long duration.

If the rhythm does not revert spontaneously to normal it may be desirable to use quinidine. In the presence of long-standing fibrillation quinidine is contraindicated lest reversion to normal rhythm dislodge a mural thrombus and result in a fatal embolism (Ernstene).

The problem of the management of the patient with hyperthyroidism, auricular fibrillation, and cardiac decompensation has been simplified by the advent of the antithyroid drugs. In such cases the risk of thyroidectomy is greatly diminished if the hyperthyroidism is completely controlled and the basal metabolic rate is within normal limits at the time of operation. When the hyperthyroidism is controlled, management of the cardiac problem is no different from that in any other surgical operation performed on a patient with heart disease.

It has been argued that the patient with cardiac decompensation may suffer permanent impairment of cardiac reserve as a result of myocardial strain incurred during the time required for the antithyroid drugs to exert their full effect. However, it is hard to believe that a patient could be so sick that a month's delay would cause serious myocardial strain and, at the same time, could be in good enough condition safely to withstand operation after preparation with only iodine.

The simultaneous use of iodine and propylthiouracil controls hyperthyroidism almost as rapidly as when propylthiouracil is given alone. When treated in this way, the patient receives the benefit of both the prompt partial remission induced by iodine and the eventual complete control resulting from propylthiouracil therapy. There is no evidence to suggest that the cardiac status of a patient will be further improved by thyroidectomy if the hyperthyroidism is already completely controlled with an antithyroid drug.

Paroxysmal auricular tachycardia and auricular flutter occasionally are associated with hyperthyroidism but this association is rare and indefinite and control of the hyperthyroidism may not correct the disturbance in rhythm. Similarly the removal of nodular goiters that are not associated with hyperthyroidism rarely corrects disturbances of cardiac rhythm. When there is doubt as to the relationship of a goiter to a disturbance in the function of the heart, the problem should be studied by an empiric trial on treatment with one of the antithyroid drugs before thyroidectomy is advised.

Diabetes

Diabetes is more common in patients with hyperthyroidism than in the population at large and the severity of established diabetes is increased in patients who develop hyperthyroidism. At times the diabetes may be difficult to control and for this reason the persons with diabetes, like those with cardiac disease, should either be treated definitively with one of the antithyroid drugs, or operated upon only after the hyperthyroidism and diabetes are well controlled.

Patients with severe hyperthyroidism have a peculiar type of glucose tolerance curve that rises to high levels in the first hour or two and then falls to normal. During the peak of the curve the blood sugar is at diabetic levels and sugar may appear in the urine. This is not a true diabetes and reverts to normal after the hyperthyroidism is controlled. It may be dependent on interference with liver function incident to the hyperthyroidism and upon failure of the damaged liver to convert glucose to glycogen as rapidly as normal, so that the blood sugar level rises abnormally high.

Tuberculosis

When hyperthyroidism complicates tuberculosis the elevated basal metabolic rate places an additional burden on the lungs and the chronic infection may cause an exacerbation of the hyperthyroidism. A vicious circle is thus established and may continue until the hyperthyroidism is controlled.

Thyroidectomy should be performed only after the hyperthyroidism is completely controlled by one of the antithyroid drugs, and then either local or cervical block anesthesia should be used. In many cases indefinite control with the antithyroid drugs may be the treatment of choice.

Pregnancy

When pregnancy is complicated by mild hyperthyroidism the patient usually goes to full term and delivers a normal baby without complication. But when the hyperthyroidism is severe there may be a miscarriage, the mother may develop cardiac decompensation during the last trimester, or after delivery the mother may experience a thyroid crisis. The increased basal metabolic rate incident to pregnancy alone may be as much as 30 per cent. This, coupled with the circulatory burden of the hyperthyroidism, may prove too much for the myocardium. When hyperthyroidism is of such severity that it cannot be controlled with iodine, more effective means of control must be used.

Prior to the development of the antithyroid drugs hyperthyroidism during pregnancy was treated by subtotal thyroidectomy done under local anesthesia after preparation with iodine. The hospital mortality rate in a series of thirty-three patients operated upon at the Cleveland Clinic prior to the introduction of thiouracil was 0. One patient died at home between stages of a divided operation. There were no miscarriages and the only known abnormality of the babies was a hydrocephalic monster.

This is an excellent record and one which is hard to compete with unless the methods of control with the antithyroid drugs can be proved to be entirely free of the danger of inducing goiter or derangements of thyroid function in the child. Since the antithyroid drugs occasionally do cause enlargement of the thyroid, we have no reason to believe that the fetal thyroid will be immune to this stimulation. Cases of congenital goiter occurring after administration of antithyroid drugs already have been reported. Consequently, we cannot assure the mother that her child's thyroid will not be affected and she must share the responsibility with the doctor if she elects to take the antithyroid drugs during pregnancy. Usually the fetus incurs no ill effects.

In theory iodine or desiccated thyroid should be helpful in controlling the enlargement of the thyroid that occurs with the use of antithyroid drugs. Unfortunately neither of these agents gives uniform protection. If the mother is taking an antithyroid drug, she should take small doses of iodine (10 mg. daily) or enough thyroid to prevent the development of hypothyroidism.

If severe hyperthyroidism were to occur in pregnancy there would be no contraindication to preparing the patient with propylthiouracil and removing the thyroid. In mild hyperthyroidism, I believe the safest course from the standpoint of the fetal thyroid is preparation with iodine and thyroidectomy. The use of radioactive iodine would be contraindicated, on theoretical grounds, after the first month or two of pregnancy.

Arthritis

Periarthritis of the shoulder is a fairly common complication of hyperthyroidism. There are no permanent joint changes, and the symptoms usually subside following control of the hyperthyroidism.

True rheumatoid arthritis is not associated in any definite way with hyperthyroidism but if coincidentally present may improve following control of the hyperthyroidism.

Pains and stiffness in the muscles and joints are common symptoms of hypothyroidism and disappear promptly when the hypothyroidism is corrected.

Disturbance in Pigmentation

Vitiligo or leukoderma may occur unpredictably and for no known cause in the course of hyperthyroidism or subsequent to its complete control by thyroidectomy. There is no known treatment for this condition. Occasionally the skin of the entire body will become darker during the course of hyperthyroidism or after it is controlled.

Localized Myxedema

Patches of localized myxedema occasionally occur on the legs either during the course of Graves' disease or after the hyperthyroidism is completely controlled. The development of this condition bears no relationship to the basal metabolic rate or to the development of myxedema elsewhere. Biopsy of the skin shows mucinous degeneration of the cutis (Netherton) (Crile). The affected area, usually on the lower leg, looks thick and has the "orange peel" appearance seen in lymphostasis. There is no known treatment for this condition. It does not spread or have serious consequence and may disappear spontaneously. In one case of McCullagh's the localized myxedema disappeared after cauterization of the pituitary performed for malignant exophthalmos.

Bibliography

1. Crile, George, *et al.:* Diagnosis and Treatment of Diseases of the Thyroid Gland. Philadelphia: W. B. Saunders Co., 1932.
2. Eaton, J. C.: Treatment of thyrotoxicosis with thiouracil. Lancet *1:* 171–174 (Feb. 10) 1945.
3. Ernstene, A. C.: Use of digitalis and quinidine sulfate in hyperthyroidism. S. Clin. North America *21:* 1365–1370 (Oct.) 1941.
4. Lehman, J. A.: Hyperthyroidism associated with pregnancy. West. J. Surg. *41:* 524–531 (Sept.) 1933.
5. Netherton, E. W., and Mulvey, E. B.: Circumscribed myxedema. J. A. M. A. *104:* 1492–1496 (April 27) 1935.

Chapter 21

CONGENITAL ABNORMALITIES OF THE THYROID AND THYROGLOSSAL TRACT

Embryology

The thyroid gland originates as an outpocketing of the pharynx. Early in embryonic life, a pouch from the midline of the buccal mucosa in the region of the foramen cecum begins to descend into the lower cervical regions, and this outpocketing is joined by cords of cells descending from the fifth pharyngeal pouch on each side. These lateral outpocketings appear to play no actual part in the development of the thyroid proper, and it is thought that under normal conditions they undergo atrophy and disappear. It is possible that these lateral cords under certain circumstances fail to undergo complete resolution and in later life develop into papillary tumors of the thyroid.

By the eighth week of embryonic life, the thyroid gland has descended from the foramen cecum and has assumed its normal position anterior and lateral to the trachea at the level of the second and third tracheal ring. The path of descent of the thyroid from the foramen cecum is marked in many instances by a well-defined structure known as the thyroglossal tract. Islands of thyroid epithelium may be scattered along this tract, or there may be islands of squamous cell or of ciliated epithelium. In most cases the tract is fibrous in nature and contains few if any recognizable epithelial cells.

This tract is of clinical importance because of its relationship to the pyramidal lobe of the thyroid; to cysts, sinuses, and tumors of the thyroglossal tract; and to the location of ectopic thyroid tissue. All lesions arising from this tract are located in the midline between the foramen cecum and the isthmus of the thyroid.

Occasionally, through failure of the thyroid to descend, the thyroid gland may be located at the foramen cecum of the tongue (lingual thyroid) or lower along the course of the thyroglossal tract. Frequently, under these circumstances, no thyroid tissue is present in its usual location. A careful exploration of the region of the thyroid should therefore be undertaken before midline ectopic thyroid glands are removed.

The pyramidal lobe of the thyroid is a remnant of the thyroglossal tract. It is a variable structure, often being entirely absent, but occasionally extending as high as the hyoid bone. A search for this lobe should always be made, and when found during the course of a thyroidectomy it should be removed. Recurrent or residual hyperthyroidism may result from overlooking this tissue, or, in the case of simple goiter, a conspicuous recurrence of the goiter may take place. A pyramidal lobe can be demonstrated in about 75 per cent of all goiters.

Cysts and Sinuses of the Thyroglossal Tract

The most common lesions of the thyroglossal tract are the epithelium-lined midline cysts and sinuses of the neck. These structures are of congenital origin, may appear at any time of life, but are most commonly noted in childhood.

Since the thyroglossal tract does not come to the surface of the neck, children are rarely born with thyroglossal sinuses (Table IX). As a rule, these sinuses are caused by surgical incision or spontaneous drainage of a thyroglossal duct cyst. After an upper respiratory infection, a small and hitherto unnoticed cyst of the thyroglossal tract may become infected, enlarge rapidly, and become tender and painful. Incision of this cyst results in a permanently draining fistula. Sometimes, depending on the location of the incision or the point of the spontaneous rupture of the cyst, the opening of the sinus may be to the left or the right of the midline, but it will never be so far from the midline as the usual location of the opening of branchial cleft sinuses.

The cyst itself is invariably located in the midline and may be either above or below the hyoid bone, its usual location being between the isthmus of the thyroid and the hyoid (Table X).

TABLE IX*
THYROGLOSSAL DISEASE

	Cysts (34 Cases)	Sinuses (26 Cases)
Sex		
Male	10 cases—29%	10 cases—39%
Female	24 cases—71%	16 cases—61%
Age at Onset		
Average	32 years	13.6 years
Present at birth	1 case	1 case
Eldest at onset	60 years	67 years
Age when First Seen		
Average	34.7 years	21 years
Youngest	5 years	6 years
Eldest	65 years	68 years
Duration of Symptoms		
Before first operation	3.1 years	3.1 years

* Through the courtesy of E. A. Gaston. Cleveland Clinic Quarterly.

TABLE X*
LOCATION OF MIDLINE CYSTS AND FISTULAS

Location	Cyst	Sunus (External Opening)
Submental	1	2
Between hyoid and thyroid cartilage	18	8
Level of thyroid cartilage	6	8
Level of cricoid cartilage	2	3
Level of isthmus of thyroid gland	3	1
Suprasternal notch	2	0
Level not stated	2	4

* Through the courtesy of E. A. Gaston. Cleveland Clinic Quarterly.

The tract is always attached to the hyoid, and hence the tract and the attached cyst rise with deglutition. Although the cyst is tense, fluctuation usually can be detected.

Thyroglossal duct cysts usually contain brownish fluid with sparkling cholesterol crystals. If infection has taken place, the cyst may be filled with pus. Above and below the cyst a cord-like tract usually is found. This tract may or may not be patent and may or may not contain epithelial cells. The epithelial cells lining the cysts may be squamous or may be ciliated, representing displaced pharyngeal mucosa.

Treatment. The treatment of thyroglossal cysts and sinuses is surgical excision. Injection of sclerosing solutions has been tried (Cutler and Zollinger), but for the greater part the results obtained by this method have been unsatisfactory.

In dealing with a sinus, it is necessary, in order to avoid the possibility of recurrence, to excise the entire thyroglossal tract upward as far as the base of the tongue. The tract usually traverses the midportion of the hyoid bone and it is necessary to resect this portion of the bone and the tract above it as far as the foramen cecum if the tract is to be eradicated. It is not necessary to resuture the divided hyoid and no disability follows its resection (Sistrunk).

If the cyst is removed intact and if there is no leak to denote the presence of a thyroglossal sinus, it is not necessary to excise the hyoid. In these cases the thyroglossal tract is not patent. If the cyst communicates with a patent thyroglossal tract, however, the entire tract must be excised.

Dissection of the tract upward as far as the hyoid bone usually is easy. A wide section of the central portion of the bone is then cleaned and a segment at least 1 cm. long is excised. At this point care must be taken not to pull too hard or the upper part of the tract may be broken and lost.

After the bone is divided the attachments to the pharynx are separated. This structure is fibrous and dense and looks almost like the sinus tract so that it may be dissected out and the pharynx opened. This accident can be avoided if it is remembered that the tract always courses cephalad. headed for the foramen cecum, and not dorsally towards the pharynx (Fig. 64). Since many tracts communicate with the pharynx at the foramen cecum it is a wise precaution to ligate them before dividing them.

If the operation is for the removal of an uninfected cyst the wound can be closed without drainage. If an infected sinus is present it is wise to leave a drain in place for three or four days. Fine 0000 chromic catgut is preferable to nonabsorbable

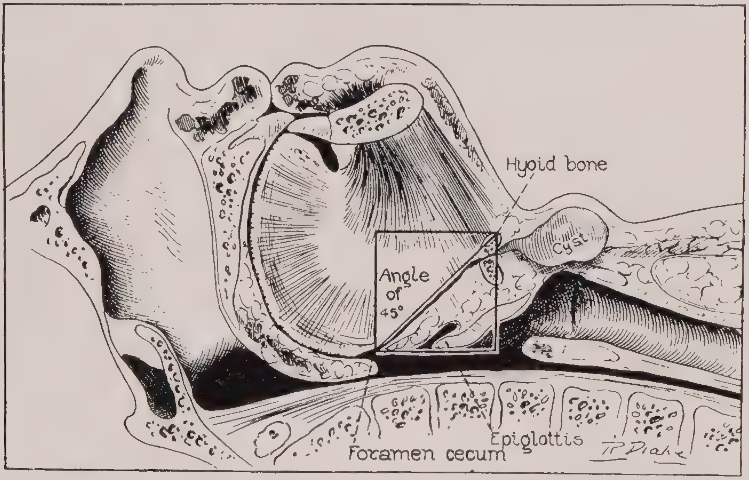


Fig. 64. The line along which the dissection must be carried in order to remove completely the thyroglossal tract. (From W. E. Sistrunk, S. Clin. North America, Oct. 1921.)

ligatures because the wounds are potentially contaminated. If infection should occur and drainage persist it would be difficult to tell whether the drainage were due to the nonabsorbable ligatures or to a persistence of overlooked epithelium.

The incision of choice is a transverse elliptical incision parallel to the natural wrinkles of the neck. Vertical incisions never should be used. The incision should include the opening of the sinus, except in the rare cases in which the opening is so low that the suprahyoid portion of the dissection could not be accomplished through the same incision. Under these circumstances, it is preferable to make the incision above the sinus and, after raising the skin flaps both upward and downward, excise the entire tract along with the central portion of the hyoid bone. Some surgeons inject the sinus with gentian violet the night before operation. Occasionally it is possible to pack the sinus with a narrow strip of gauze (using a probe to fill the tract with the gauze) to render it easily palpable.

In a series of sixty cases of thyroglossal cysts and sinuses operated upon at the Cleveland Clinic and reported by Gaston there was only one recurrence, this having occurred in a case in which the operation was not carried above the hyoid bone. In the majority of cases the central portion of the hyoid was excised.

A true lingual thyroid is a rare finding, only one such case having been observed at the Cleveland Clinic. Exploration of the thyroid should be performed to confirm the presence of a normally situated gland before complete removal of a lingual thyroid is undertaken.

Bibliography

1. Cutler, E. C., and Zollinger, R.: Use of sclerosing solutions in treatment of cysts and fistulae. Am. J. Surg. *19:* 411–418 (March) 1933.
2. Gaston, E. A.: Cysts and sinuses of neck. Cleveland Clin. Quart. *3:* 311–322 (Oct.) 1936.
3. Sistrunk, Walter E.: S. Clin. North America *1:* 1509 (Oct.) 1921.

Chapter 22

CLASSIFICATION OF MALIGNANT TUMORS OF THE THYROID

Clinical Aspects

From the clinical point of view carcinomas of the thyroid can be divided into two main groups, the papillary and the nonpapillary. Papillary carcinomas generally behave as lymphangio-invasive tumors and metastasize to lymph nodes, whereas nonpapillary carcinomas are hemangio-invasive and metastasize chiefly through the blood stream. The great differences in the clinical behavior and prognosis of these two groups of tumors can be explained by their respective tendencies to invade lymphatics and blood vessels.

Papillary carcinomas tend to be non-encapsulated, or at least non-enucleable. (Figs. 65, 66, 67.) If a capsule is present it is formed by sclerosis and is densely adherent to the surrounding thyroid tissue so that it cannot be "shelled out" like the differentiated nonpapillary carcinomas. It is perhaps because the papillary carcinomas originate in the parenchyma of the thyroid, which is well supplied with lymphatic vessels, that they tend to invade lymphatics. If the nonpapillary tumors arise in adenomas the absence or paucity of lymphatics in these adenomas may explain their tendency to invade blood vessels rather than lymphatics.

Papillary tumors occur frequently in children and young adults, whereas nonpapillary tumors follow more closely the general age distribution of most other carcinomas. This tendency to occur in the young cannot fail to suggest the possibility that papillary carcinomas arise in congenital rests and are not related to the presence of endemic goiter. Nonpapillary carcinomas, on the other hand, may arise more often in adenomas, tend to be more common in regions of endemic goiter, and are diminishing in frequency as goiter becomes less common.

Papillary carcinomas carry a much more favorable prognosis than nonpapillary carcinomas. Even when there is extensive metastasis to regional lymph nodes, cures usually are affected by removal of the tumor and the metastatic nodules. When nonpapillary tumors metastasize to lymph nodes the prognosis usually is hopeless.

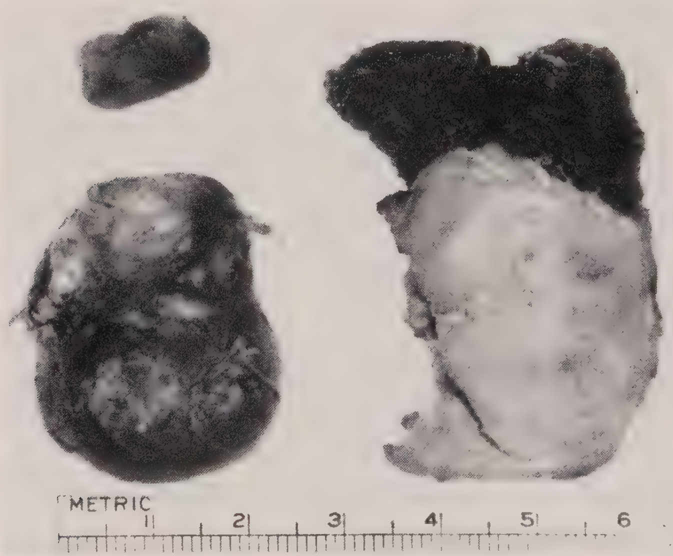


Fig. 65. Papillary carcinoma of the thyroid with metastasis to lateral cervical nodes. Note lack of encapsulation and infiltration of the normal thyroid by the tumor. This type of tumor cannot be enucleated from the surrounding thyroid.

More than twenty years ago Dr. Allen Graham recognized these fundamental differences between the papillary and nonpapillary tumors of the thyroid, and he named the nonpapillary tumors "malignant adenomas." This term stemmed from his belief that the nonpapillary tumors originated in adenomas and became malignant. All such tumors, whether highly differentiated angio-invasive adenomas or undifferentiated carcinomas, he classified as malignant adenomas, a term which was misunderstood because the word "adenoma" implied a benign quality which the term as used by Graham did not imply. Hence we have modified Graham's classification, renaming the malignant adenoma "nonpapillary carcinoma." (Table XI.)

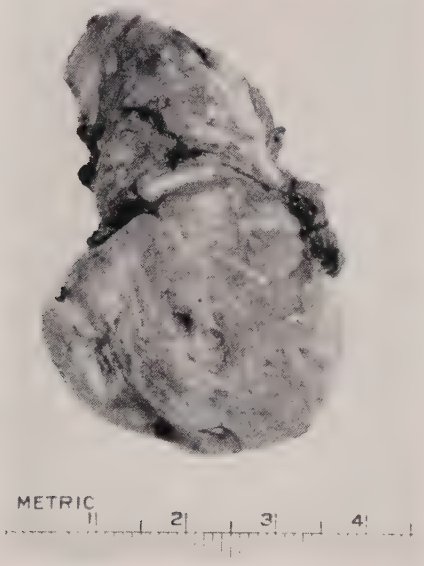


Fig. 66. Well encapsulated nonpapillary carcinoma of the thyroid. Such a tumor can be enucleated from the surrounding thyroid.

This classification retains Graham's two great groups: (1) the lymphangio-invasive papillary carcinomas which are non-encapsulated or at least non-enucleable, occur in young people, possibly as congenital rests, invade lymphatics, and metastasize to the regional lymph nodes; and (2) the hemangio-invasive nonpapillary tumors which, if they originate in adenomas, are encapsulated and enucleable until the capsule is invaded, occur in an older age group, invade blood vessels, metastasize distantly through the blood stream, and carry a much more grave prognosis (Table XII).

Special Types. In addition there are three special types of carcinoma of the thyroid, which are rare and are not included in the two main groups of papillary and nonpapillary tumors. This special group includes the consistently fatal squamous cell and metastatic carcinomas, and a third unusual lesion, described as non-encapsulated sclerosing tumor. This last

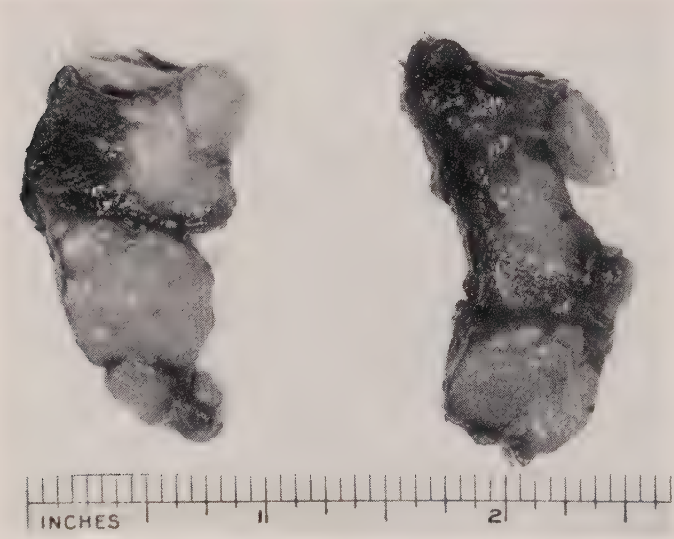


Fig. 67. Papillary carcinoma of the thyroid. Note that there appear to be multiple primary tumors in the thyroid and that they are not encapsulated and enucleable like well differentiated nonpapillary carcinomas.

type is classified by Graham as adenocarcinoma not originating in adenoma, and by Goetsch as carcinoma of the hyperplastic thyroid. These tumors are small, rarely exceeding 2 cm. in diameter, and are usually incidental findings in the course of a thyroidectomy done for other causes. They are of questionable malignancy, hence are designated as non-encapsulated sclerosing tumors rather than as carcinomas. It is quite pos-

TABLE XI

Classification of 64 Consecutive Malignant Tumors of the Thyroid, 1936 through 1945

Type	No. of Cases
Carcinoma	
1. Papillary carcinoma	34
2. Nonpapillary carcinoma	22
a. Angio-invasive adenoma	(3)
b. Adenocarcinoma	(8)
c. Undifferentiated carcinoma	(11)
3. Special types	4
a. Non-encapsulated sclerosing tumor	(3)
b. Squamous cell carcinoma	(1)
c. Metastatic carcinoma	(0)
Sarcoma	
1. Lymphoma	3
2. Spindle cell sarcoma	1

TABLE XII

Comparison of Characteristics of Papillary and Nonpapillary Carcinomas

	Papillary Carcinoma	Nonpapillary Carcinoma
Origin	? Congenital rest	? In an adenoma
Goiter	Probably no relationship to endemic goiter	Relationship to endemic goiter
Incidence	Children and young adults	Adults and aged
Encapsulation	Absent or poor	Enucleable until capsule is invaded by tumor
Behavior	Lymphangio-invasive Metastasis to lymph nodes	Hemangio-invasive Metastasis through blood stream
Prognosis	Good if locally removable	Fair to poor, depending on degree of anaplasia

sible they should not be included among the malignant tumors of the thyroid gland.

Pathologic Aspects*

Papillary Carcinoma. Papillary carcinomas are defined as epithelial neoplasms, formed by cuboidal or columnar epithelium, partly or wholly in papillary arrangement. The capsule is either absent or is invaded by the tumor so that the tumor is not enucleable. Papillary carcinomas usually are unilateral but occasionally foci are apparent in the contralateral lobe. Encapsulated papillary tumors with intact capsule and without evidence of blood vessel invasion are, of course, regarded as adenomas. Neoplasms which are partly papillary but which are in part undifferentiated are classified in the more malignant group. Among the papillary carcinomas there are several variants.

Cystic or Adenocarcinoma Variant. The epithelial cells are well differentiated, often paler than the usual thyroid epithelium. In the same tumor there may be cystic areas or areas of compact growth formed by closely packed acini. Some tumors are predominantly of the latter type, but on search papillary areas are found. Nineteen of the thirty-four papillary neoplasms encountered in the decade of 1936 through 1945 show this variation. Eleven had metastasized to the lateral cervical lymph nodes.

Tall Cell Variant. These are often bulky tumors, in this series of nine cases averaging 5.9 cm. in diameter. The epithelial cells are tall, usually 15 to 25 microns in height, and are more oxyphilic than usual. In some cases all of the cells of the tumor are tall and in others only part of them show this variation. In some of the tall cell tumors there is marked lymphocytic infiltration of the stroma.

Medullary Variant. These are grossly circumscribed tumors, though histologically showing capsular invasion. Usually they are not large. Histologically they are formed by cells

* Courtesy of Dr. J. B. Hazard, Department of Pathology, Cleveland Clinic Foundation.

of medium size, arranged in solid sheets or trabeculae and with infrequent areas of papillary arrangement. Both in staining properties and arrangement, they simulate transitional epithelial cells. The nuclei are well differentiated and uniform. These tumors may be confused from the histologic standpoint with a more malignant form of nonpapillary carcinoma unless it is recognized that the cells are well differentiated and that there are areas of papillary arrangement.

Six of these medullary variants were encountered in this series. Five were grossly encapsulated and one partly encapsulated although, histologically, the capsule was invaded in all cases. Metastases to the cervical lymph nodes were noted in three instances. The average size of the tumors was 3.6 cm.

Nonpapillary Carcinoma. In the nonpapillary carcinomas are included all carcinomas of the thyroid except the papillary carcinomas and the special types as indicated on the table of classification.

The twenty-two carcinomas of the nonpapillary group in this series include three angio-invasive adenomas, eight adenocarcinomas, and eleven undifferentiated carcinomas. Encapsulation was noted in the angio-invasive adenomas and partial encapsulation in the adenocarcinomas. The majority of the undifferentiated carcinomas were diagnosed by biopsy; in the few in which the whole specimen was available no encapsulation was observed. Blood vessel invasion was a common feature of the nonpapillary group. Two of the adenocarcinomas were oxyphilic or so-called Hürthle cell carcinomas.

Prognosis

None of the nineteen patients with cystic or adenocarcinoma variants died of carcinoma. Three of the nine patients with the tall cell variant died of their disease. There were no deaths due to thyroid carcinoma in either the adenocarcinoma or the medullary variants although one patient of each of the latter groups is living with recurrence.

In the nonpapillary group fourteen of twenty-two patients died. The survivors include two of three patients with angio-invasive adenomas; three of eight patients with adenocarcinomas (two living with recurrence) and none of eleven patients with undifferentiated carcinoma. Of the special types, only the three patients with non-encapsulated sclerosing tumor survived (Table XIII).

TABLE XIII

SURVIVAL STATISTICS, 64 MALIGNANT TUMORS OF THE THYROID, 1936–1945

Type	Total	Living and well over 2 years	Living with recurrence	Died of disease	Died of other causes	Not followed
Papillary Carcinoma	34	20	2	3	3	6
Nonpapillary Carcinoma	22					
Undifferentiated Carcinoma	11			8		3
Adenocarcinoma	8	1	2	5		
Angio-invasive Adenoma	3	2		1		
Special Types	4					
Non-encapsulated Sclerosing Tumor	3	3				
Squamous Cell Carcinoma	1			1		
Sarcoma	4					
Lymphosarcoma	3			3		
Fibrosarcoma	1					1

Lymphoma. Many so-called round cell sarcomas of the thyroid may be undifferentiated carcinomas. Occasionally a lymphosarcoma or reticulum cell sarcoma is seen and these may respond to irradiation. Many do not. The prognosis is bad and thyroidectomy is of little value.

Spindle Cell Sarcoma. Spindle cell sarcoma of the thyroid behaves like spindle cell sarcoma elsewhere. Death usually occurs rapidly as a result of local invasion before metastasis can take place. Roentgen therapy has not proved effective. In fibrosarcomas, neurogenic sarcomas, and myosarcomas the prognosis is universally poor.

Bibliography

1. Goetsch, E.: New concept regarding origin of so-called primary carcinoma of hyperplastic thyroid. Ann. Surg. *118:* 843–858 (Nov.) 1943.
2. Graham, A.: Criteria of malignancy. Radiology *37:* 521–532 (Nov.) 1941.
3. Graham, A.: Malignant tumors of thyroid; epithelial types. Ann. Surg. *82:* 30–44 (July) 1925.
4. Graham, A.: Interstate Post Graduate Medical Proceedings, 1927.
5. Ward, R.: Malignant goiter; survey of geographical types. West. J. Surg. *43:* 494–504 (Sept.) 1935.

Chapter 23

INCIDENCE OF CARCINOMA OF THE THYROID

Explanation of Reported High Incidence of Carcinoma of the Thyroid

There is a discrepancy between the high incidence of cancer of the thyroid encountered by surgeons (Cole) and the low incidence of fatal cancer of the thyroid reported in vital statistics (Williams). Although surgeons often state that 5 to 10 per cent of nontoxic nodular goiters are malignant, this does not reflect the true incidence of cancer of the thyroid in this condition (Hinton and Lord). The incidence of malignancy, as observed by the surgeon, is high because he is dealing with the selected group of nontoxic nodular goiters that are subjected to thyroidectomy.

The patients who come to the surgeon have been carefully screened, first by the patient himself, who does not often consult a doctor unless the nodule is giving evidence of growth or functional activity; second by the family physician or internist, who detects the obvious benign quality of soft, poorly-defined involutionary nodules in the thyroid and hesitates to advise surgery; and finally by the surgeon himself, who recognizes the innocuousness of small soft multinodular goiters, reassures the patient, and discourages operation. Therefore, the fact that the surgical pathologist finds 8 per cent of nontoxic nodular goiters malignant merely means that this proportion of suspicious adenomas was proved to be cancerous. In the millions of nontoxic, symptomless, and innocuous goiters which never are removed, the incidence of carcinoma is so low that vital statistics rate the thyroid sixteenth in the list of organs affected by malignant disease (Pack and Livingston).

Another cause for the discrepancy between the surgeons' and the internists' statistics is the confusion as to what constitutes a carcinoma of the thyroid. For example, some small carcinomas of the thyroid may exist for many years without enlarging or causing serious symptoms (Crile). Such tumors may escape detection because the thyroid is not examined routinely in all autopsies. This may explain the difference between the incidence of carcinoma of the thyroid, as reported by the surgical pathologist, and that observed by the pathologist who confines his work to postmortem examinations and who does not examine the thyroid unless there are special indications.

A third cause of variation between the surgeon's statistics and those of the internist is the method of presentation of facts. An erroneous impression as to the frequency of carcinoma of the thyroid in solitary nodules may be conveyed by inclusion in the statistics of all frank carcinomas of the thyroid even when the clinical diagnosis is clear and when widespread metastasis is present. This is as misleading as it would be to include all ulcerating carcinomas, regardless of size, infiltration, or metastasis, in a survey of the malignant potentialities of benign gastric ulcer, and to exclude from this survey all gastric ulcers which healed under medical treatment and were not resected. The clinical carcinomas have been added to the total, and the obvious benign lesions that were not operated upon have been subtracted from the total, with the result that the figures, although accurate, create a false impression.

Presentation of Material

As an indication of how the presentation of material may influence the statistical conclusion, I analyzed my experience with carcinoma of the thyroid.

In a series of 768 thyroidectomies thirty malignant tumors were found, an incidence of 3.9 per cent. During this same period five inoperable malignancies of the thyroid were encountered, three of which have been excluded from this study because the clinical diagnosis was not confirmed by biopsy. The incidence of malignant tumors in all nodular goiters (with and without hyperthyroidism) was 5.6 per cent. Ten and nine-tenths per cent of nontoxic goiters were malignant, including 24.5 per cent of the solitary tumors (Table XIV).

TABLE XIV
INCIDENCE OF MALIGNANCY IN NODULAR GOITER, 1937–1946

	Incidence of Malignancy %
In 537 nodular goiters (toxic, nontoxic, benign, and malignant) 30 malignant tumors were present	5.6
In 263 nodular goiters with hyperthyroidism 0 malignancy was present	0.0
In 274 nodular goiters without hyperthyroidism 20 malignancies were present	10.9
Of 176 multinodular goiters, 6 were malignant	3.4
Of 98 solitary tumors, 24 were malignant	24.5

A definite diagnosis of malignancy was made preoperatively in twenty-seven of the thirty patients with confirmed malignancy of the thyroid. In two more cases the diagnosis of malignancy was suspected but not favored. In only one case was malignancy not diagnosed or suspected preoperatively.* In this case a nodule was removed because of its hardness and proved to be a papillary carcinoma (Table XV).

These data lend themselves to several forms of misleading deductions. It can be shown that carcinoma of the thyroid is commonly present in apparently innocent solitary adenomas. Three of thirty proved carcinomas occurring in ninety-eight solitary nodules of the thyroid were not *definitely* diagnosed before operation. It would be correct to state that over 3 per cent of the solitary nodules that I have removed proved to be carcinomas undiagnosed before operation. On the basis of

* This accuracy of diagnosis is abnormally high and will doubtless be altered by inevitable mistakes, some of which already have been made in cases seen since these figures were prepared. A diagnostic accuracy of 90 per cent could be considered satisfactory.

TABLE XV

Accuracy of Preoperative Diagnosis of Malignancy in 537 Nodular Goiters

98 solitary tumors with hyperthyroidism	24 maligancies	21 definitely diagnosed preoperatively
		2 suspected but not diagnosed preoperatively
		1 not suspected or diagnosed preoperatively
	74 benign tumors	61 diagnosed as benign
		13 suspected of being malignant but proved benign
		0 diagnosed as malignant but proved benign
176 multinodular goiters without hyperthyroidism	6 malignancies	6 definitely diagnosed preoperatively
		0 suspected but not diagnosed preoperatively
		0 not suspected or diagnosed preoperatively
	170 benign tumors	164 diagnosed as benign
		6 suspected of being malignant but proved benign
		0 diagnosed as malignant
263 nodular goiters with hyperthyroidism	0 malignancies	
	263 benign tumors	262 diagnosed as benign
		1 suspected of being malignant but proved benign
		0 diagnosed as malignant

these statistics a patient with a solitary nodule in the thyroid could be informed that there was one chance in thirty that the tumor was malignant even though there was no clinical evidence of cancer.

Approaching the subject from a different angle, it can be proved unlikely that a solitary nodule contains an unsuspected carcinoma. Although the diagnosis was not made before operation in three of the ninety-eight cases it was suspected in all but one. Hence, it would be correct to say that unsuspected carcinoma was found in only 1 per cent of the solitary nodules of the thyroid (Table XV).

To estimate the true incidence of carcinoma of the thyroid it is necessary to know how many patients with solitary nodules were observed at the Cleveland Clinic during the same period. Analysis of the charts of 500 consecutive patients, excluding those who entered with the complaint of thyroid disease or in whom operations on the thyroid were advised or performed, indicates that approximately 4 per cent had symptomless nodular goiters. These were incidental findings of the physical examination. Of those with nodular goiters about 25 per cent appeared to have solitary nodules. By projecting this experience over the period of observation, approximately 1237 patients with solitary nodules of the thyroid probably have been examined and advised against having the goiter removed. It is impossible to state how many, if any, of these nodules subsequently proved to be malignant; however, I have not yet encountered a carcinoma of the thyroid in any of these patients. The claim, might be made therefore, that the incidence of unsuspected carcinoma of the thyroid in innocuous appearing solitary adenomas is 1 in 1335.* This is a fallacious line of reasoning because there is no proof that ultimately some carcinomas will not appear.

Most of the carcinomas which are not suspected or diagnosed before operation are of the slowly growing, highly differentiated type. Since most of these are curable even after they have been

* 1237 not operated on plus 98 operated on.

present for years, and since most of the undifferentiated carcinomas are incurable regardless of how early they are removed, it is not likely that earlier recognition and removal of carcinomas would alter the ultimate prognosis in more than one case in five. Thus if we were to institute a policy of removing all solitary adenomas of the thyroid regardless of history, size, or consistency we would have to remove 6675* solitary adenomas to prevent one patient from dying of cancer. Regardless of the safety of thyroidectomy, it is doubtful if 6675 goiters could be removed without more than one postoperative death. And this does not take into account the morbidity from technical accidents or the economic aspects of surgery performed on such a scale.

Such deductions as these which are based on statistical surveys of unfollowed cases are clearly misleading. Any conclusion regarding the innocuousness of nodular goiters based on reasoning such as this is as mistaken as an opposite conclusion based on selected surgical cases would be. Until we know more accurately how often benign adenomas become malignant it would seem wise to base indications for thyroidectomy on clinical judgment rather than on statistical surveys of selected or unfollowed cases.

Indications for Removal of Nodular Goiters without Hyperthyroidism

Surgeons realize that conservative treatment of adenomatous goiters is frequently unwise. Often a patient with a hard enlarging tumor of the thyroid has been reassured by a physician, given a little iodine, and advised to disregard the goiter. Such tumors are often malignant, and delay in treatment may prevent cure. These occasional errors have encouraged an overstatement of dangers of carcinoma of the thyroid in nodular goiter. Surgeons who suggest that all nodular enlargements of the thyroid should be removed regardless of history, physical findings, or the apparent benign quality of involutionary nodules are conscientiously attempting to give their patients maximum

* 5×1335 total patients with solitary nodules $= 6675$.

protection against carcinoma. However, indiscriminate thyroidectomy, performed on everyone with nodular goiter, probably would entail a morbidity and mortality quite out of proportion to the number of cases of fatal cancer that it might prevent.

An enlarging adenoma of the thyroid, an adenoma which is firm and of different consistency from the rest of the gland, or one which is giving pressure sensations denoting growth should not be disregarded. Conspicuous adenomas should be removed for cosmetic reasons. All adenomas in children must be regarded with grave suspicion, as must discrete adenomas in adults, regardless of age. However, small, soft, nodular enlargements which have been examined and considered innocuous by a physician thoroughly familiar with diseases of the thyroid may be disregarded. Removal of such goiters is not justified and is comparable to indiscriminate removal of uteri and breasts for minimal benign lesions.

The physician who has not had specialized training may have difficulty in recognizing the possible malignancy of a tumor of the thyroid. For this reason it is urged that the decision relative to removal of a tumor of the thyroid should be made by a physician or surgeon particularly qualified by experience and training.

Age. Carcinoma of the thyroid is not necessarily a disease of old age. Since the tumors appear before the age of 20 in about one-fourth of the patients with papillary carcinoma, and since the average age of patients with papillary carcinomas and lateral cervical metastasis is only 31.9 years, it is important to remember that a tumor of the thyroid in a child is more apt to be malignant than one in a woman of 70 (Crile). Carcinoma is almost as common in young adults as it is in older people.

Size of Tumor. The presence of carcinoma cannot be excluded merely because the tumor has remained the same size. A tumor which has already metastasized to many cervical glands may not enlarge for years and may never metastasize from the neck. For more than twenty years we have observed a patient with proved metastasis from a papillary carcinoma of the thyroid who has refused all treatment (Crile). The nodules in the thyroid and lateral cervical region are only a little larger than when they first appeared twenty-seven years ago.

Most malignant tumors of the thyroid are hard or at least firm, and usually are of a different consistency from the nontumorous thyroid. The firmness and discreteness of the tumor is the most reliable indication in establishing suspicion of carcinoma of the thyroid.

Relation to Benign Adenomas. Although the incidence of carcinoma is higher in nodular goiters it is difficult to prove that carcinomas have their origin in benign adenomas. It is reasonable to suppose that many if not most carcinomas of the thyroid are carcinomas from the beginning and arise from the parenchyma of the thyroid as do benign adenomas. There is little proof that a benign tumor of the thyroid becomes malignant more often than the goitrous thyroid parenchyma.

Since we cannot prove that carcinomas of the thyroid often arise within the substance of a benign adenoma, and since the incidence of carcinoma of the thyroid is so low, even in areas in which endemic goiter is prevalent, there is little possibility that a given adenoma of the thyroid will become malignant. The pertinent concern is whether or not the adenoma is cancerous at the time of examination. There is probably less chance that a benign adenoma will become malignant at some future date than that carcinoma will develop in the apparently normal uterus or breast.*

Effects of Subtotal Thyroidectomy. The conventional subtotal thyroidectomy performed "prophylactically" for nontoxic nodular goiter does not give more than partial protection against the subsequent development of carcinoma in the remnants of the gland. A rapidly growing and fatal carcinoma of the thyroid has been observed to develop in a patient who had undergone "prophylactic" thyroidectomy thirty years before.

* Carcinoma of the breast is more than ten times as common as carcinoma of the thyroid (Pack). Carcinoma of the thyroid is only about seven times as common in areas of endemic goiters as it is in nongoitrous areas (Ward). The goitrous thyroid, therefore, does not develop carcinoma as frequently as the apparently normal breast.

No surgeon would willingly subject a patient with a presumably benign goiter to the certainty of myxedema and the risk of tetany which are involved in a total ablation of the thyroid. Remnants of the thyroid tissue remain after "prophylactic" subtotal thyroidectomy and since these remnants have been subjected to the same pathologic stimulation that originally caused the development of the adenoma, a further development of adenomas or carcinomas is always possible. Moreover a malignant tumor may be overlooked and left in the remnants of the thyroid. We have removed a papillary carcinoma of the thyroid less than a year after a "prophylactic" thyroidectomy had been performed for adenomatous goiter without hyperthyroidism. Neither surgeon nor pathologist discovered the carcinoma at the first operation, although we feel certain that it must have been there at that time.

Thyroidectomy for nodular goiter should be accomplished in such a way as to remove completely any carcinoma which may be present. Unfortunately, the same surgeon who advises the removal of an adenoma as a prophylaxis against the development of carcinoma frequently leaves carcinomatous tissue just as he would leave normal thyroid tissue in operation performed for benign lesions. Since the tumor had not been completely removed, the operation has failed its purpose.

Surgeons should accustom themselves to thinking of discrete tumors of the thyroid not as benign adenomas which may become malignant at some remote time, but rather as tumors which may be cancerous at the time of operation. If they did this they would remove the entire tumor and should the tumor prove to be a carcinoma the chances of cure would be increased.

Summary

1. Ten and nine-tenths per cent of surgically removed nontoxic nodular goiters and 24.5 per cent of surgically removed nontoxic solitary tumors of the thyroid proved to be malignant.

2. The diagnosis of malignancy was made or suspected and so recorded before operation in 96.6 per cent of the patients with malignancy of the thyroid.

3. These figures can be so presented as to indicate that (a) over 3 per cent of nontoxic solitary nodules of the thyroid are undiagnosed malignant tumors; or (b) there is only one chance in 6675 that removal of a nontoxic solitary nodule in the thyroid will give protection against death from carcinoma of the thyroid.

4. It is impossible, without better definition of histologic criteria of malignancy and without better autopsy and clinical statistics on the incidence of adenomas and carcinomas of the thyroid, to make an accurate statistical report of the true incidence of carcinoma of the thyroid in nodular goiter.

5. The high incidence of carcinoma of the thyroid reported by surgeons is to a large measure dependent on the fact that the obviously benign nodules in the thyroid are screened out by the patient or by the internist and are not seen by the surgeon.

6. Solitary adenomas of the thyroid in patients of any age should be viewed with suspicion, especially (a) in children; (b) when enlarging or giving symptoms of discomfort or pressure; (c) when firm or hard; (d) when discrete and of a different consistency from the remainder of the thyroid.

7. Adenomas large enough to be of cosmetic importance should be removed.

8. Soft involutionary nodules in the thyroid, especially when multiple and not large enough to be conspicuous, can be disregarded if they are not enlarging or causing symptoms.

9. The majority of malignant tumors of the thyroid can be recognized or at least suspected if a high index of suspicion is maintained regarding discrete adenomas.

10. The danger is not that a discrete adenoma may become malignant, but rather that it is already malignant.

11. If a discrete adenoma of the thyroid is to be removed, the operation should be so designed as to remove all of the tumor and cure the cancer if it is present.

12. Until better statistics on the true incidence of carcinoma in adenomas of the thyroid are available, it is suggested that indications for removal of nodular goiters be based on clinical judgment rather than on statistical surveys.

Bibliography

1. Cole, W. H., Slaughter, D. F., and Rossiter, L. J.: Potential dangers of nontoxic nodular goiter. J. A. M. A. *127:* 883-888 (April 7) 1945.
2. Crile, G., Jr.: Papillary carcinoma of thyroid and lateral cervical region; so-called "lateral aberrant thyroid." Surg., Gynec. & Obst. *85:* 757–766 (Dec.) 1947.
3. Hinton, J. W., and Lord, J. W., Jr.: Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? J. A. M. A. *129:* 605–606 (Oct. 27) 1945.
4. Pack, G. T., and Livingston, E. M., editors: Treatment of Cancer and Allied Diseases. By One Hundred and Forty-Seven International Authors. New York: Paul B. Hoeber, Inc., 1940.
5. Rogers, W. F., Asper, S. P., Jr., and Williams, R. H.: Clinical significance of malignant neoplasms of thyroid gland. New England J. Med. *237:* 569–576 (Oct. 16) 1947.
6. Ward, R.: Malignant goiter; survey of geographical types. West. J. Surg. *43:* 494–504 (Sept.) 1935.

Chapter 24

PAPILLARY CARCINOMA OF THE THYROID*

Papillary carcinomas of the thyroid are of a low degree of malignancy and rarely metastasize distantly. They tend to infiltrate the thyroid, and often are surrounded with zones of fibrosis. They may become extensively hyalinized or even calcified. The true papillary carcinoma does not tend to be encapsulated. Encapsulated tumors which can be shelled out of the thyroid and which invade blood vessels should be classified as nonpapillary carcinomas even if papillary areas are present.

In one group of papillary carcinomas of the thyroid, the primary tumor is small and manifests itself first and chiefly by its lateral cervical metastases (Figs. 68, 69, 70, 71). In a second group the tumor in the thyroid is large, appears first, and metastasis is a rare or late occurrence. Strange as it seems, the prognosis is better in the tumors that first manifest themselves by metastasis than it is in those whose primary manifestation is the primary tumor (Fig. 72).

Since there are no histologic differences between these two clinical types of carcinoma, the division is of necessity an arbitrary one based entirely on the history and physical findings.

Papillary Carcinoma of the Thyroid with Cervical Metastasis

The type of papillary carcinoma that metastasizes early and widely to the lateral cervical region and which in the past has often been designated as lateral aberrant thyroid is referred to henceforth as "papillary carcinoma of the thyroid with cervical metastasis." The type in which the tumor in the

* Reprinted in part by permission of Surgery, Gynecology and Obstetrics.

thyroid is large and metastasis occurs late if at all will be referred to as "papillary carcinoma, nonmetastasizing type."

Papillary Carcinoma of the Thyroid with Lateral Cervical Nodules. Small papillary tumors of the thyroid, often appear-

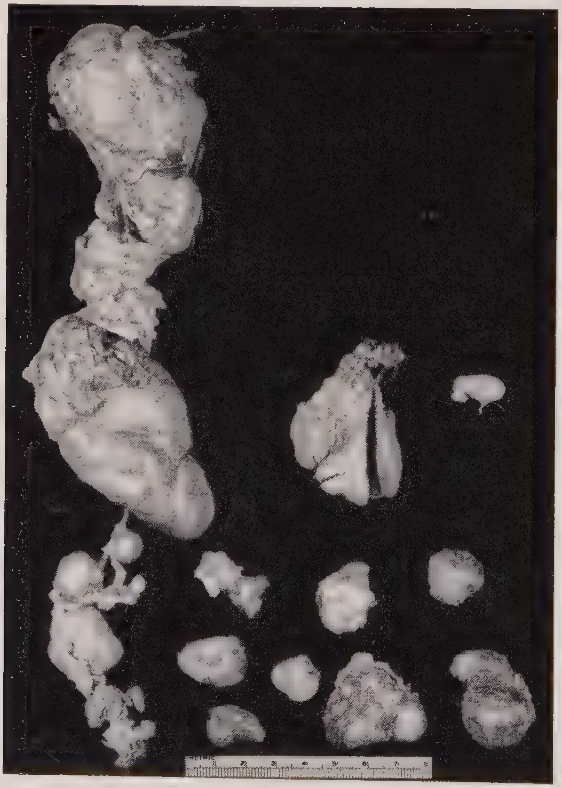


Fig. 68. Surgical specimens showing papillary carcinoma of the thyroid, a long chain of cervical lymph nodes filled with metastatic carcinoma, and nine separate nodes all showing metastatic carcinoma.

ing benign from a histologic standpoint, may be associated with multiple cervical nodules of the same histologic appearance. When the primary tumor in the thyroid is so small as to escape detection these tumors often have been considered to be lateral aberrant thyroids.

The ability of these tumors to metastasize, as shown by the reports of Pemberton, Lahey, and others and by the progress of our patients, indicates that regardless of their histology and regardless of their relatively benign clinical behavior, these tumors must be considered malignant. Yet they must be considered in a separate category of malignancy, one in which

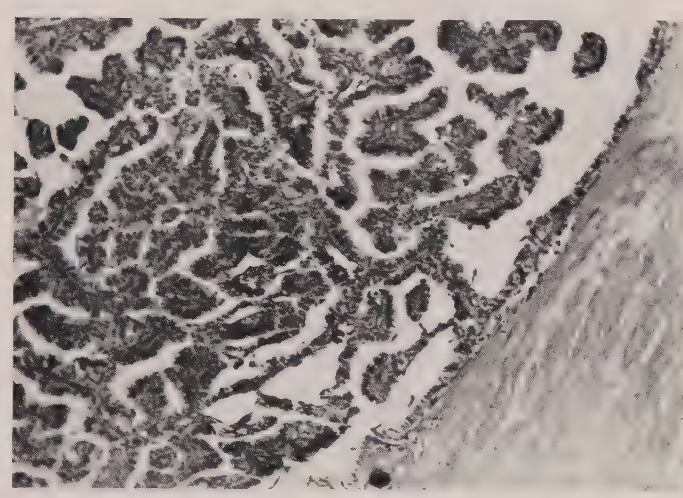


Fig. 69. The primary papillary carcinoma in the thyroid (same patient as in Fig. 68).

metastasis is recognized yet cognizance is taken of their usual tendency to grow extremely slowly. They can be characterized as having the following qualities:

1. A marked tendency, regardless of histologic criteria of malignancy, to metastasize locally to the lymph nodes of:

   a. The lower and midcervical region behind and around the carotid sheath.
   b. The region posterior to the thyroid along the trachea and along the course of the recurrent nerve.
   c. The superior mediastinum.

d. The posterior triangle of the neck.
e. The upper part of the neck in relation to the carotid sheath.
f. The midline along the thyroglossal tract.
g. The other side of the neck (usually in these cases a second primary tumor on the other lobe is demonstrable).

2. A slight tendency to metastasize distantly.
a. Via the blood stream, especially to the lungs.
b. Via the lymphatics to the axilla.

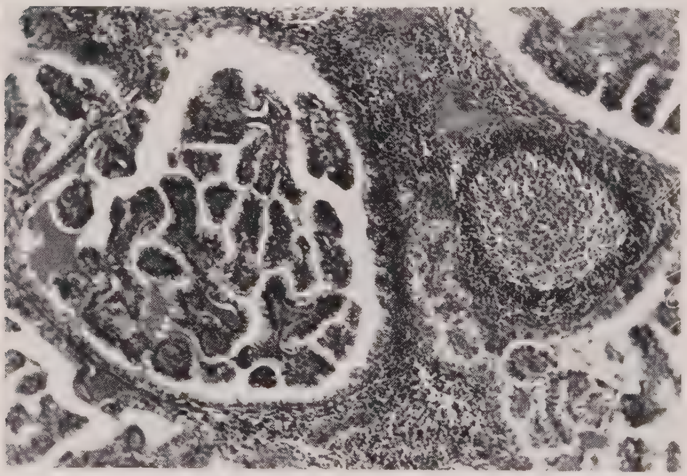


Fig. 70. Metastatic carcinoma in cervical node (same patient as in Figs. 68 and 69).

3. A marked tendency for the tumor in the thyroid to calcify, scarify, or even to ossify, the primary tumor often failing to enlarge significantly over a period of many years in spite of the fact that its metastases may show steady growth and increasing numbers.

4. A tendency for the lateral cervical metastases to grow slowly over a period of many years and to remain encapsulated, noninvasive, and freely movable (Fig. 73).

Twenty-one patients with metastases to the lateral cervical nodes from papillary tumors of the thyroid have been followed from five to twenty years or until their death. The survival record of these patients lends support to the theory that in some cases, at least, the lateral cervical nodules are multiple primary tumors of benign behavior. Yet in one case we have incontrovertible proof of the malignancy of these tumors and of their ability to metastasize distantly, and in a second there is strong evidence that this is the case.

Fig. 71. Same patient as in Figs. 68, 69 and 70, alive and well ten years after removal of papillary carcinoma of the thyroid and its cervical metastases.

Two of our twenty-one patients have died with distant metastases, one to the brain (not proved) and one to the axilla and mediastinum (proved by biopsy). One patient died with a local recurrence of the thyroid tumor. Two have died of other causes, apparently free from cancer, eighty-four months and fifty-nine months, respectively, after operation. One patient, who has had only a biopsy, is alive and well after twenty years with multiple tumors in both lobes of the thyroid and throughout both cervical regions. One patient died after operation (Fig. 74). The remaining fourteen patients are alive and well with no evidence of local recurrence or distant metastasis.

The three patients who died as a result of recurrence or metastasis of the tumor died eighteen years, fifteen years, and nine years, respectively, after their original operations. Similar cases have been reported by others, and hence we must conclude that in dealing with this type of cancer five years is no measure of a cure. The thyroid and lateral cervical region of the patient who has persistently refused operation and irradiation for twenty years is filled on each side with nodules ranging in size from 1 to 3 cm. in diameter. Although the tumors are much more numerous than they were at first, they have never attained such a size as to produce symptoms or a significant

Fig. 72. Large recurrent papillary carcinoma of the thyroid. Complete surgical removal impossible. Did not respond to x-ray treatment. Death from carcinoma occurred nineteen years after first operation.

visible deformity of the neck. The fact that the number of tumors has increased from three to twenty or more suggests metastasis but could be interpreted as the progressive appearance of multiple independent tumors of congenital origin.

One of the three patients who died of carcinoma developed a massive local recurrence fifteen years after the original thyroidectomy. Associated with the recurrence was a single lateral cervical nodule, grossly and histologically identical to the

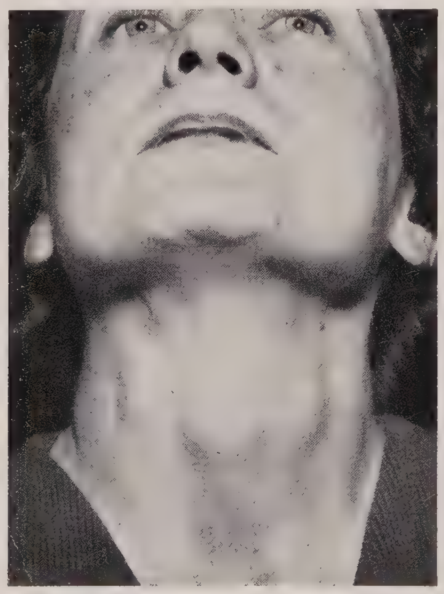


Fig. 73. Appearance of thyroid carcinoma and lateral cervical metastases twenty-one years after the lateral nodules were proved by biopsy to be papillary carcinoma of the thyroid. Patient has received no irradiation or surgical treatment in the interim.

tumors that in the past we have called lateral aberrant thyroids. There was present in this case the rich pedicle of blood vessels so characteristic of the lateral aberrant thyroids and so different from the blood supply of other types of metastases in lymph nodes. Yet metastatic carcinoma histologically identical to that seen in the thyroid and lateral cervical region was later found in the axilla. It is inconceivable that axillary thyroid tissue could be of congenital origin. The patient died four and one-half years after the second operation and over nineteen years after removal of the original papillary tumor.

The second patient was reoperated upon for a local recurrence of the thyroid tumor nine years after the original operation, and again a single lateral cervical nodule, grossly and

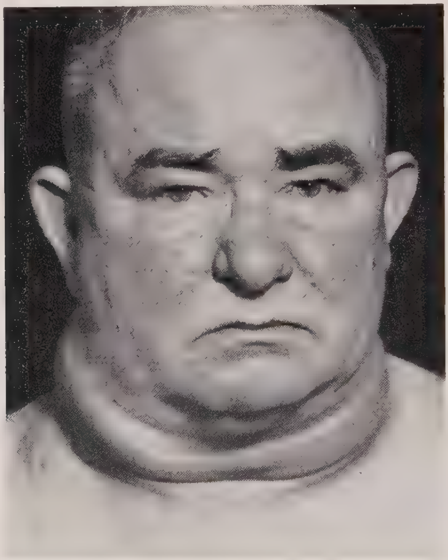


Fig. 74. Papillary carcinoma of the thyroid with large, fixed cervical metastases on each side and with metastases to the mediastinum.

histologically similar to those described as lateral aberrant thyroids, was found. Six years later (fifteen years after the original carcinoma of the thyroid was removed) this patient died, apparently with cerebral metastasis, although a post-mortem examination was not done.

The third patient developed a large carcinoma of the thyroid which appeared a few months after a lateral cervical nodule was removed. In spite of x-ray therapy she died with local recurrence of the tumor nine years after the original operation.

The remarkable survival record of the other patients with or without surgical removal of the tumors is demonstrated in Table XVI.

A primary tumor has been found in the thyroid gland in every one of sixteen consecutive cases in which I have explored the thyroid or removed one of its lobes. In four cases the tumors were bilateral, but in all others the primary tumors in the thyroid were single. In three cases the tumor has infiltrated the gland more or less diffusely, forming an adenopapillomatous infiltration of the affected lobe, but in no case has there been more than one distinct tumor nodule in a lobe of the thyroid. The fact that in sixteen consecutive cases there have been multiple lateral cervical nodules and only one nodule in the lobe of the thyroid would seem an argument against the hypothesis that the tumor in the thyroid is, as some believe, a metastasis from a primary malignancy in the lateral cervical region. These observations tend to substantiate Pemberton's theory that most, if not all, of the lateral cervical nodules are metastases of a carcinoma primary in the thyroid.

Against this view we have five patients followed from five to fourteen years after removal of a lateral cervical nodule who have never developed any palpable tumor in the thyroid. That this does not rule out the presence of a primary tumor in the thyroid is illustrated by an additional case in which six years intervened between the removal of a lateral cervical nodule and a second operation for recurrent lateral cervical nodules. Prior to the second operation no tumor was palpable in the thyroid, yet at the time of the second operation a tumor 1.5 cm. in diameter was found in the lobe of the affected side. The tumor was surrounded by dense scar tissue. It is quite likely that many of the primary tumors in the thyroid do not enlarge significantly over a period of years and escape detection unless they are searched for. Yet these same tumors may, as in this case, continue to give rise to actively growing metastases while the primary tumor fails to enlarge.

Even a partial lobectomy does not rule out the presence of a

Case Age at onset Sex	First symptom and duration before operation	Palpable tumor in thyroid	Preoperative diagnosis	X-ray or radium	Number and type of operation	Number and location of nodules	Bilateral cervical nodule
1 32 F	Lateral cervical tumor 18 mo.	0	Hodgkins	0	1. Removal nodule	1. Carotid	0
2 26 F	Lateral cervical tumor 18 mo.	Firm	Tuberculosis	0	1. Lobectomy neck dissection thyroidectomy incision 2. Removal recurrent nodules	28, low and mid. carotid mediastinal and posterior to thyroid	+
3 14 F	Lateral cervical tumor 72 mo.	Hard	Correct	Radium seed at op.	1. Lobectomy and neck dissection ant. sternomastoid incision	7, high low and middle carotid and posterior to thyroid	0
4 19 M	Lateral cervical tumor 1 wk.	Hard	Correct	0	1. Lobectomy and neck dissection left 2. Lobectomy and neck dissection right (ant. sternomastoid incisions) 3. Removal nodules	40 or more bilaterally along carotid from angle of jaw to mediastinum and behind thyroid	+
5 56 F	Lateral cervical tumor 36 mo.	0	Branchial cyst	0	1. Removal nodule and part of thyroid (thyroidectomy incision)	1, middle carotid	0
6 53 F	Hyperthyroidism	0	Nodular goiter with hyperthyroidism	0	1. Removal of nodules and part of thyroid (thyroidectomy incision)	3, middle carotid	0
7 36 M	Tumor thyroid 12 mo.	Firm	Adenoma of thyroid	800 r. after 1st. op.	1. Partial thyroidectomy 2. Complete lobectomy and removal of nodules (thyroidectomy incision)	2, middle carotid	0
8 52 F	Lateral cervical tumor	0	Cervical abscess	5450 r. without significant regression or control	1. Removal lateral cervical nodule 2. Partial lobectomy (Thyroidectomy incision)	2, middle carotid	0

Bilateral thyroid tumor	Size of thyroid tumor	Operation on thyroid	Location of recurrences	Sclerosis of thyroid tumor	Associated benign adenoma	Pathology	Present status
–	–	0	0	–	–	Papillary adenoma	Died other causes free of recurrence proved by autopsy 59 mo. after operation
0	2.5 cm.	Complete lobectomy	Mediastinum	0	0	Papillary adenoma	No recurrence 97 mo. postoperative
0	2.5 cm.	Complete lobectomy	0	Bone formation	0	Papillary carcinoma	No recurrence 64 mo. postoperative
+	1.5 cm. each lobe with diffuse infiltration	Complete thyroidectomy	Carotid above field of op. at level of jaw angle	0	0	Papillary carcinoma	No recurrence 64 mo. postoperative
0	–	Incomplete thyroidectomy without examination posterior surface	0	–	+	Papillary adenoma	No recurrence 101 mo. postoperative
0	–	Incomplete thyroidectomy without examination of posterior surface	0	–	+	Papillary adenoma	Died other causes ("stroke") without recurrence
0	4.5 cm.	1. Incomplete thyroidectomy 2. Complete lobectomy	Middle carotid	Calcium	+	Papillary adenoma	Died of cerebral metastasis and local recurrence 180 mo. after first operation
0	4.5 cm.	Partial lobectomy; impossible to remove all of tumor	Thyroid	0	–	Papillary adenoma	Died of local recurrence 112 mo. postoperative

TABLE XVI. SUMMARY OF

Case Age at onset Sex	First symptom and duration before operation	Palpable tumor in thyroid	Preoperative diagnosis	X-ray or radium	Number and type of operation	Number and location of nodules	Bilateral cervical nodule
9 16 F	Later cervical tumor 72 mo.	None at first, now bilateral hard	Tuberculosis	80% erythema dose in 3 treatments without improv.	1. Biopsy	Only 2 of many removed, 20 or more now palpable	+ palpable, no operation
10 27 F	Lateral cervical tumor 2 mo.	Enlarged right lobe	Correct	0	1. Lobectomy and neck dissection (anterior sternomastoid incision) 2. Removal nodule	20 or more Entire length of carotid, mediastinum behind thyroid; 1 nodule other side	1 on the other side
11 15 F	Lateral cervical tumor 36 mo.	0	Correct (previous biopsy)	4000 r. with only transient regression followed by continued growth	1. Biopsy (elsewhere) 2. Removal nodules 3. Removal nodules and lobectomy 4. Removal nodules and tumor in other lobe (Thyroidectomy incision)	15, low carotid, mediastinum and posterior to thyroid, bilateral	+
12 28 F	Lateral cervical tumor 30 mo.	Firm	Correct	0	1. Biopsy (elsewhere 2. Lobectomy and removal of nodules (Thyroidectomy incision)	4, middle carotid	0
13 9 F	Tumor thyroid 12 mo.	Hard	Correct	0	1. Lobectomy and dissection lower neck (Thyroidec. incision) 2. Removal nodules	6, middle carotid	0
14 33 F	Tumor in thyroid 144 mo.	Goiter (no description)	Adenoma	0	1. Thyroidectomy 2. Removal nodules 3. Removal nodules (all in 3 mo. period)	8, middle carotid	0

Bilateral thyroid tumor	Size of thyroid tumor	Operation on thyroid	Location of recurrences	Sclerosis of thyroid tumor	Associated benign adenoma	Pathology	Present status
+ palpable, no operation	Estimated 1–2 cm.	0	Bilateral high and low jugular	—	—	Papillary adenoma	Alive and well with multiple small tumors throughout thyroid and lateral cervical region. Has had no treatment. Now 249 mo. since biopsy and 27 yr. since tumors were first noticed
0	3 cm. diffuse infiltration	Complete lobectomy	2 yrs. post-op. noted tiny nodule in midline above thyroid; removed 8 yrs. postoperative, 1 cm. diameter	Calcium	+	Papillary adenoma	No recurrence 108 mo. after operation
+	1 cm. each lobe	Tumors removed from both lobes of thyroid	Low carotid and mediastinum	Scar	0	Papillary adenoma	No recurrence 115 mo. since first operation and 72 mo. since last
0	2 cm.	Complete lobectomy	0	Calcium	+	Papillary adenoma	No recurrence 83 mo. since operation
0	2.5 cm.	Complete lobectomy	1 yr. postoperative noted tiny nodule left carotid. Enlarged slowly, removed 7 yrs. later	0	+	Papillary adenoma	No recurrence; well 97 mo. after operation
0	3 cm.	Partial thyroidectomy	Persistent tumors in middle-carotid area removed 1 wk., 3 mo. after thyroidectomy	Calcium	+	Papillary adenoma	No recurrence 206 mo. postoperative

Case Age at onset Sex	First symptom and duration before operation	Palpable tumor in thyroid	Preoperative diagnosis	X-ray or radium	Number and type of operation	Number and location of nodules	Bilateral cervical nodule
15 21 F	Lateral cervical tumor 12 mo.	0	Tuberculosis	X-ray ? amt.	1. Removal nodules 2. Removal nodules and lobectomy	3, middle carotid	0
16 24 F	Lateral cervical tumor 1 wk.	0	Correct (previous biopsy)	0	1. & 2. Removal nodule 3. Removal nodule 4. Removal nodule, 5 & 6 (?) Removal of nod. (elsewhere)	4+ ? low, carotid	0
17 38 M	Lateral cervical tumor 12 mo.	Hard	Correct	0	1. Removal nodules 2. Neck dissection and lobectomy (ant. sternomastoid incision)	25, along carotid, and mediastinum	0
18 43 M	Tumor in thyroid 4 year duration	Hard	Correct (previous op.)	17 treatments amount unknown, no improvement	1. Thyroidectomy (elsewhere) 2. Complete lobectomy and block dissection of neck	13, along carotid, posterior to thyroid and in mediastinum	+
19 20 F	Lateral cervical tumor 24 mo.	Hard	Tuberculosis	12 treatments amount unknown, no improvement	1. Removal nodules 2. Bilateral lower neck dissection Thyroidectomy incision	12, mediastinum, behind thyroid bilateral middle carotid	+
20 48 F	Lateral cervical tumor 30 mo.	0	Correct	7 treatments amount unknown, no improvement	1. Neck dissection and lobectomy	5, middle carotid and mediastinum	0
21 33 M	Tumor thyroid 24 mo.	Hard	Correct	Large amount, no improvement	1. Thyroidectomy 2. Excision nodule and lobectomy	1, Posterior triangle	0

Bilateral thyroid tumor	Size of thyroid tumor	Operation on thyroid	Location of recurrences	Sclerosis of thyroid tumor	Associated benign adenoma	Pathology	Present status
0	1.5 cm.	Partial lobectomy	Thyroid tumor and nodules middle-carotid area removed 6 yrs. after 1st operation	Scar	+	Papillary carcinoma	No recurrence 124 mo. after first and 24 mo. after 2nd operation
0	—	0	Tumors keep recurring low carotid area	—	—	Papillary adenoma	Living and well 168 mo. since original operation but is said to have had recurrences removed since last operation at Cleveland Clinic
0	3.5 cm.	Complete lobectomy	2nd operation 6 wk. after 1st.	Calcium	0	Medullary carcinoma with invasion of veins; frankly malignant	No recurrence 113 mo. postoperative
0	3.5 cm.	Complete lobectomy	Contralateral and in mediastinum and thyroid and carotid area	0	+	Papillary carcinoma	Died after 2nd operation. First operation was 10 yrs. before
+	3 cm. one lobe. 1 cm. other	Complete lobectomy on right partial on left	Bilateral carotid, mediastinum and thyroid	Calcium	+	Papillary carcinoma	No recurrence 175 mo. after first and 3 mo. after 2nd operation
0	1 cm.	Complete lobectomy	0	Calcium	+	Papillary carcinoma	No recurrence 60 mo. postoperative
0	Very large	Complete lobectomy	Local recurrence thyroid nodule in posterior triangle	+	0	Papillary adenoma	Died with axillary and mediastinal metastasis (proved) 227 mo. after operation

small primary tumor. I have recently removed a papillary carcinoma of the thyroid and a number of lateral cervical nodules a little over a year after a "thyroidectomy" had been performed. At the time of the first operation neither the surgeon nor the pathologist was aware of the presence of this tumor which, as is so often the case, lay on the posteromedial aspect of the thyroid, an area avoided by many surgeons. On another occasion, before I was aware of the significance of the lateral cervical nodules in respect to the thyroid tumor, I explored the thyroid of a girl with lateral cervical nodules and reported it normal, only to reoperate for recurrent cervical nodules a year later and find that there was indeed a tiny nodule less than 1 cm. in diameter on the posteromedial aspect of the thyroid. Thus, failure to demonstrate a tumor in the thyroid at operation or in the portion of the gland removed does not by any means rule out the possibility that a tumor in the posteromedial remnants was overlooked.

The extreme slowness of growth of certain of the tumors in the thyroid is illustrated by the case of a girl 20 years old whose thyroid contained a nodule estimated to be 1.5 cm. in diameter. Lateral cervical nodules were removed, but the thyroid tumor was not disturbed. Fifteen years later more lateral cervical nodules and the thyroid were removed, but after all these years the tumor in the thyroid was only 2 cm. in diameter. The fact that no tumor appears in the thyroid even ten or fifteen years after removal of lateral cervical nodules does not prove that there is no primary tumor in the thyroid. It means only that the tumor in the thyroid is small, lies deep on the posterior surface of the gland, and either is growing very slowly or its growth is prevented by calcification and scarring.

In every one of the sixteen patients whose thyroid glands I have explored, I have found a tumor in one or both lobes of the thyroid. The fact that in five cases tumors were found in both lobes of the thyroid suggests that the thyroid tumors originate in some congenital rest or anomaly of development. The youth of the patients (six had developed lateral cervical nodules by the age of 20) also suggests a congenital origin (Fig. 75), as does the histologic appearance of some of the cervical nodules. Yet in other cases the lateral cervical nodules are clearly metastases in lymph nodes, and it is reasonable to assume that most if not all of the lateral cervical nodules are metastases from the thyroid.

Regardless of the origin of these tumors or of their classification in respect to malignancy, their treatment should be surgical excision. It is indeed a strange type of cancer that can be con-

Fig. 75. Girl aged 9 with papillary carcinoma of the thyroid and several metastases in the lateral cervical region. Alive and well eight years after operation.

trolled for fifteen or twenty years by local excision of the primary tumor and individual removal of fifteen or twenty or more metastatic nodules. It is also a curious type of malignancy which, without any form of treatment, grows so slowly that in over twenty years the nodules have not enlarged appreciably and have merely become more numerous. It is almost as if these tumors were metastasizing congenital rests having little or no energy of growth. Yet in other cases the tumors enlarge fairly rapidly and sometimes attain considerable size. When the primary tumor of the thyroid rather than the lateral cervical nodules is noticed first, the growth appears to be greater. Three of the four patients who eventually died as a result of tumor developed a bulky tumor of the thyroid as the initial symptom. There were only two other patients in the entire group whose thyroid tumors were noticed before the lateral cervical nodules. The patients whose initial symptoms are referable to bulky tumors of the thyroid and in whom lateral cervical nodules are late developments should perhaps be placed in a different category from those in whom the lateral cervical nodules are the initial and most striking manifestations of the disease.

Complete removal of the tumors involving the posteromedial aspect of the thyroid and of the metastatic nodules along the trachea and the course of the recurrent nerve is often very difficult. The scarring and calcification of the tumors in this location render them adherent and may make it difficult to identify, isolate, and preserve the recurrent nerve. Often it is necessary to isolate and dissect out the entire cervical portion of the nerve. Even when it is adherent to the tumor it may be possible to separate it from the mass without either leaving tumor tissue or damaging the nerve. When the choice lies between sacrifice of the nerve and removal of all tumor the nerve should be sacrificed.

Most of the patients in this series have had more than one operation and some have had three. All of the patients who have had three operations were operated upon early in our experience before we were aware of the fact that a tumor is usually, if not always, present in the thyroid. Metastasis continued to occur from the thyroid tumors until they were removed.

Even after the importance of the thyroid tumor was recognized many of the patients with fifteen or more lateral cervical nodules required a second operation for removal of one or more overlooked nodules. In several instances the recurrence was contralateral or mediastinal and in one it was in the thyroglossal tract. In only one case was the recurrence in the field of the first operation, and only in this case would a block dissection of the neck have eradicated the tumor any more completely than the mere removal of the nodules.

In most of the patients the recurrences were first noticed within a few months of the first operation, and most of these patients were operated upon promptly and have remained well from five to ten years. In two instances the recurrences were noted early, but operation was deferred for four or five years as the result of the war. The nodules enlarged slowly and no more developed, suggesting that if the source of the trouble in the thyroid is eradicated the tendency for additional lateral cervical nodules to develop is controlled.

Cases Illustrating Slowness of Growth. Case 1. A patient was seen in 1925 complaining of lumps in the neck of six years' duration, first noticed at the age of 16. Several large soft glands were palpable in the left lateral cervical region. A diagnosis of tuberculous adenitis was made. Three x-ray treatments (two with 30 per cent erythema dose and one with 20 per cent) were given without benefit. A biopsy was reported as revealing metastasis of a papillary carcinoma of the thyroid or an aberrant papillary adenoma of the thyroid. The patient refused further treatment. In 1939, fourteen years later, the patient had a hard tumor 2.5 cm. in diameter in the left lobe of the thyroid, a hard tumor 2 cm. in diameter in the midline above the isthmus, as well as a tiny hard nodule in the right lobe of the thyroid and numerous lateral cervical nodules beneath the sternomastoid on each side. None of these nodules was large enough to be visible except the one above the isthmus. In 1946, *twenty-one years after biopsy and twenty-seven years after the nodules had first been noticed the patient writes that she has no symptoms referable to the tumors and has "only one small tumor in the front of her throat."*

Case 2. A woman, aged 21, first noted "glands" in the right side of her neck a year before entry. There was a large, round, fluctuant, cystic mass 6 cm. in diameter at the base of the neck on the right under the sternomastoid. There was a firm nodule 1.5 cm. in diameter in the superior pole of the right lobe of the thyroid and two firm round masses 2 cm.in diameter under the sternomastoid on the right. A diagnosis of tuberculous adenitis or branchial cyst was made. Eleven light x-ray treatments were given without improvement. Four of the lateral cervical masses were removed and the pathologist reported multiple cervical papilliferous cysts of the lateral aberrant thyroid. The thyroid was not explored. The patient returned fourteen years after operation and more than sixteen years from the time the tumor was first noticed. She had no symptoms referable to the cervical tumors, but examination revealed a hard nodule 2 cm. in diameter at the right lobe of the thyroid and bilateral cervical nodules. The left lobe of the thyroid seemed normal.

At operation there was a partly calcified papillary carcinoma of the right lobe of the thyroid gland 3 cm. in diameter and a similar tumor 1 cm. in diameter in the left lobe. There were eight lateral cervical nodules, some present on each side in the neighborhood of the thyroid as well as posterior to the carotid sheath and in the superior mediastinum. Convalescence was uneventful, and three months later there was no evidence of recurrence. This case is interesting because it shows how long these tumors can be present in the thyroid without enlarging appreciably or causing symptoms other than those referable to the lateral cervical metastases. It also indicates that, as was the case in the left lobe, a tumor may be present without being palpable prior to operation.

Cases Showing That Metastatic Nodules May Continue To Develop until the Primary Tumor in the Thyroid Is Removed. Case 1. A girl, aged 18, had noticed lumps in the right lateral cervical region for three years. Later similar lumps developed on the left side and enlarged steadily. A biopsy of one of the lumps was reported as metastatic adenocarcinoma. Twenty-one x-ray treatments with a total of 4000 r units were given, and the nodules decreased slightly in size for a few weeks and then began to enlarge again. Examination revealed nodules 3 cm. in diameter beneath the sternomastoid on each side, but no abnormality of the thyroid was noted. Through a thyroidectomy incision Dr. George Crile, Sr., removed five cystic nodules from the region of the carotid sheath on each side. One of the tumors was removed from the mediastinum at the level of the arch of the aorta. The thyroid was examined and reported as normal. The pathologist reported the tumors as multiple benign intracystic papillomas of lateral aberrant thyroid origin.

Six months later the patient noticed a recurrent tumor in the right lateral cervical region. Examination showed several small firm nodules behind the lower part of the sternomastoid on the right and an enlargement of the left lobe of the thyroid. At operation a tumor 3 cm. in diameter was removed from the region of the carotid sheath on the right. The left lobe of the thyroid containing a tumor 1 cm. in diameter also was removed. The right lobe of the thyroid was examined and found to be normal. The pathologist reported a small localized papillary adenomatous growth in the left lobe of the thyroid. It was thought that this tumor and the lateral cervical nodule, which was of similar histology, were both benign.

The patient remained well for three years and then developed a small firm nodule in the right lobe of the thyroid 1 cm. in diameter. At operation the right lobe of the thyroid containing a small tumor was removed, and nine separate nodules were removed from the lateral cervical region and superior mediastinum. The pathologist again reported papillary adenomas of the thyroid and of lateral aberrant thyroid origin.

It is over six years since the last operation and the patient has had no further recurrences. It was not until the two primary tumors in the thyroid were resected that the lateral cervical nodules stopped forming.

Case 2. A woman, aged 29, had developed a lump in the right side of her neck five years before entry. In 1932 aberrant thyroid tissue had been removed from the right side of her neck at the Royal Infirmary, Edinburgh, Scotland. Shortly after operation the lump reappeared. It was again removed in 1936.

Examination showed a nodule 2.5 cm. in diameter beneath the lower part of the sternomastoid on the right. The thyroid was normal.

In 1937 Dr. George Crile, Sr., removed a nodule from the region of the carotid sheath low on the right. It was reported as a cystic papillary adenoma of lateral aberrant thyroid.

A month later another tumor was noticed in the same location, and five months later three papillary adenomas were removed from the same region. A month later there were no masses palpable in the lateral cervical region, but a tiny nodule could be felt in the thyroid gland. The patient returned to England but her sister informs us that the patient has had several more nodules removed from her neck. It is now fifteen years since the onset. I do not doubt that she will continue to form nodules until the primary tumor in the thyroid is removed.

The following cases in which there were twenty or more lateral cervical nodules illustrate the excellent prognosis (at least for the first five or ten years) which may follow surgical removal of the primary tumor in the thyroid and lateral cervical nodules, regardless of their number and distribution.

Case 1. A boy was first seen at the age of 10, at which time he had a soft diffuse enlargement of the thyroid which was treated as an adolescent goiter by administration of iodine. The thyroid was examined repeatedly for the next nine years, and no abnormality of the thyroid other than a slight diffuse enlargement of the entire gland was noted.

At the age of 19, he developed nodules in both lateral cervical regions from the angle of the jaw to the clavicle and a hard nodule the size of a pea in the right lobe of the thyroid. A diagnosis of carcinoma of the thyroid with metastasis was made, and through anterior sternomastoid incisions dissections of the neck were performed without removal of either jugular vein or sternomastoid muscle. There were tumors in both lobes of the thyroid. All of the right lobe and almost all of the left lobe were removed.

Numerous lateral cervical nodules, estimated at over twenty on each side, were removed from the region posterior to the thyroid from the superior mediastinum and from along the entire length of the carotid sheath. One month later two nodules were noted beneath the angle of the jaw on the right at the upper aspect of the previous operation. These were removed. The pathologist reported papillary carcinoma of both lobes of the thyroid

Fig. 76. Distribution of metastases of a papillary carcinoma of the thyroid. Patient is alive and well ten years after operation. The thyroid and all the metastatic nodules were removed through a transverse thyroidectomy incision.

with bilateral metastasis to the cervical glands. The tissue was very cellular, having some tendency to form glands, papillomatous growths, and large solid masses of closely packed cells. The patient has remained well and free of recurrence for over six years, and x-rays of the chest show no abnormalities.

Three other patients with extensive thyroid and lateral cervical involvement by carcinoma, each of whom had twenty-five or more lateral cervical nodules and one of whom had a frank malignancy with invasion of veins by the tumor, are well from eight to ten years following operation (Figs. 76, 77, 78, 79).

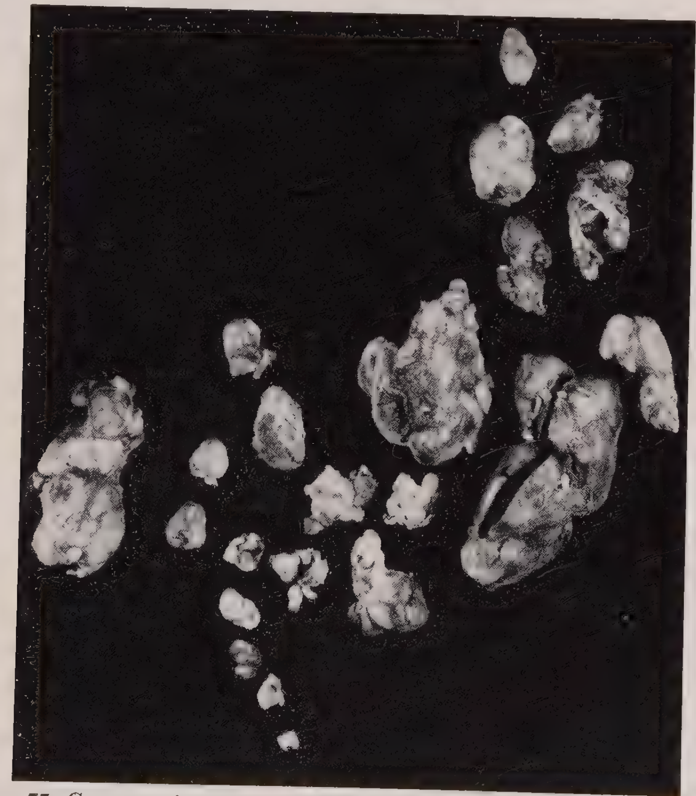


Fig. 77. Gross specimen of papillary carcinoma of the thyroid shown in Fig. 76.

It is clear that the prognosis in these cases is not entirely dependent either on the histologic appearance of the tumor or on the extent of the lateral cervical metastasis. The four patients who have died as the result of papillary tumors of the thyroid with lateral cervical nodules all had tumors which were originally reported as benign from a histologic standpoint, and in three of the four cases metastasis to the lateral cervical region did not appear for many years. It is urged that regardless of the extent of the lateral cervical metastasis and regardless of

Fig. 78. Papillary carcinoma of the thyroid and largest of twenty or more lateral cervical metastases. Patient is alive and well ten years after operation.

the apparent malignancy of the lesion, papillary tumors in the thyroid, lateral cervical region, and mediastinum should be removed surgically. Since none of the three patients in this series who had adequate x-ray treatment showed either primary regression or permanent control of the tumor, x-ray cannot always be relied upon to control this type of cancer. We have reserved its use for those cases in which surgery has failed.

The outstanding characteristics of papillary tumors with lateral cervical metastasis can be summarized as follows:

1. Twenty-one patients have been followed from five to twenty-one years or until their death, and only three have died from cancer, one with local recurrence in the thyroid and two with distant metastasis.

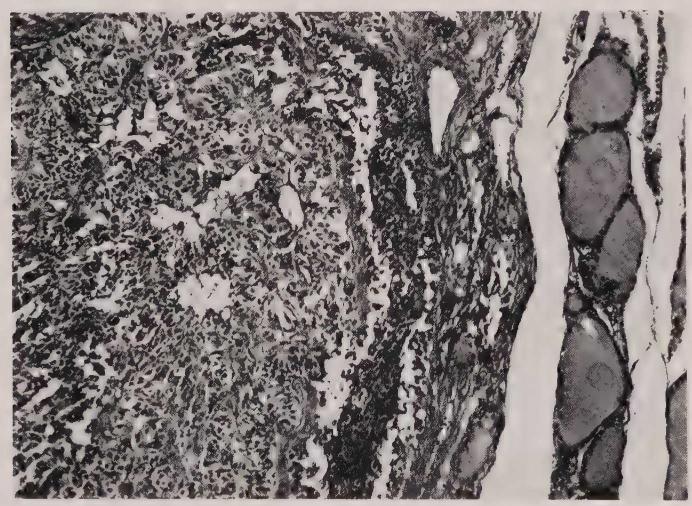


Fig. 79. Papillary carcinoma of the thyroid. Photomicrograph of specimen shown in Fig. 78. Note that there is very little suggestion of papillary arrangement in this tumor.

2. The patients who died of cancer lived for nine, fifteen, and nineteen years, respectively, after the original thyroidectomy.

3. One patient who has refused all treatment is living and well twenty-seven years after the appearance of lateral cervical nodules and twenty-one years after these nodules were proved to be papillary tumors of the thyroid.

4. In judging the results of treatment of papillary carcinoma of the thyroid the usual five-year period is meaningless. Twenty

or more years may be required before one can be sure that the patient is cured.

5. In sixteen consecutive cases with papillary tumors of the lateral cervical region, when the thyroid was carefully examined a primary tumor in the thyroid was found.

6. It is thought that the lateral cervical nodules are probably metastases from a tumor of the thyroid rather than, as I previously believed, primary tumors of congenital origin.

7. Lateral cervical tumors may continue to form until the primary tumor in the thyroid is removed. Following this no more lateral cervical nodules appear.

8. In the few cases in which x-ray has been given the results have been disappointing.

9. The results of excision of the primary tumor and the lateral cervical and mediastinal metastases have been excellent. Four patients who had twenty or more lateral cervical and mediastinal nodules are well and free of recurrence from six to ten years after operation.

10. The lateral cervical nodules rarely invade muscles or blood vessels, and block dissection of the neck is therefore not necessary. Since most of the patients are young women, whose necks one would hesitate to mutilate needlessly by a block dissection, it is an advantage to perform the operation through a thyroidectomy incision or, in the more extensive cases, through an incision parallel to the sternomastoid.

11. The tumor in the thyroid may be very small and often is not palpable before operation. On several occasions it was not found until the gland was rotated up out of its bed to expose the posteromedial surface.

12. The tumor in the thyroid usually is scarred or calcified and may not enlarge appreciably over a period of many years in spite of the fact that it continues to give rise to lateral cervical metastases.

13. Regardless of the benign histologic appearance of some of the tumors and regardless of their apparent hopelessness as suggested by the extent of metastasis, the primary tumor in

the thyroid and the lateral cervical and mediastinal metastases should be excised.

Lateral Aberrant Thyroids

In addition to the lateral cervical carcinomas which are probably metastases from a primary tumor in the thyroid, there may be occasional instances of true lateral aberrant thyroids. I have not seen such a tumor and am not convinced of its existence. The nonpapillary adenomas which occasionally are found separate from the thyroid in the lateral cervical region may represent adenomas which have been pinched off from the parent gland and have attached themselves to the lateral cervical tissues. Others may represent true ectopic thyroid tissue, but these are rare. The papillary tumors found in the lateral cervical region have, in my experience, invariably been associated with a primary tumor of the same structure in the thyroid.

Papillary Carcinoma of the Thyroid (Non-metastasizing Type)

This type of carcinoma appears as a slowly growing tumor of the thyroid. Its separation from the group with lateral cervical metastases is of necessity an arbitrary one, and there are borderline cases which could fit into either group. Eventually metastases may occur in this type of tumor, but they are rare and tend to occur late.

It is impossible to classify all patients in either one category or the other. For example, I have reported a group of twenty-one patients with papillary tumors of the thyroid with cervical metastases. Three of these cases in reality belong in the category of "non-metastasizing type" because the patients developed a bulky and invasive tumor of the thyroid many years before the appearance of the lateral cervical nodules. Since I cannot arbitrarily withdraw these three cases from the group with lateral cervical metastases I have reported them again under "non-metastasizing type" in order to give a true picture of this group. These three patients eventually died of carcinoma ten, fifteen, and nineteen years after the original operation.

When a middle-aged patient develops a bulky papillary carcinoma of the thyroid without lateral cervical metastases it is unlikely that metastasis will take place. If it should occur, it would probably be only after many years and then only to the regional nodes. The great danger in these cases is local recurrence of the tumor (Fig. 80).

Fig. 80. Papillary carcinoma of the thyroid, non-metastasizing type. A bulky tumor is present in the thyroid. These tumors tend to occur in patients beyond mid-life.

Prognosis. If the tumor can be removed to the satisfaction of the surgeon the outlook is excellent. In sixteen cases in which the tumor was apparently completely removed there was only one recurrence. In twelve cases in which the operation was admittedly incomplete there were ten recurrences, eight fatal, and two in which the patients are still living with recurrence over ten years after operation. In two cases the tumor eventually metastasized to the regional lymph nodes.

TABLE XVII

25 Cases of Papillary Carcinoma (Non-metastasizing Type)

Age: from 24 to 72	Average—48	
Sex:	6 male, 22 female	
Duration:	Average—10 years (5 had recently enlarged)	
Size:		
a. Large, filling neck		9
b. Medium, 2 to 3 in. in diameter		11
c. Small, 1 to 2 in. in diameter		8
Consistency:		
a. Very hard	16	
b. Hard	4	
c. Firm	3	
d. Cystic	2	
e. No Statement	1	
Diagnosed carcinoma preoperatively		16
Tumor apparently completely removed		16
Treated by x-ray or radium		18
a. Primary regression		1
b. Failure to control		8
Metastasis		3
Cervical and mediastinal	1	
Cervical and axillary	1	
Cervical and ? cerebral	1	
Died of carcinoma		9
Local recurrence	8	
Died other causes without recurrence (14, 3, 3, and 2 years postoperatively)		4
Alive and Well (2 to 22 years postoperatively average—9 years 11 over 5 years)		13
Cystic areas grossly visible		7
Benign adenomas present in thyroid		7

The prognosis depends almost entirely on whether or not the tumor can be removed completely and does not appear to be correlated with the histology of the tumor. Tumors which were reported as benign have recurred after incomplete removal and have caused death, whereas unmistakable papillary carcinomas, if completely removed, usually are cured. It is questionable whether any papillary tumor of the thyroid, if it be of significant size, should be classified as benign regardless of its histologic appearance. The tiny papillary adenomas that are occasionally discovered as incidental findings can be considered benign if they are perfectly encapsulated and show no evidence of invasion of capsule or blood vessels.

Surgical Removal. The bulky invasive tumor of the thyroid may be difficult to remove. Nevertheless, a tumor which at first seems to be inoperable and which, if more malignant, would be hopelessly incurable, often can be removed completely and the patient cured.

The extensive fibrosis that sometimes surrounds these tumors simulates invasion. Despite these difficulties a clean sharp dissection may enable the surgeon to remove all of the tumor and effect a cure.

Irradiation Therapy. Irradiation, either by interstitial radium or roentgen therapy, has not often effected a marked primary regression or even controlled the growth of these tumors. Sometimes the papillary tumors grow very slowly, and if this is the case any irradiation that has been given may be credited with retarding their growth. Although I have seen one case in which x-ray produced a dramatic primary regression followed by control for ten years, and although I do not doubt that in some instances satisfactory regressions have been obtained, the numerous references in the literature to the radiosensitivity of papillary tumors of the thyroid may be based to some extent on the natural slowness of growth of this type of tumor. For example two patients are living and well over ten years after incomplete removal of papillary carcinomas. Both have small symptomless recurrences. One received roentgen therapy, the other did not. Had x-ray been given to both the x-ray might have been credited with the longevity of both patients.

When confronted with a massive invasive papillary tumor which cannot be excised completely it is best to remove as much as possible, implant radon seeds in the rest, and give intensive roentgen therapy. If the tumors take up radioactive iodine, the administration of I^{131} is the preferred treatment. One patient treated by this means has shown some regression in the size of the tumor.

Bibliography

1. Crile, G., Jr.: Papillary carcinoma of thyroid and lateral cervical region; so called "lateral aberrant thyroid." Surg., Gynec. & Obst. *85:* 757–766 (Dec.) 1947.
2. Crile, G., Jr.: Tumors of lateral aberrant thyroid origin. J. A. M. A. *113:* 1094–1097 (Sept. 16) 1939.
3. King, W. L. M., and Pemberton, J. deJ.: So called lateral aberrant thyroid tumors. Surg., Gynec. & Obst. *74:* 991–1001 (May) 1940.
4. Lahey, F. H., and Ficarra, B. J.: Lateral aberrant thyroid. Surg., Gynec. & Obst. *82:* 705–711 (June) 1946.

Chapter 25

NONPAPILLARY CARCINOMA OF THE THYROID

Growth and Dissemination

The nonpapillary carcinoma often arises in an adenomatous goiter. It may be so highly differentiated that it is hardly distinguishable from a benign adenoma, as in the angio-invasive adenoma type (Figs. 81, 82); it may be a frank adenocarcinoma, or it may be an undifferentiated carcinoma. Sometimes there may be papillary areas, but if there are also areas of undifferentiated carcinoma, or if the tumor tends to invade blood vessels, it will behave as a nonpapillary carcinoma and should be classified as such.

Nonpapillary carcinomas invade the capsule of the thyroid and the surrounding tissues. The tumor tissue exhibits a striking tendency to invade venous channels, to grow in the veins, and to disseminate itself to the lungs and bones via the blood stream. Invasion of the veins by tumor tissue is, as Graham has shown, an excellent criterion of potential malignancy. Any tumor of the thyroid in which neoplastic tissue can be demonstrated within the lumen of the veins is potentially malignant and may already have metastasized through the blood stream. Some tumors of this type form grossly visible tumor thrombi in blood vessels, and cases have been reported in which the tumor has extended down the great veins of the neck and into the heart (Figs. 83, 84).

Lymphatic dissemination of nonpapillary carcinoma of the thyroid is relatively rare. It is possible that the paucity of lymphatics in the encapsulated adenomatous tissue where the tumor originates is responsible for this failure of the tumor to metastasize early to lymph nodes. When such metastasis does occur, it is usually in cases in which the tumor has broken through the capsule to invade the parenchyma of the thyroid or the contiguous structures of the neck. Vital structures may be involved or the tumor may have metastasized through the blood stream. For these reasons, metastasis to the cervical lymph nodes from nonpapillary tumors is a sign of incurability, and operations designed to cure nonpapillary carcinomas by resection of the cervical lymphatics are apt to be futile.

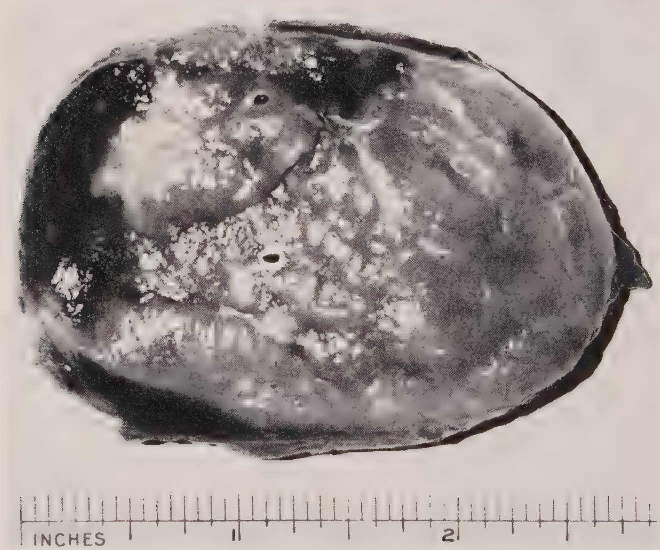


Fig. 81. Hyperplastic adenoma of the thyroid indistinguishable clinically and on gross examination from a well differentiated nonpapillary carcinoma (see Fig. 82).

In a series of forty-nine cases of nonpapillary carcinoma, there were twenty local recurrences of the tumor. In four of the eight cases in which the recurrent tumor was excised, the recurrence could be demonstrated to be within the veins of the neck.

Since resection of the venous channels draining the affected lobe of the thyroid eradicates the most common site of local recurrence, both distant metastasis and local recurrence of nonpapillary carcinomas of the thyroid may be diminished if the veins into which the tumor so frequently extends are resected along with the affected lobe of the thyroid.

Diagnosis

History. The average age of our patients with nonpapillary carcinoma of the thyroid gland was 51 years. The youngest patient was 18 years of age and the oldest 75. Sixty-eight per cent of the patients were women (Figs. 85 and 86).

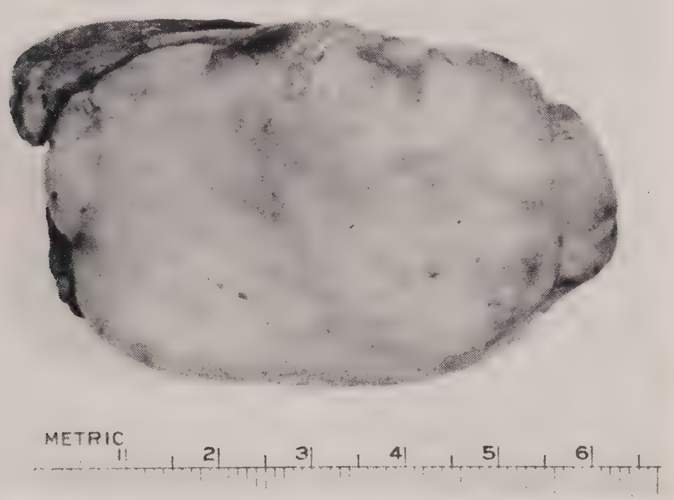


Fig. 82. Well differentiated nonpapillary carcinoma of the thyroid indistinguishable clinically and on gross examination from a hyperplastic adenoma (see Fig. 81).

The most common symptoms of which the patients complained at entry were referable to the pressure caused by enlargement of the tumor (82 per cent), but 18 per cent complained chiefly of systemic symptoms such as nervousness, loss of weight, palpitation, or fatigue. Hyperthyroidism was suspected in a few of these cases, but objective evidence to substantiate such a diagnosis usually was lacking. There were no instances in this series where the clear cut clinical picture of hyperthyroidism was associated with a high basal metabolic

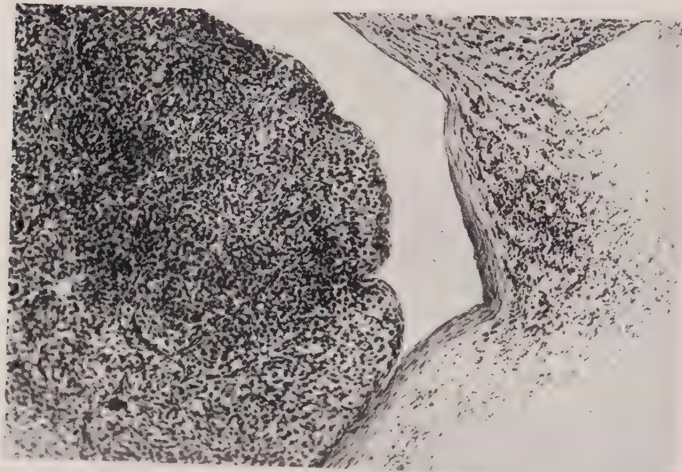


Fig. 83. Nonpapillary carcinoma growing in a vein.

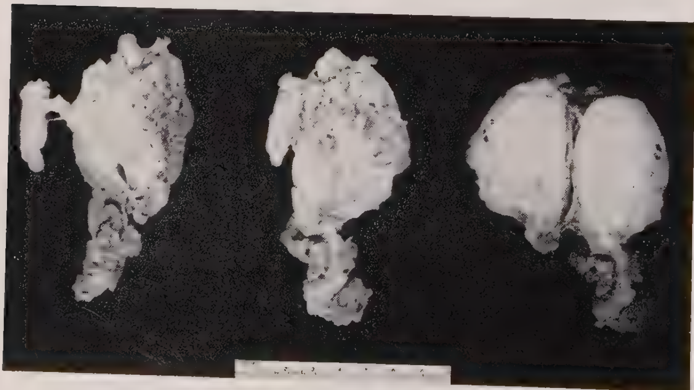


Fig. 84. Nonpapillary carcinoma of the thyroid with extension of tumor into lateral thyroid and internal jugular veins.

rate. The average basal metabolic rate in those cases in which metabolic studies were made was plus 4 per cent. Although there is no reason why in an adenomatous goiter one adenoma should not become toxic and another malignant, the chances of this occurring in the same gland are slight. It is also rare for a tumor of the thyroid to be sufficiently neoplastic to be classified as a carcinoma and at the same time to produce thyroid hormone. In the presence of frank hyperthyroidism, the diagnosis of malignant tumor of the thyroid must be made with hesitancy. The case recently reported by Marinelli *et al.*, in which the metastases of a thyroid carcinoma produced hyperthyroidism

Fig. 85. Early nonpapillary carcinoma of the thyroid, moderately differentiated. (Nelson Loose-Leaf Surgery; Vol. 2. Courtesy Thomas Nelson and Sons.)

and were shown to take up radioactive iodine, indicates that malignant tumors of the thyroid occasionally may retain function. On the other hand I have observed a case in which severe hyperthyroidism was associated with a carcinoma of the thyroid whose metastases did not take up any radioactive iodine.

The majority of the patients in this series had noticed an enlargement of the thyroid gland for a number of years prior to the development of the malignant tumor. The duration of the rapid enlargement was 12.2 months. Pain was a complaint of 14 per cent of the patients.

Although it is impossible to recognize all carcinomas of the thyroid before operation, a high index of suspicion of solitary nodules and careful evaluation of the history and physical findings by a physician who is experienced in diseases of the thyroid will result in a correct diagnosis or at least in suspicion of the presence of most malignancies.

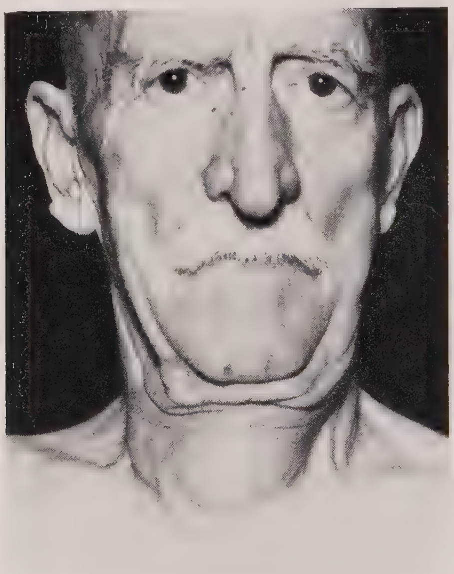


Fig. 86. Advanced nonpapillary carcinoma of the thyroid, poorly differentiated. Generalized metastasis through blood stream.

Physical Findings. In 71 per cent of the cases the tumor was described as being hard, and in 22 per cent it was fixed to the deep structure of the neck so that it did not move with deglutition. The hardness of most carcinomas of the thyroid is not the stony hardness of a scirrhous carcinoma of the breast but is a tense rubbery firmness dependent upon the expansion of a soft, rapidly growing tumor within a tense capsule. The diagnosis of cancer was made before operation in 59 per cent of the patients. In recent years the accuracy of diagnosis has been higher.

In 16 per cent preoperative paralysis of one or both vocal cords was present. Since the incidence of preoperative paralysis in simple goiter is extremely low (0.3 per cent), the finding of an abductor paralysis of one or both vocal cords associated with a goiter on which no previous operation has been performed is strong presumptive evidence that the goiter is malignant. Of four cases in which a preoperative laryngeal paralysis was associated with a simple goiter, two were large intrathoracic adenomas, one was a retrotracheal adenoma, and the fourth was a large adenoma which had displaced the trachea. If it is borne in mind how extremely rare it is to find paralysis of a vocal cord associated with simple goiter and how equally rare frank hyperthyroidism is associated with malignancy of the thyroid, an incorrect clinical diagnosis of carcinoma often can be avoided.

Indications for Radical Operation. A history of recent enlargement of a preexisting goiter and the finding of a hard, uncalcified tumor in one lobe of the thyroid indicate an excision of the affected lobe. Although calcification by no means rules out the possibility of carcinoma, calcified adenomas rarely enlarge rapidly and the calcification affords an explanation of the hardness which otherwise would imply malignancy.

Subacute or chronic thyroiditis may be mistaken for malignant tumors, but as a rule tenderness of the gland, pain on swallowing, the relatively small size of the tumor mass, or the diffuse enlargement of one or both lobes will make the diagnosis clear.

Riedel's struma, in which only one lobe may be involved in a bulky proliferative thyroiditis invading the surrounding structures, is an exception and may be indistinguishable clinically from carcinoma. Other types of thyroiditis tend to involve both lobes diffusely and do not form distinct tumor masses. The tissue in thyroiditis is hard and avascular as compared to the friable vascular tissue of a carcinoma. It is far safer, in view of the hopeless prognosis of incompletely removed cancers, to treat a suspected tumor as malignant and to remove it completely.

Indications of Incurability. Extensive bilateral involvement of the thyroid by a malignant tumor is usually associated with invasion of contiguous structures and indicates incurability. Likewise, paralysis of one or both vocal cords before operation

Fig. 87. Nonpapillary carcinoma of the thyroid with metastases to the ileum. Note huge soft tissue tumor and destruction of bone.

shows extracapsular extension. There is no case in the Cleveland Clinic series in which a permanent cure has been obtained when laryngeal paralysis was present before operation.

Pain associated with a malignant tumor of the thyroid is likewise an unfavorable prognostic sign. No permanent cures resulted in a group of seven patients who complained of pain. Pain does not occur until invasion of the capsule and cervical plexus has taken place. Similarly, fixation of the tumor signifies that extracapsular extension has taken place and that the disease is incurable.

In the presence of one or more of these signs or in the presence of demonstrable metastases in the lungs or bones, a radical operation is futile (Fig. 87). Roentgen therapy or radioactive iodine must be relied on for palliation in these patients. It is advisable to perform a biopsy to rule out the possibility of an atypical thyroiditis. A tracer dose of radioactive iodine should be given to the patient before the operation so that the tumor's ability to take up radioactive iodine can be evaluated.

Operative Technic

Although a radical resection of the affected lobe of the thyroid, of the jugular vein, and of the thyroid veins is the treatment of choice for a nonpapillary carcinoma of the thyroid, often this technic is rendered impractical either as a result of the extensive infiltration of an incurable tumor or by the fact that the diagnosis cannot be established with sufficient certainty to warrant the more radical procedure. Whenever possible, a radical operation should be performed.

After the wide transverse skin incision is made at the level of the cricoid cartilage, the skin flaps are dissected upward and downward to enable the operator to separate the pretracheal fascia and muscles in the midline and examine the thyroid. This examination is carried out gently and with care not to break the capsule of the gland. If it is evident that the tumor is malignant the skin incision is extended vertically from the midpoint of the lower flap straight down to the suprasternal notch (Fig. 88). The skin flap including the subcutaneous fat is then dissected free of the platysma and the deep cervical fascia on each side and is retracted. The pretracheal (sternothyroid, sternohyoid, and omohyoid) muscles are separated in the midline from the thyroid cartilage to the suprasternal notch. The muscles and cervical fascia on the side of the tumor are clamped and divided transversely as high as possible so as to afford adequate exposure of the superior pole. At this level the sternomastoid is well lateral to the tumor and need not be divided.

The muscles and the cervical fascia are again clamped and divided transversely just above the insertion of the muscles into the sternum (Fig. 89). A careful attempt is then made to separate the muscles from the underlying capsule of the thyroid, and if they are not adherent they are elevated like a trap door and retracted laterally to expose the thyroid and the carotid

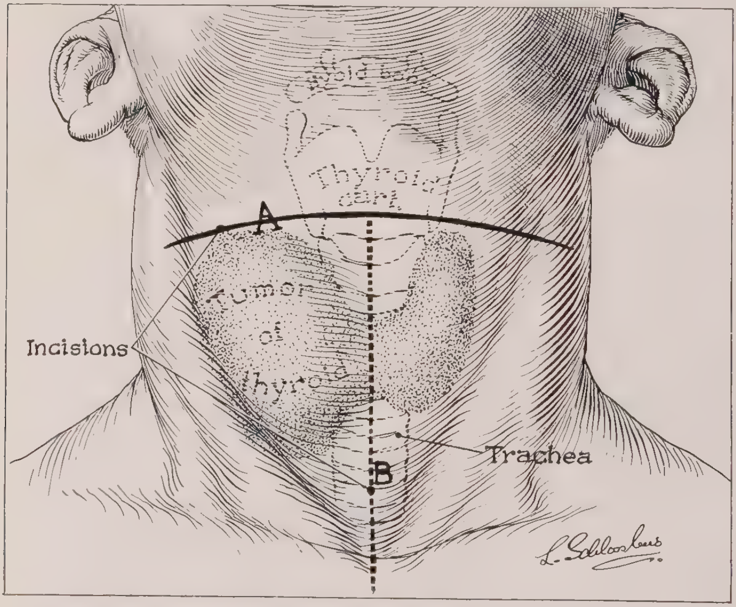


Fig. 88. High transverse incision for carcinoma of thyroid. (Vertical incision is added when diagnosis and operability are confirmed by exploration.) (Courtesy of Surgery, Gynecology and Obstetrics.)

sheath (Fig. 90). If the muscles are adherent to the capsule of the thyroid and their separation from the thyroid would entail risk of cutting into tumor tissue, it is better not to attempt this separation but to connect the lateral ends of the two transverse incisions by a vertical incision, expose the jugular vein by this means, and resect the overlying muscles along with the lobe of the thyroid.

Before any further manipulation of the tumor is attempted, the internal jugular vein should be isolated, doubly ligated, and severed low in the neck and again ligated and severed as high as possible—always well above the point of entry of the lateral thyroid vein (Fig. 91). The inferior thyroid veins likewise should be ligated and severed as far as possible from the tumor.

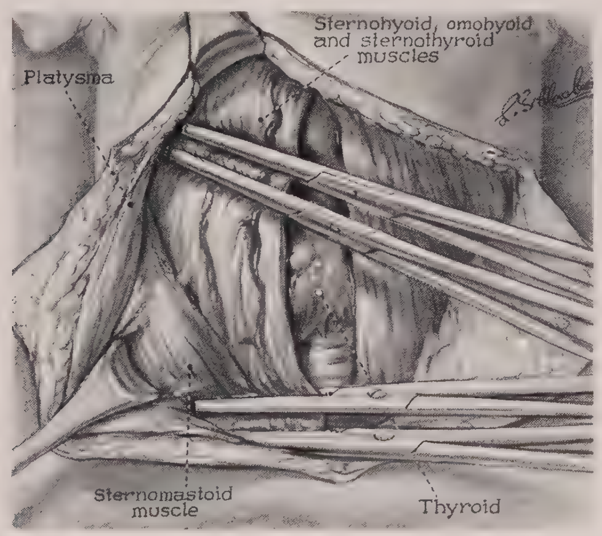


Fig. 89. Muscles are divided transversely high in neck and again at base of neck to afford wide exposure. The muscles may be removed with the tumor or reflected laterally depending on whether or not they are adherent to the tumor.

The internal jugular vein and the lateral thyroid veins are then dissected out and are resected along with the entire affected lobe of the thyroid. In the course of the lobectomy, no attempt should be made to preserve the recurrent laryngeal nerve if it is involved by tumor. Such attempts result only in unnecessary manipulation with attendant liability to dissemination of the tumor. The slight hoarseness that results from paralysis of one vocal cord is a negligible consideration as compared with the possibility of recurrence of the tumor.

The arterial blood supply of the thyroid should be ligated before the gland is dissected off the trachea. The superior and inferior thyroid arteries are isolated, clamped, and divided well away from the gland in order to avoid manipulation of the

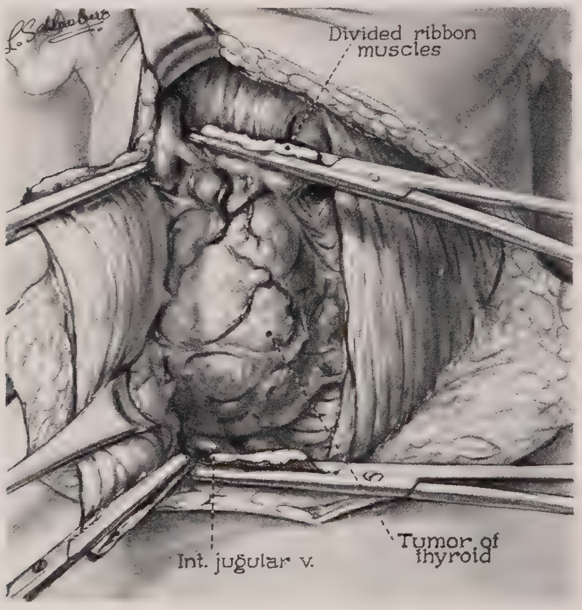


Fig. 90. The jugular vein and the tributary veins draining the thyroid are excised with the affected lobe of the thyroid.

tumor. The isthmus is then divided, and the affected lobe is dissected free of the trachea. Complete removal of the tumor is most readily accomplished by sharp dissection and by avoiding clamps on the tumor even if slight oozing does occur.

During the course of the operation the capsule is not broken by the insertion of hemostats or traction clamps. Any desired rotation of the gland from its bed is obtained by inserting the finger behind and drawing it forward.

At the close of the operation the trachea and the carotid artery on the affected side are bare. When there is extensive bilateral involvement, a condition which usually occurs only in advanced and incurable cases, the tumor is fixed to the trachea and has invaded all contiguous structures. This type of tumor rarely can be removed completely, and a radical operation is not only

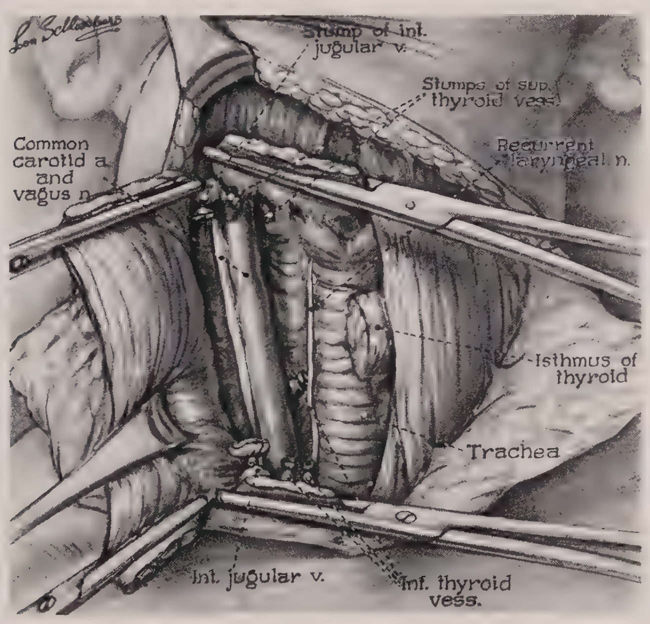


Fig. 91. After excision of the veins and the entire lobe of the thyroid the trachea is left bare. Often the recurrent nerve can be preserved, as shown in this diagram, but if it is involved by the tumor no attempt should be made to save it.

dangerous but futile. In any case, bilateral ligation of the internal jugular vein should not be attempted at the same operation.

When complete excision cannot be accomplished it is still of value to ligate the jugular vein, excise as much of the tumor as possible, implant radon seeds in the remaining portions, and treat with roentgen therapy.

Oftentimes in advanced cases operations designed to relieve respiratory obstruction by decompression of the trachea are undertaken. As a rule such procedures are of no value because the obstruction is more apt to be secondary to actual invasion of the trachea by the tumor or to compression at the thoracic inlet than from pressure from the front. When dyspnea has progressed to the point that death from anoxemia is imminent, a tracheotomy, performed if possible below the tumor, is the treatment of choice. Roentgen therapy then can be given a trial. After an adequate airway is established radon seeds may also be implanted with safety.

Prognosis of Nonpapillary Carcinoma

Fortunately the two most common types of malignant tumor of the thyroid, the papillary and moderately differentiated nonpapillary carcinomas, carry a relatively favorable prognosis. In most other types, such as undifferentiated carcinoma, squamous cell carcinoma, lymphosarcoma, and spindle cell sarcoma, there is little or no prospect of permanent cure.

Forty-nine patients with nonpapillary carcinoma were selected for study. In all these cases, sufficient tissue for definite classification was available, the histories were complete, and the follow-up was complete to the time of the patient's death or to the fourth year after operation. Twenty-six per cent of these patients were alive and apparently free from cancer from three to seventeen years after operation, an average cancer-free survival period of slightly over seven and one-half years.

At the end of five years 35 per cent were alive; 2 per cent were alive at the last report but had been lost in the follow-up; 2 per cent had died of other causes and apparently were free from cancer, and 61 per cent had died from cancer.

At the end of ten years 68 per cent of the patients were dead from cancer, and at the end of fifteen years 70 per cent were known to be dead from cancer.

It is apparent that when a permanent cure is not effected the majority of patients die in the first three years. A few run a prolonged course but eventually die from cancer.

In the majority of cases in this series a course of postoperative roentgen therapy was given and in some instances this appeared to hold the cancer in check. On the other hand, it is extremely difficult to evaluate the effects of roentgen therapy because of the great variability in the natural course of the disease. One patient, for example, who received no roentgen therapy, is alive and apparently cancer-free more than six years after the original operation and more than two years after the excision of the second of two local recurrences in the veins of the neck. Had this patient been given roentgen therapy her longevity might well have been ascribed to this treatment.

Excision of the veins of the neck was not performed routinely in these patients and sufficient time had not elapsed to allow any evaluation of the results of the radical operation. There were, however, four patients in whom the internal jugular vein on the affected side was ligated or excised at the time of operation. In one of these, complete removal of the tumor was impossible and the patient died within a month as a result of a local recurrence. The other three patients, in each of whom a section of the jugular vein was excised, all lived more than nine years. Generalized metastases developed eight years after the original operation in one patient; the second patient died apparently free from cancer eight and one-half years after operation, and the third is cancer-free seventeen years after the original thyroidectomy.

Detailed studies of the group of forty-nine cases of nonpapillary carcinoma indicate that the prognosis is more dependent on the extensiveness of the tumor and on the surgeon's ability to excise it completely than on the age of the patient, the duration of the recent enlargement of the goiter, the extent of microscopic invasion of blood vessels, or the degree of anaplasia of the tumor as based on histologic grading.

Age. Fifty per cent of the patients under 45 years of age lived three years after operation, and 50 per cent of those over 55 lived three years after the operation.

Duration of the Enlargement of Goiter. If the duration of the recent enlargement of a preexistent quiescent goiter is taken as a measure of the duration of the cancer before operation, it is found that the curability rate was higher in patients in whom the duration of the enlargement was the longest. Thirty-one per cent of the sixteen patients who had first noticed enlargement of a preexisting goiter or who had first noticed a goiter less than four months before entry were alive at the end of three years as compared to 55 per cent of the patients who had noticed enlargement of the goiter for more than four months. It is possible that the invasive and incurable tumors give symptoms earlier as a result of extension to contiguous structures and hence impel the patient to seek aid earlier than do the noninvasive varieties.

Invasion of Blood Vessels. It was found that 55 per cent of the patients in whom microscopic examination showed extensive invasion of the blood vessels by tumor tissue were alive at the end of two years as compared with 40 per cent in whom lesser degrees of blood vessel invasion were demonstrable microscopically. It is possible that the rapidly growing, invasive, and anaplastic tumors destroy the capsule and its vessels so rapidly that the blood vessel invasion is not easy to demonstrate, whereas the more slowly growing malignancies tend to grow in the lumen of veins without destroying their walls.

When tumor thrombosis of veins was visible on *gross* examination the prognosis was found to be somewhat worse than when gross evidence of blood vessel invasion could not be detected. Gross invasion of the blood vessels is often associated with extension of the tumor thrombi into the veins of the neck, a condition which is incurable unless these veins are resected with the tumor.

Anaplasia. In general the prognosis of malignant tumors of the thyroid correlates well with the degree of anaplasia which is present. Few of the patients with undifferentiated carcinomas live longer than one year whereas the majority of the patients with highly differentiated angio-invasive adenomas live for several years or are permanently cured. Those with moderately differentiated adenocarcinomas stand between these extremes (Table XIII).

Completeness of Excision of the Tumor. The most reliable index of prognosis was the completeness or the incompleteness of the excision of the tumor. When the tumor was apparently completely excised, 76 per cent of the patients were alive at the end of three years, whereas only 12.5 per cent of those in whom the excision was apparently incomplete were alive at the end of this period. The outlook for the patient in whom the disease is in a sufficiently early stage that the tumor can be excised to the satisfaction of the surgeon is therefore six times as good as that of the patient in whom complete excision of the tumor is rendered impossible by its extensiveness or invasiveness.

TABLE XVIII

Relationship of Completeness of Excision to Survival After Operation

	Lived 3 years after operation	Died less than 3 years after operation
Incomplete excision	3	21
Complete excision	19	6

The impression of the surgeon as to whether or not he is able to remove the entire tumor is the most valuable single criterion for determining the prognosis in patients with nonpapillary carcinomas of the thyroid.

Lahey's experience with malignancy of the thyroid using a different classification is detailed in the following table.

TABLE XIX

Carcinoma of the Thyroid

Five Years Survival Rate, 231 Cases

	Per Cent
Adenoma with blood vessel invasion	71
Papillary cystadenoma, malignant	62
Papillary adenocarcinoma	80
Alveolar adenocarcinoma	27
Small cell carcinoma	22
Giant cell carcinoma	17
Fibrosarcoma	33

Treatment of Carcinoma of the Thyroid with Radioactive Iodine

Most carcinomas of the thyroid do not produce hyperthyroidism and do not take up radioactive iodine. Occasionally, however, carcinomas of the thyroid and their metastases produce true hyperthyroidism and take up and store radioactive iodine exactly like a toxic goiter. Such a case has been reported by Seidlin, Marinelli, and Oshry. A similar case has been reported by Keston, Ball, Frantz, and Palmer. Leiter *et al.* reported two cases of adenocarcinoma of the thyroid with functioning metastases and showed that the effect of thiouracil on the basal metabolic rate, plasma cholesterol, protein-bound blood iodine, and excretion of radioactive iodine was similar in these patients to the responses already described in the literature in ordinary thyrotoxicosis.

Seidlin *et al.* report the results of a three-year study of the therapeutic effects of radioactive iodine in a case of metastatic carcinoma of the thyroid in which all demonstrable metastases were shown to pick up the radioactive iodine. The bulk of these metastases was estimated at 300 cc. Mixtures of two isotopes, I^{130} and I^{131}, were used. Over a period of three years nearly 249.3 mc. were given, making an equivalent r dose of 40,000 to each of the metastatic tumors.

Following treatment with radioactive iodine the basal metabolic rate fell from plus 40 to minus 27. The x-ray appearance of the metastases improved, and the symptoms disappeared. There were no significant changes in the blood, and no apparent damage to other organs. After this therapy there was still some uptake of radioactive iodine by the tumor, and the patient is still undergoing treatment.

Hare has stated that 6000 r given by x-ray is ineffective in controlling the growth of this type of tumor. The gamma ray dose by interstitial radon necessary to treat this type of tumor successfully is given by Hare as 20,000 r, a value well beyond the reach of external radiation. Since 1 mc. of eight-day iodine destroyed per gram of tissue gives approximately 150 equivalent r, to achieve a dosage equivalent to 20,000 r at least 133 mc. must be concentrated in each gram of carcinoma. Although theoretically a tumor weighing 400 gm. requires only 40 mc. to be fixed in the tumor, the actual amount that it is necessary to feed to the patient may be several times the theoretical requirement, because of loss of iodine by excretion and by disposition in other tissues, especially if normal thyroid tissue is still present.

Seidlin reports that four patients with metastatic carcinoma of the thyroid, without clinical hyperthyroidism, have shown selective localization and two of these are now under treatment. He does not believe that it is possible as yet to state which of the isotopes is the most effective.

This experience with radioactive iodine in the treatment of carcinoma of the thyroid gives hope for the patients with well differentiated metastatic tumors that are capable of taking up and storing iodine. Unfortunately only a small percentage of all carcinomas of the thyroid have this ability. Nevertheless, all patients with inoperable carcinomas of the thyroid should be tested for the ability of the tumors to take up iodine. A Geiger counter held over a metastasis a few hours after a tracer dose of 500 mc. of radioactive iodine has been given will provide the necessary information, or a biopsy can be taken of the tumor after radioactive iodine has been given and this can be tested with a counter or by placing it on an unexposed film. The presence of normal thyroid tissue invalidates the results of Geiger counter studies made on the primary tumor. So far I have found only one carcinoma of the thyroid that takes up radioactive iodine, a colloid-containing papillary carcinoma with pulmonary metastases. In this case hyperthyroidism was not present.

There is evidence indicating that removal of all of the normal thyroid, or destroying it with radio-iodine, will in some cases stimulate the metastatic tumor to take over the function of the thyroid (Rawson). A trial of this method would be worth while in differentiated carcinomas which do not take up iodine.

It is also possible that the administration of one of the anti-thyroid drugs might modify the behavior of a well differentiated colloid-forming metastasis in respect to its ability to take up radioactive iodine. Rawson first inactivated the thyroid gland by thyroidectomy or treatment with radioactive iodine. The patient was then given a course of thiouracil in the hopes that this therapy would exhaust the stores of colloid in the metastases and cause a hyperplasia. After the administration of

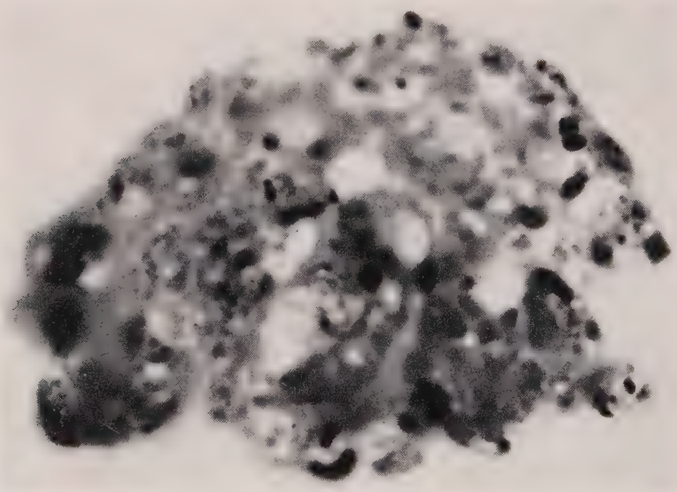


Fig. 92. Radio-autograph of multinodular goiter showing irregular take-up of radioactive iodine by the thyroid tissue.

thiouracil was stopped, the tumor was shown to take up much more radioactive iodine than before. These speculations are interesting but the results have not as yet been evaluated. Certainly every patient with inoperable or metastatic carcinoma of the thyroid should be studied from the standpoint of the tumor's ability to take up radioactive iodine, and tracer doses of radioactive iodine should be given to patients suspected of having carcinoma prior to operations so that radio-autographs of the tumor can be made (Fig. 92).

Bibliography

1. Graham, A.: Malignant tumors of thyroid; epithelial types. Ann. Surg. *82:* 30–44 (July) 1925.
2. Hare, H. F.: Radiation treatment of carcinoma of thyroid. Am. J. Roentgenol. *46:* 451–453 (Oct.) 1941.
3. Holt, W. L., Jr.: Extension of malignant tumors of thyroid into great veins and right heart. J. A. M. A. *102:* 1921–1924 (June 9) 1934.
4. Keston, A. S., Ball, R. P., Frantz, V. K., and Palmer, W. W.: Storage of radioactive iodine in metastasis from thyroid carcinoma. Science *95:* 362–363 (April 3) 1942.
5. Lahey, F. H.: Carcinoma of thyroid. Am. J. Roentgenol. *46:* 469–475 (Oct.) 1941.
6. Leiter, L., Seidlin, S. M., Marinelli, L. D., and Baumann, E. J.: Adenocarcinoma of thyroid with hyperthyroidism and functional metastases; studies with thiouracil and radio-iodine. J. Clin. Endocrinol. *6:* 247–261 (March) 1946.
7. McClintock, J. C., Klinck, G. H., Jr., and Conrad, J. E.: Carcinoma of thyroid gland. Surg., Gynec. & Obst. *72:* 150–156 (Feb.) 1941.
8. Pemberton, J. deJ., and Lovelace, W. R., Jr.: Malignant lesions of thyroid gland. S. Clin. North America *21:* 1037–1062 (Aug.) 1941.
9. Rawson, R. W., *et al.:* Pending publication. Tr. Am. Goiter Soc.
10. Seidlin, S. M., Marinelli, L. D., and Oshry, E.: Radioactive iodine therapy; effect of functioning metastases of adenocarcinoma of thyroid. J. A. M. A. *132:* 838–847 (Dec. 7) 1946.

Chapter 26

NONENCAPSULATED SCLEROSING TUMOR OF THE THYROID*

No discussion of malignant tumors of the thyroid would be complete without reference to a small but important group of tumors which never until recently have been described adequately. They are tiny tumors whose presence is unsuspected before operation and which are found incidentally in the course of a thyroidectomy or more often found only by the pathologist either at autopsy or in surgically removed thyroids (Figs. 93 and 94). Since they usually are reported as adenocarcinomas and since it is not for some days following operation that this report is made, the question of more radical operation or of irradiation therapy always arises. In most cases further treatment is unnecessary because they do not tend to recur or metastasize.

One of the best descriptions of these tumors and their behavior is contained in a personal communication from Dr. Allen Graham reviewing his experience with twenty cases of this unusual tumor. I quote from this description: ". . . Whether or not these lesions which I have classified as 'adenocarcinoma not arising in an adenoma' represent a 'precancerous' stage of something which tends to progress to a frankly malignant phase will have to be left open for further observation and experience. I feel that there is some evidence that such may be the case. . ." Their behavior and appearance can be summarized as follows:

"1. There are no clinical manifestations.

"2. Their presence has not been suspected at operation, except possibly in two cases of the twenty.

---

* Called also "Adenocarcinoma not arising in an adenoma"—Graham, or "Primary carcinoma of the hyperplastic thyroid"—Goetsch.

"3. They are discovered by the pathologist during examination of the tissue removed . . .

"4. *Gross Pathology*. They are usually situated immediately beneath the capsule of the upper or lower pole, along the lateral border, on the anterior surface, or occasionally on the tracheal surface. Rarely are they deeply situated in the lobe. Their size varies from a few millimeters to 1.5 cm. in diameter. The smaller ones sometimes suggest small scars, but the larger

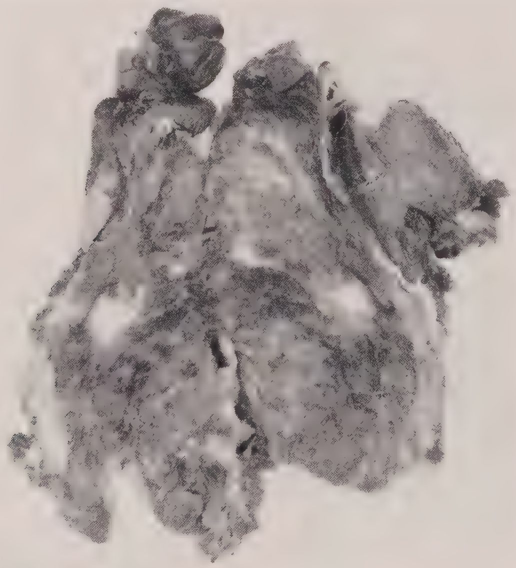


Fig. 93. Non-encapsulated sclerosing tumor of the thyroid. The tiny white area seen in the outer portions of the split lobe is the tumor. It resembles a small scirrhous carcinoma of the breast.

ones can be readily distinguished from scar tissue. They can be distinguished from an adenoma by the fact that they are not encapsulated and there is no clear-cut line of demarcation between the lesion and the surrounding thyroid. Their cut surface almost exactly duplicated the appearance of a small adeno or scirrhous carcinoma of the breast. In no instance have they been grossly cystic, papillomatous, necrotic, or stained by blood pigment as frequently occurs in intracystic papillomas, cystic papillary carcinomas, and in the lateral aberrant lesions . . .

"5. *Microscopically.* The one thing that cannot be predicted is the histologic appearance of the lesions. Generally they have a glandular structure but the range of variations is very great. Sometimes they are like mature thyroid; in other instances they are like the acini of an adenoma. The epithelium varies from

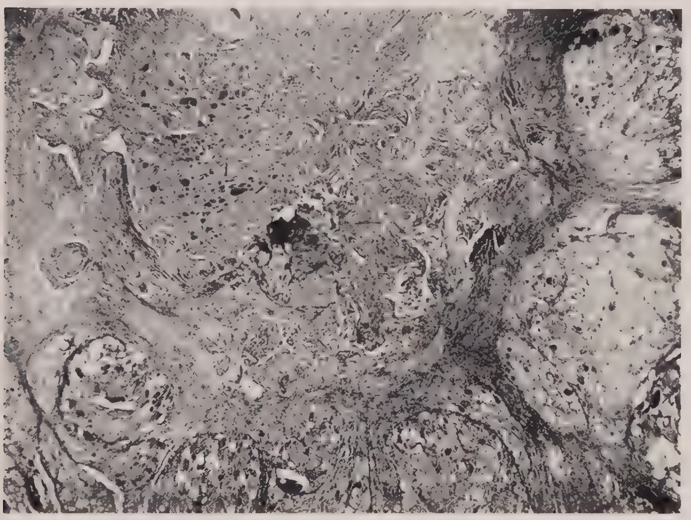


Fig. 94. Low power photomicrograph of non-encapsulated sclerosing tumor of the thyroid.

flat to columnar, usually in a single layer. In some instances there are minute spaces with infoldings, polypoid projections, or even papillomatous growths partially or almost completely filling the spaces. Generally the epithelium is distinctly different from that of the surrounding thyroid—whether the latter be colloid goiter or hyperplastic goiter. In some instances, with or without the above features, the epithelial cells may be arranged in solid cords or small masses having little or no tendency to form glandular structures. This is the nearest approach to what might be called 'histologic cancer.' One of the most constant features is the presence of a noteworthy amount of dense, sometimes hyalinized connective tissue or scar tissue in the center, and radiation of this connective tissue out into the surrounding thyroid stroma without the intervention of anything even suggestive of a capsule. Degenerative changes in both the connective tissue and epithelial elements are frequently observed, but significant inflammatory reaction usually is not seen. Calcareous deposits and blood pigment granules are not striking. The epithelial elements of the peripheral zone, the more viable and potentially active or less degenerated portions, appear to infiltrate the stroma of the surrounding thyroid or the overlying capsule. This is generally interpreted as evidence of malignancy even in cases where the histologic and cytologic characteristics of the epithelium are not consistent with a diagnosis of carcinoma. I have never observed infiltration beyond the capsule of the thyroid. Nor have I observed unequivocal invasion of lymphatics or blood vessels. Occasionally there are metaplastic changes in the epithelium to something suggestive of squamous type, but I have not noted intercellular bridges or keratinization. Generally there is little or no colloid even in the more differentiated lesions.

"6. So far as I know, not a single one of the patients included in the list has ever shown any evidence of recurrence or metastasis, despite the fact that in no case was carcinoma suspected and the operations were performed without resort to unusual precautions to prevent recurrence or metastasis.

"7. Whatever may be the pathologic interpretation of these lesions, the important clinical fact is that follow-up observations have proved the lesions under discussion to be entirely innocuous. They do not require extensive surgery nor postoperative irradiation.

"8. *Classification.* A satisfactory name to apply to these lesions has not been evolved. 'Carcinoma' seems too formidable. 'Carcinoid' might be acceptable except for its well known association with argentaffinomas. It is inevitable that these lesions, on morphological grounds (local infiltration and atypical epithelium), will be called carcinomas by those of limited experience with them. That this is so is indicated by the many cases that have been brought to my attention from various parts of this country, all having been designated as carcinoma, and raising the question of further surgical operation or irradiation, I have regularly advised against further treatment. The only conclusion I can arrive at is that whatever the pathologic diagnosis or the designation given to these lesions, they should be segregated in a special category and not included among other types of carcinoma. I shall probably continue to call them 'Adenocarcinoma, not arising in adenoma,' and consider them to be clinically benign.

"As for references to publications, there is very little to say. The first reference by me to these lesions was at the meeting of the Interstate Post Graduate Medical Assembly of North America (Proceedings, 1927).

"Occasionally I have noted among the illustrations contained in articles dealing with malignant goiter, typical gross lesions but, except for Goetsch's article, there has been no intimation that these lesions are of a particular nature. They have been simply included among the carcinomas. . . ."

Bibliography

1. Goetsch, E.: New concept regarding origin of so-called primary carcinoma of hyperplastic thyroid. Ann. Surg. *118:* 843–858 (Nov.) 1943.
2. Graham, A.: Personal communication.
3. Graham, A.: Malignant epithelial tumors of thyroid. Surg., Gynec. & Obst. *39:* 781–790 (Dec.) 1924.
4. Graham, A.: Malignant tumors of thyroid; epithelial types. Ann. Surg. *82:* 30–44 (July) 1925.

Chapter 27

THYROIDITIS*

There are three main and distinct clinical types of thyroiditis: (1) subacute (pseudotuberculous, or giant cell) thyroiditis, (2) struma lymphomatosa (Hashimoto's thyroiditis), and (3) Riedel's struma (woody or ligneous thyroiditis). There are other types of thyroiditis that either have not been classified or represent incomplete or atypical forms of the above. In addition thyroiditis may complicate bacterial or virus infections and may be the result of parasitic disease. It is not within the scope of this chapter to discuss the rare and atypical types of thyroiditis but rather to define more clearly the recognized types and to discuss their treatment.

Subacute Thyroiditis

Subacute thyroiditis is a self-limited disease of unknown etiology. It runs a variable course of weeks or months and eventually subsides without treatment and without significant interference with the function of the thyroid.

This type of thyroiditis has been variously named tuberculous, pseudotuberculous, or giant cell thyroiditis because of the histologic appearance of pseudotubercles with giant cells. Tubercle bacilli cannot be demonstrated in the lesions, and the etiology of the disease is unknown. Bacteria have not been demonstrated in the thyroid. The possibility that the disease represents a virus infection has not been excluded. The pseudotubercle or giant cell reaction represents a reaction of wandering cells to colloid, which they appear to be phagocytizing.

Many surgeons do not operate on patients with subacute thyroiditis and hence are not aware that this well recognized

* Reprinted in part by permission of Annals of Surgery.

TABLE XX. COMPARISON

	Riedel's Struma	*Struma Lymphomatosa*
	11 cases treated by partial thyroidectomy	14 cases treated by partial thyroidectomy*
Age	42 to 74; Av. 51 (7 over 50)	30 to 72; Av. 49 (8 over 50)
Sex	10 F, 1 M	12 F, 2 M
Duration	3 mo. to 7 yrs. Av. 29 mo. (8 were 1 yr. or more)	1 mo. to 8 yrs. Av. 20 mo. (7 were 1 yr. or more)
Leading Symptom	Pressure 6, goiter 2, nervousness 1, pain 2	Goiter 7, systemic symptoms 4, pressure 3 (Pain at onset only 3)
Tender Thyroid	1	0
Pain on Swallowing	1	1 at onset only
Pain radiating to ear	0	0
Temperature	Av. 98.7°	Av. 98.6°
Pulse Rate	80 to 120; Av. 88	64 to 128; Av. 86
Loss of Weight	Av. 9 lbs.	Av. 6 lbs.
B.M.R.	−20 to +28; Av. +2%	−24 to +18; Av. −8%
Sedimentation Rate	1 case 1.6 mm./min.	1 case 0.22
Diagnosis Preop.	Thyroiditis 2; Ca. or Riedel in 2; Adenoma 1; Ca. in 6	Thyroiditis 3; nodular goiter without hyperthyroidism 9; calcified adenoma 1; ca. or thyroiditis 1

OF TYPES OF THYROIDITIS

Subacute Thyroiditis 15 cases (14 treated with x-ray and 1 by undulant fever vaccine)	*Giant Cell or Pseudotuberculous Thyroiditis* 12 cases treated by partial thyroidectomy	
20 to 61; Av. 41	34 to 57; Av. 47	Age
14 F, 1 M	9 F, 3 M	Sex
Few days to 6 mo. Av. 6 wks.	3 wks. to 11 mos. Av. 11 wks.	Duration
Pain in thyroid 15	Pain 11; no pain 1 (systemic symptoms)	Leading Symptom
15	10; not tender 2	Tender Thyroid
12; no pain 0; no statement 2	5; no pain 4; no statement 3	Pain on Swallowing
6; no ear pain 2; no statement 7	6; no statement 6	Pain radiating to ear
97.8° to 101°; Av. 99.4° (5 had temp. over 100°)	98.4° to 102.5°; Av. 99.9° (4 over 100°)	Temperature
72 to 160; Av. 113 (6 over 120)	96 to 152; Av. 108 (2 had pulse over 120)	Pulse Rate
0 to 12 lbs. Av. 6 lbs.	0 to 30 lbs. Av. 13 lbs.	Loss of Weight
−19 to +29. Av. +10%	−13 to +41. Av. +10%	B.M.R.
8 cases, average 1.46 mm./min. (normal 0.4)	4 cases average 0.96	Sedimentation Rate
15 correct diagnosis	9 recognized before op., 3 not recognized	Diagnosis Preop.

TABLE XX.

Bilateral	5; unilateral 6; (2 of unilateral later involved the other lobe)	12; unilateral 2 (no biopsies of other lobe)
Und. Fever Skin Test	None tested	None tested
Hyperthyroidism	None	None
History of Upper Resp. Infect. at Onset	1 questionable	None
Proved by Exam. of Tissue	11 (7 had associated adenomas)	14 (none had associated adenomas)
X-Ray Therapy	3 cases; 2 with apparent arrest but no regression; 1 with no improvement after 2550 r.	1 case; no improvement; amount unknown
Surgery	Removal of part of each lobe 4: 3 pts. well. 1 hypothyroidism postop. Removal of part of 1 lobe 7: 3 pts. well; 2 developed recurrences in other lobe; 1 had persistent tumor in other lobe; 1 had persistence of spontaneous preop. tetany resulting from destruction of parathyroids by fibrosis	Thyroidectomy 10; 3 are well; 5 have hypothyroidism or some systemic disorder poorly controlled with thyroid; 1 has bilateral paralysis of vocal cords; 1 died postop. Lobectomy 4; 2 are well; 1 is improved but does not feel well; 1 has persistence of other lobe but feels well
Larynx	2 pts. developed spontaneous paralysis of vocal cord on affected side.	No. preop. paralysis

* 6 of the cases included in this series were previously reported by Dr. Allen Graham; ref. 2. The other 8 are unreported cases.

(Concluded)

12; unilateral 3; (creeping type 2)	12; unilateral 0	Bilateral
neg. 4; strongly pos. 1, weakly pos. 1	2 cases both neg.	Und. Fever Skin Test
None in 12; questionable in 3	None in 7, questionable in 5	Hyperthyroidism
3	4	History of Upper Resp. Infect. at Onset
2 (biopsy only)	12 (2 had associated adenomas)	Proved by Exam. of Tissue
14 cases 300 to 1050 r. Av. 620 r. Well in 1 wk. to 3 mos. Av. 19 days; all improved in 3 wks.	0	X-Ray Therapy
Thyroidectomy 0 Lobectomy 0 Biopsy 2	Thyroidectomy 6; 5 well postop. Hypothyroidism 1 Lobectomy 6, 3 well postop.; 3 had symptoms due to persistence or recurrence in other lobe but eventually recovered.	Surgery
No laryngeal paralysis	No preop. paralysis	Larynx

clinical entity is, from the histologic standpoint, identical with pseudotuberculous or giant cell thyroiditis. In order to prove to my own satisfaction that the two diseases are the same, I have analyzed fifteen cases of subacute thyroiditis in which roentgen treatment was given and compared the history and physical findings with those of twelve cases in which operation was performed. To further confirm the fact that the clinical entity of subacute thyroiditis is indeed identical to the pathologic entity of giant cell or pseudotuberculous thyroiditis, biopsies of the thyroid were taken in two typical cases of subacute thyroiditis, and the patients were then treated with x-ray. The biopsies showed typical giant cell or pseudotuberculous thyroiditis; the response to x-ray was prompt, complete, and typical of that of subacute thyroiditis. In Table XX the two groups are compared, and it is clear that the cases are similar in most respects, the only difference being that the cases treated surgically were in general less acute and of longer duration. Many of these cases probably represent the subsiding phase of the disease.

Clinical Course. The onset of subacute thyroiditis is usually sudden and in about a fourth of the cases follows an acute upper respiratory infection. This history is difficult to evaluate because patients cannot always differentiate between a sore throat and a sore thyroid gland. The disease is six times more common in women than in men and tends to occur in the mid-forties.

Pain on swallowing and pain radiating up to the ear are characteristic of subacute thyroiditis. Usually the gland is exquisitely tender. A low grade elevation of the temperature is present (Fig. 95) and the sedimentation rate is elevated, often to high levels. There may be a marked systemic reaction. The patient feels nervous, weak, and tired, and the pulse rate is elevated out of proportion to the temperature, sometimes as high as 160. Sweating and tremor are often prominent symptoms, so that the clinical picture may closely simulate hyperthyroidism. The basal metabolism, however, is not often elevated above the upper limits of normal and it is questionable whether true hyperthyroidism is present. The average basal metabolic rate is plus 10, but about one-third of the patients have basal metabolic rates over plus 15 per cent. The picture is that of a toxic reaction rather than of true hyperthyroidism. There is usually loss of weight, but since the duration of the disease is short the loss is slight. The eye signs of hyperthyroidism are not present. Only about 5 per cent of a tracer dose of radioactive iodine is taken up by the thyroids of these patients.

Tenderness of the thyroid is almost always present, especially in the early stages when the gland is exquisitely sensitive to pressure. The entire gland is diffusely involved in most cases.

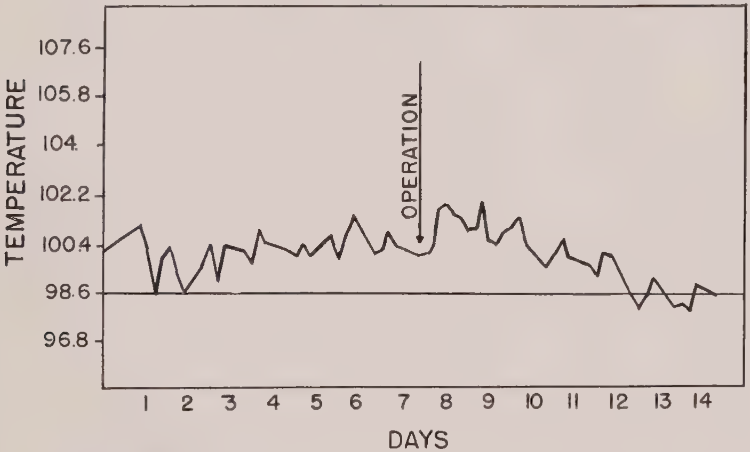


Fig. 95. Temperature chart of patient with subacute thyroiditis. Before admission to the hospital she had been observed for two months and the symptoms had not improved. Only one lobe of the thyroid was removed but the temperature and pulse rate fell promptly to normal. Elevations of temperature such as this are frequently seen in subacute thyroiditis. (From George Crile, Jr., Annals of Surgery, volume 127, J. B. Lippincott Co.)

Its consistency is abnormally firm or hard. Occasionally the process will start in one lobe and spread gradually to involve the entire gland ("creeping" type of thyroiditis).

The diagnosis of subacute thyroiditis usually is unmistakable and is suspected from the first. In only six of the twenty-seven cases was the diagnosis missed by the first examiner.

The natural course of the disease appears to be toward spontaneous recovery without permanent derangement of the function of the thyroid. This course is shortened by thyroidectomy, x-ray therapy, or, it is said, by treatment with thiouracil. This type of thyroiditis does not go on to either Hashimoto's or Riedel's disease, nor in our experience has suppuration occurred.

Pathology. Subacute thyroiditis is characterized by a diffuse involvement of the entire thyroid in a subacute inflammatory process. There is infiltration with leukocytes and numerous foreign body giant cells are present. The arrangement in formations somewhat resembling tubercles gives rise to the name pseudotuberculous thyroiditis. The foreign body reaction is probably a response to the colloid in the degenerating follicles, and histiocytes can be seen phagocytizing this material.

The thyroid rarely contains adenomas. The glands are not enlarged to more than two or three times their normal size, and the enlargement tends to be symmetrical. The cut surface of the gland is white and avascular. It is quite brittle and will not hold a hemostat. The capsule is only very lightly adherent to surrounding structures, and there is no tendency to infiltration and fixation, as in Riedel's struma. Tubercle bacilli have not been identified in this lesion (Fig. 96).

Treatment. Subacute thyroiditis responds promptly and completely to x-ray therapy. Six hundred to 800 r usually suffices to effect a resolution in a few weeks. The pain and tenderness subside in a few days. The average time at which fifteen patients treated with x-ray were considered to be entirely well was nineteen days after the start of treatment. By this time the thyroid is rarely either tender or palpably enlarged. In two of our cases, two or more courses of therapy over a period of three months were required before a complete cure was effected. In three cases the patients considered themselves well in one week.

One patient developed a severe systemic reaction to an undulant fever skin test, and this was accompanied by an exacerbation of the pain and tenderness in the thyroid and was followed by complete resolution of the thyroiditis in a matter of a few days. Whether this was a specific or nonspecific reaction to the undulant fever vaccine will never be known. Eight other patients had negative tests, and one a weakly positive skin test, for undulant fever.

Thyroidectomy is a satisfactory means of controlling subacute thyroiditis, but since the disease is essentially self limited and since x-ray effects such prompt and complete resolution, operation is not often indicated. Most of the patients reported here as having been subjected to operation were seen before we recognized the value of x-ray.

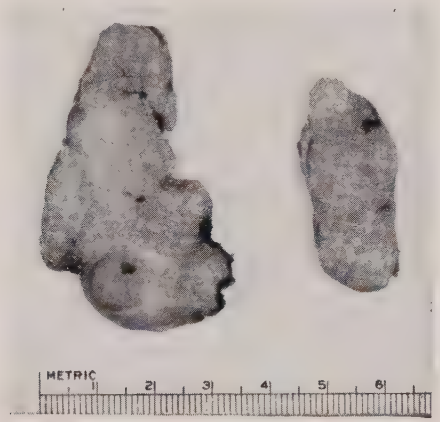


Fig. 96. Gross appearance of subacute thyroiditis. The small adenoma is an unusual finding. (From George Crile, Jr., Annals of Surgery, volume 127, J. B. Lippincott Co.)

Thyroidectomy was performed on six patients; five of these are well and one has developed hypothyroidism.

A single lobe was removed in six cases. Three of these patients developed a recurrence or suffered from persistence of symptoms due to involvement of the remaining lobe. All eventually recovered.

Since x-ray has given entirely satisfactory results we have not used thiouracil in the treatment of subacute thyroiditis. If the foreign body reaction is indeed due to the presence of colloid, the beneficial action of thiouracil could be explained on the basis of its interference with the formation of this substance.

Case 1. Subacute (pseudotuberculous or giant cell) thyroiditis.

The patient was a woman 32 years old. Two months before entry she had noted sudden onset of pain in the right side of the neck. This area was tender. There was palpitation, insomnia, nervousness, and an elevation of temperature to over 100°. She had lost 6 pounds in weight. Iodine had been given without improvement.

Examination showed a diffuse enlargement of the entire thyroid to one and one-half times the normal size. Both lateral lobes and the isthmus were stony hard and tender. The temperature was 99.6° and the pulse was 108. There was a coarse tremor and the skin was dry. There were no eye signs of hyperthyroidism. The basal metabolic rate was plus 3 per cent.

A biopsy 2 mm. in diameter was taken from the isthmus of the thyroid and the pathologist reported chronic thyroiditis with marked granulomatous reaction to colloid (so-called pseudotuberculous thyroiditis). There was a fairly marked increase in connective tissue with the remaining follicles of small or medium size formed of flat or cuboidal epithelium, fairly well filled with colloid, and with some of the follicles partly filled by cells of the histiocyte or macrophage type. Colloid was markedly reduced or absent in the follicles containing these cells. Also present were fairly frequent accumulations of mononuclear cells and foreign body giant cells which in several instances enclosed small lakes of colloid. The stroma contained a slight to moderate infiltration of lymphocytes and some plasma cells and polymorphonuclear leukocytes (Fig. 97).

A total of 700 r was then given to the thyroid area in five treatments distributed over a period of nine days. At the end of this time the patient stated that she felt entirely well. There was no pain or tenderness of the thyroid, and the gland had returned to normal size, but the right lobe was still fairly firm. The consistency of the left lobe was normal.

Four weeks later the thyroid was soft and barely palpable, and the patient remained well.

Comment. The clinical features of this case and the response of the thyroid to x-ray treatment are typical of those encountered in other cases of subacute thyroiditis. Biopsy of the thyroid showed changes characteristic of the so-called pseudotuberculous or giant cell thyroiditis. In a second case subjected to biopsy the clinical course and response to x-ray therapy were similar, and the pathologist reported a similar lesion in the thyroid. There can be little doubt that the clinical disease, subacute thyroiditis, is from the pathologic standpoint pseudotuberculous or giant cell thyroiditis. This disease responds promptly to x-ray treatment and does not necessitate thyroidectomy.

Fig. 97. Subacute or giant-cell thyroiditis. Biopsy obtained in case 1. Prompt and complete resolution following x-ray treatment (× 50). (From George Crile, Jr.: Annals of Surgery, volume 127, J. B. Lippincott Co.)

Struma Lymphomatosa

Struma lymphomatosa is a progressive disease of the thyroid, possibly associated with systemic disorders, in which there is extensive acidophilic degeneration of the epithelial elements of the thyroid and replacement by lymphoid and fibrous tissue. Hypothyroidism or at least a peculiar type of hypometabolism that does not always respond specifically to desiccated thyroid is apt to develop. The etiology of the disease is unknown. It does not progress to Riedel's struma nor is it the end result of subacute thyroiditis. An excellent description of this disease was given by Joll in the British Journal of Surgery in 1939.

Clinical Course. Struma lymphomatosa occurs most commonly in the late forties or early fifties. Although it is rarely seen in men, two such cases are reported in this series of fourteen cases. True struma lymphomatosa is rare and is not to be confused with lymphoid infiltration of the thyroid or nonspecific types of lymphoid thyroiditis, from which it can be distinguished by the acidophilic degeneration of the epithelium. True Riedel's struma is more rare than struma lymphomatosa. In my experience Riedel's struma and struma lymphomatosa are only about one-fifth as common as subacute thyroiditis. In the course of approximately 900 thyroidectomies I have records of two operated and fifteen unoperated cases of subacute thyroiditis, three operated cases of struma lymphomatosa, five cases of Riedel's struma, and one of suppurative thyroiditis, as well as several cases that are unclassified.

The onset of struma lymphomatosa is insidious. Pain may be noted at the onset and occasionally persists, but this is the exception to the rule. None of our earlier patients had pain radiating to the ear, and only one had noticed pain on swallowing. More recently I have observed two patients with struma lymphomatosa in which pain was one of the leading symptoms. The glands are not tender, there is no fever, and rarely is there any systemic reaction except that associated with hypothyroidism and a peculiar lack of feeling of well-being which does not always respond to treatment either by thyroidectomy or by administration of desiccated thyroid. It is interesting to note that in the only two patients who had gastric analyses there was no free acid. Graham observed anacidity or hypoacidity in six of his fourteen cases. In one patient who died, postmortem examination showed generalized lymphoid hyperplasia. Mild anemia may be present.

Half of the patients in this group complained merely of goiter. Four had systemic symptoms such as nervousness or loss of weight, and three complained of pressure symptoms from the enlarging gland. There was no consistent elevation of the temperature or pulse rate, and the basal metabolic rates averaged minus 8 per cent. In five of the fourteen cases the basal metabolic rates were less than minus 10 per cent, minus 24 being the lowest.

The average duration of the goiter or of the symptoms prior to operation was twenty months. The sedimentation rate was normal in the only patient in whom this was tested.

The entire gland usually is involved. In two cases it was stated that only one lobe was involved, but biopsies were not taken from the other lobe. The glands were described preoperatively as firm and "adenomatous." It is noteworthy that the gland does not appear to be as symmetrically involved in struma lymphomatosa as in subacute thyroiditis. Certain areas may enlarge more rapidly than others, giving a firm irregularity which in the majority of cases suggested the diagnosis of adenomatous goiter without hyperthyroidism. Once a calcified adenoma was suspected, once carcinoma or thyroiditis, and in only three cases was the diagnosis of chronic thyroiditis made before operation.

In three cases the tumor had enlarged to the point of causing tracheal compression. Most of the thyroids were four or five times normal size and when, as was occasionally the case, the growth encircled the trachea, symptoms of obstruction developed.

There does not appear to be any tendency to spontaneous remission or cure of this disease. One patient had had symptoms and an enlargement of the thyroid for eight years prior to operation. McClintock has reported a case of struma lymphomatosa in which thyroidectomy was repeated two and a half years after the first operation and the histology of the gland was essentially unchanged.

Pathology. Graham has said that there is no single clinical or pathologic feature of struma lymphomatosa that is characteristic or pathognomonic of this condition but that the entire clinical and pathologic picture, particularly the state of the thyroid gland as a whole, must be considered. Under these circumstances a fairly good case may be made out for either the Riedel or the Hashimoto type as a clinico-pathologic group, even if not an entity.

Struma lymphomatosa is characterized by acidophilic degeneration of the thyroid epithelium with replacement by lymphocytes and fibrous tissue. The lymphoid tissue often predominates and shows well developed germinal centers. There is no extension of the inflammatory process outside of the capsule and little or no tendency for the gland to become adherent to surrounding structures.

The thyroid is firm, friable, and not very vascular. Its cut surface is gray and lobulated and is sometimes mistaken for a hyperplastic goiter. Usually it is recognized as a thyroiditis at the operating table, but occasionally even pathologists fail to recognize it in the group examination. The diffuse enlargement of the entire gland tends to form retrotracheal extensions which may render the gland difficult to deliver. In none of the fourteen patients were there adenomas in the thyroid

Treatment. It has been said that x-ray treatment affords an effective means of controlling this type of thyroiditis. Since until recently we have rarely recognized the disease before operation we have not treated it often with x-ray. One patient was treated before she came to us by an unknown amount of irradiation without improvement.

In the past year I have twice made the clinical diagnosis of struma lymphomatosa and confirmed it by biopsy. In both cases the disease was typical from both clinical and histologic standpoints. The thyroids were enlarged to only two or three times normal size and the symptoms were of short duration. The Silverman liver biopsy needle gives an excellent biopsy which can be taken in the office.

After confirmation of the diagnosis by biopsy both of these patients were treated by roentgen therapy. In one case the symptoms of pressure disappeared a week after the beginning of treatment and within three weeks the thyroid had become soft and was scarcely palpable. 700 r were given. In the other case the symptoms of pressure were controlled within two weeks of the onset of treatment but the gland did not change in size or consistency. The patient was not seen again for six months, but on her return the thyroid was no longer palpable and although systemic symptoms persisted, the sensation of pressure was relieved. 800 r were given to each lobe of the thyroid.

In both of these cases the glands showed considerable fibrosis and it was surprising that so complete a resolution could have been effected. I do not know if roentgen therapy would be successful in cases in which the thyroiditis is of longer duration and in which the bulk of tissue and amount of fibrosis was greater. Nevertheless, since small amounts of roentgen therapy can do no harm and may cause complete resolution of the thyroiditis, I believe that it is worth trying before subjecting the patient to thyroidectomy.

Thyroidectomy was performed in ten of the fourteen patients. Three of the patients subjected to thyroidectomy are well, five have hypothyroidism and require desiccated thyroid, one had a bilateral paralysis of the recurrent laryngeal nerves, and one died during operation with an unexplained convulsion. The high morbidity and mortality in this series would suggest that conservative operations which do not attempt to remove all the gland may be preferable if the nature of the disease is apparent at the time of operation.

In four cases only a single lobe was removed. Two of these patients are well, one is improved, and one has a persistent enlargement of the other lobe but feels well. The record of lobectomy in this small group of cases appears to be better than that of thyroidectomy.

Although x-ray may be the treatment of choice, it will never be widely used unless the diagnosis can be made more often than it has been in the past. Recent experience makes me believe that struma lymphomatosa can be recognized if it is searched for. When struma lymphomatosa is first recognized during the operation it would seem best to perform a very conservative thyroidectomy, removing only enough of the isthmus and the lobes to relieve the pressure and leaving a moderate amount of thyroid tissue to help to prevent the development of hypothyroidism. This treatment is empiric and unsatisfactory, but unless we can establish the diagnosis before operation and treat it with roentgen therapy, and until we know more of the etiology of the disease and of its response to roentgen therapy, a conservative thyroidectomy is justified.

Case 2. Struma lymphomatosa (Hashimoto).

The patient was a woman 50 years of age who had been under treatment for three years for symptoms assumed to be due to the menopause. One month before entry her physician had noted an enlargement of the thyroid. She had noted tachycardia and palpitation, nervousness, and dyspnea on exertion. She had lost six pounds in weight.

Fig. 98. Gray color and lobulated appearance of struma lymphomatosa. (From George Crile, Jr., Annals of Surgery, vol. 127, J. B. Lippincott Co.)

Examination showed the temperature to be 98.3°, pulse 80, and blood pressure 160/90. There was a nontender, movable mass 6 cm. in diameter in the right lobe of the thyroid and slight enlargement of the left lobe.

The basal metabolic rate was 0. The red blood cells numbered 4,000,000 and the hemoglobin was 88 per cent.

The preoperative diagnosis was nodular goiter without hyperthyroidism. At operation there was found a firm nodular goiter involving chiefly the right lobe. The capsule was only slightly adherent. There was a large retrotracheal and retrosternal extension of the right lobe. The gland was vascular, pale, and firm. A diagnosis of struma lymphomatosa was made, and nearly all of the right lobe and part of the left lobe were removed. The left lobe was not so large as the right.

The specimen consisted of the greater part of the right and left lobes of the thyroid and weighed 90 gm. (Fig. 98).

The thyroid epithelium was hypertrophic and acidophilic and there was great variation in the size and staining reaction of the nuclei. The colloid was diminished. The thyroid tissue was lobulated with slight increase of interlobular stroma and considerable lymphoid tissue distributed diffusely throughout and present also in numerous large hyperplastic lymphoid follicles. There were many plasma cells present (Fig. 99).

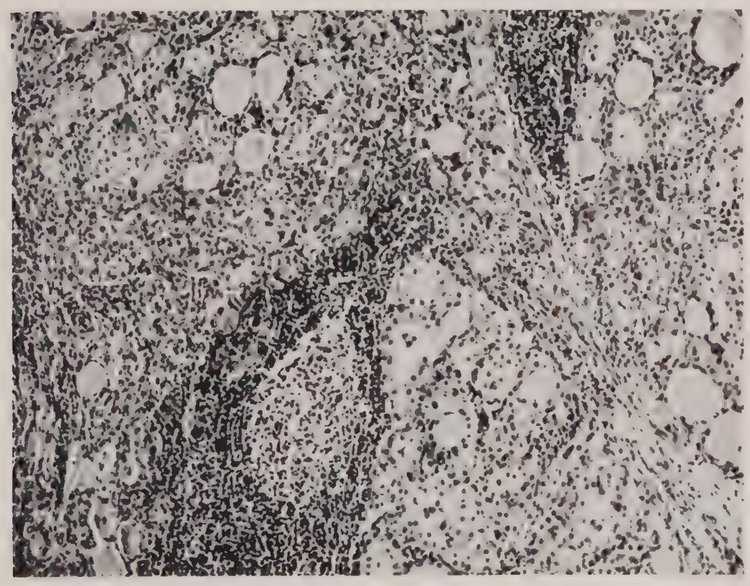


Fig. 99. Photomicrograph, struma lymphomatosa (× 50). (From George Crile, Jr., Annals of Surgery, volume 127, J. B. Lippincott Co.)

Convalescence was uneventful. Four months after operation the basal metabolic rate was minus 3 per cent, but the patient had the appearance of hypothyroidism and was given ½ grain of desiccated thyroid daily. Fissures occurring at the corners of the mouth suggested a deficiency of vitamins.

Two years later the patient had no specific complaints but did not feel well. Thyroid feeding had not effected any improvement. Five years after operation the patient writes, "The effects of my operation are leaving me awfully weak, otherwise no trouble. I wonder why my system is so weak."

Comment. This case is typical in that (1) the symptoms before operation were poorly defined and vague, (2) the presence of a goiter was the chief complaint, (3) the preoperative diagnosis was adenomatous goiter without hyperthyroidism, (4) the true nature of the disease was first suspected at the time of the operation, (5) after operation clinical evidence of hypometabolism and vitamin deficiency were apparent but did not respond to treatment, and (6) the patient still feels weak five years after operation.

Case 3. The patient was a woman 44 years of age who entered with complaints referable to nearly every system of the body. She had been under medical care constantly for fifteen years. For the past four years she had noted an intermittent tender swelling of the neck with pain radiating up to the ears. Among her other complaints were headache, fatigue, gain of 50 pounds in weight, swelling of the entire body, tightness of the shoulders, numbness of the extremities, dizziness, nervousness, and shortness of breath.

Examination was essentially negative except for a blood pressure of 148/112, obesity, and a hard enlargement of the entire thyroid to about twice its normal size. The left lobe was larger than the right. The gland was only slightly tender. She was a little hoarse.

Examination of the larynx showed thickening of the anterior end of the right vocal cord consistent with a chronic laryngitis. Urinalysis, blood counts, the level of blood sugar, Wassermann and Kahn tests, and an x-ray of the chest were within normal limits. Gastric analysis showed 36 units of free acid and 50 total. The basal metabolic rate was minus 22 per cent and the level of blood cholesterol was 120 and on a later test 179 mg. per 100 cc.

A diagnosis of struma lymphomatosa was made and confirmed by biopsy. The specimen showed dense fibrous tissue with several broad patches of lymphocytes and plasma cells intermingled with a few epithelial elements resembling thyroid epithelium. Other fragments showed similar architecture with broad patches of dense lymphocytic infiltration, one area including some patches of acidophilic epithelium.

Roentgen therapy was advised and 800 r was given to each lobe of the thyroid. The symptoms of pressure were relieved promptly, but two months after treatment was started there was little diminution in the size of the thyroid and it was still firm.

Six months after the beginning of treatment the thyroid was not palpable and the patient remained free of local symptoms. The systemic symptoms persisted and did not respond to treatment with desiccated thyroid and benzedrine.

Riedel's Struma

Riedel's thyroiditis is a chronic proliferating, fibrosing, inflammatory process involving usually one but sometimes both lobes of the thyroid as well as the trachea and the muscles, fascia, nerves, and vessels in the vicinity of the thyroid. It produces a bulky tumor that may be indistinguishable preoperatively from an inoperable carcinoma. It is not the end result of either subacute thyroiditis or struma lymphomatosa but is a separate entity whose etiology is unknown. No specific organisms have been isolated from this lesion. In many instances the inflammatory reaction appears to center about a degenerating adenoma, and this may be a clue to its etiology.

Riedel's struma affects women more often than men and tends to occur beyond the age of 50.

Clinical Course. The onset is insidious and usually painless. In none of our eleven cases did the pain radiate to the ears, and only one of the patients had pain on swallowing. Tenderness was present only once.

The tumor grows slowly, the average duration of the enlargement having been twenty-nine months before operation.

Symptoms of pressure predominated in over half of the cases and often were severe with tracheal obstruction. Two patients had a symptomless goiter, and one patient complained only of nervousness. The temperature and pulse rate are not often elevated, there are few if any systemic symptoms, and little weight is lost. The basal metabolic rate usually is normal (average plus 2 per cent) although in one case with almost total destruction of both lobes of the thyroid hypothyroidism was present and the basal metabolic rate was minus 20 per cent.

The sedimentation rate was moderately elevated in the only case in which it was tested.

Characteristically the tumor in the thyroid involves only a part of the gland. In two of the unilateral cases the other lobe eventually became involved in the same process, once after a few months and once several years later.

The thyroid is stony hard and fixed to the surrounding tissues. Only two cases were correctly diagnosed before operation. In six cases carcinoma was suspected, in two cases the examiner could not decide between Riedel's struma and carcinoma, and in one case the preoperative diagnosis was adenoma. In all cases the true nature of the lesion was recognized at the time of operation.

In two cases a unilateral paralysis of the recurrent nerve developed spontaneously.

Pathology. In seven of the eleven cases adenomas or remnants of degenerating adenomas were present in the center of the proliferating fibrous tissue. Whether or not this finding is of etiologic significance I do not know, but in most of the specimens in which the major portion of the affected lobe was removed, degenerating adenomas were found. In several cases it was impossible to judge whether the major portion of the lobe had been removed, as the operation had been accomplished by piecemeal technic and the specimen consisted of innumerable chips of fibrous tissue.

The microscopic picture is of a chronic inflammatory reaction and replacement of thyroid by fibrous tissue. Bulky tumors five or six times as large as the original lobe are formed in this manner and these tumors infiltrate the capsule of the thyroid, the trachea, the muscles, the tissues of the carotid sheath, and the recurrent laryngeal nerves in such a way as to render it impossible to find any natural plane of cleavage outside of the capsule of the thyroid. The disease is in reality a diffuse fibrosis of the neck with the thyroid at its center.

From the histologic standpoint there is nothing specific by which Riedel's thyroiditis can be recognized, but the gross appearance of the lesion is unmistakable.

The entire lobe of the thyroid is stony hard, adherent, and avascular. It can be cut in any direction without bleeding except from an occasional vessel which can be seen protruding from the fibrous tissue. The blood supply has been choked off by fibrosis. The gland is brittle and white, and cuts almost like cartilage. The difference between Riedel's and subacute thyroiditis is in the degree of destruction of the thyroid epithelium, the relative scarcity of foreign body giant cells, in the extent of the extracapsular fibrosis, in the size of the gland, and in the fact that in Riedel's there is apt to be a degenerating adenoma at the center of the process. The fibrous tissue seems to be laid down in layers around this adenoma to form concentric rings, like an onion.

Treatment. An adequate trial of x-ray therapy was made in three of these cases without significant results. In two cases in which one lobe had been removed and a recurrence later took place on the other side the x-ray seemed to prevent further proliferations although there was no change in the size of the tumor. In a third case, in spite of 2550 r of x-ray, pain and symptoms of compression continued, hypothyroidism developed, and the process extended to involve the parathyroids and produced tetany. We must assume, therefore, that x-ray has little to offer in the treatment of this disease.

Complete surgical removal of the involved portion of the thyroid may be rendered utterly impossible by the extent of the extracapsular fibrosis. Serious damage to the trachea, carotid sheath, or recurrent nerves may take place if the true nature of the lesion is not recognized and radical extirpation is attempted. In this disease one must often be content to do the best he can within the bounds of safety to relieve obstruction.

On the other hand, if one remembers the fact that in most cases, at the center of the fibrosed lobe, there is a degenerating adenoma and that around this adenoma the fibrous tissue is deposited in concentric laminations which afford natural cleavage planes, it is often possible, without jeopardizing the vital structures adherent to the capsule of the thyroid, to split the lobe open and enucleate this central core (Fig. 100). The results following this simple procedure have been excellent in the three cases in which I have found it practicable. Pressure symptoms have been relieved, the bulk of the tumor has been strikingly diminished, and the progress of the inflammatory and productive process appears to be arrested. It is well to remember that the most severe obstruction to respiration usually is associated with retrotracheal adenomas that compress the trachea from behind and that this can be demonstrated before operation by a lateral x-ray of the trachea. If the surgeon is not aware of the retrotracheal tumor he is apt to overlook it in a thyroid which cannot be mobilized and rotated from its bed.

Six of the eleven patients who had portions of the thyroid removed for Riedel's struma are well. In seven patients only one lobe was removed, and in two of these the process recurred

Fig. 100. Case 3. Riedel's struma. The specimen represents only the portion of the lobe that was enucleated. Note adenoma encased in dense, concentrically laminated fibrous tissue. (From George Crile, Jr., Annals of Surgery, volume 127, J. B. Lippincott Co.)

on the other side. One patient had bilateral involvement and has a symptomless persistence of the disease after removal of part of one lobe. One patient has hypothyroidism, and one chronic tetany which developed spontaneously before operation, probably as a result of destruction of the parathyroids. The thyroid is so extensively destroyed that this patient also has hypothyroidism.

Case 4. The patient was a woman 46 years old. She had noticed an enlargement of the left lobe of the thyroid two years before entry, and a few months later she became hoarse. Three months before entry an attempt was made to do a thyroidectomy, but the surgeon stated that the tumor was an inoperable carcinoma. A biopsy was interpreted as either Riedel's struma or carcinoma.

Symptoms of pressure continued, but there was no loss of weight and no symptoms of systemic disease.

Examination showed a stony hard, fixed tumor involving the left lobe of the thyroid and the cervical musculature. The left vocal cord was paralyzed. The basal metabolic rate was plus 2 per cent.

A diagnosis of Riedel's struma or inoperable carcinoma was made. At operation the entire left side of the neck was involved in a dense prolifera-

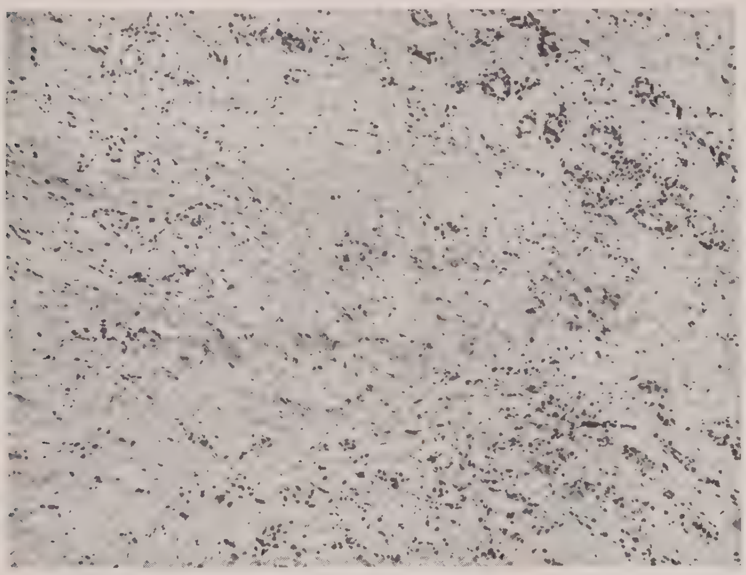


Fig. 101. Case 3. Photomicrograph, Riedel's struma (× 50). From George Crile, Jr., Annals of Surgery, volume 127, J. B. Lippincott Co.)

tion of fibrous tissue which had invaded the trachea and the prethyroid muscles. The lobe was exposed and the anterior half removed. It was white, brittle, and avascular. The cleavage plane surrounding the central adenoma was located, and a degenerating adenoma was shelled out in a capsule of fibrous tissue (Fig. 100). The right lobe was normal.

The pathologist reported chronic inflammation and complete replacement of thyroid tissue with fibrous tissue (Fig. 101). There was a degenerating colloid adenoma in the center of the fibrous mass.

Convalescence was uneventful and the symptoms of pressure were completely relieved.

Comment. This case is typical of Riedel's struma in that (1) the initial diagnosis was carcinoma of the thyroid, (2) there was no systemic reaction or alteration of thyroid function, (3) there was extensive fibrosis of the thyroid and of the perithyroid structures, (4) there was a degenerating adenoma in the center of the fibrous mass, (5) symptoms were relieved by enucleation of the adenoma from the surrounding fibrous tissue.

Other Types of Thyroiditis

During the same period of time in which these cases of specific thyroiditis were seen, there have been at least ten cases of well-defined thyroiditis which do not fit into any definite category. There have also been three cases of suppurative thyroiditis occurring in degenerating adenomas. I have seen no proved syphilis or tuberculosis of the thyroid.

Summary

Although there may be many causes of thyroiditis and many types of thyroiditis, three main groups—subacute thyroiditis, struma lymphomatosa, and Riedel's struma—emerge as clinicopathologic entities. Our knowledge of these may be summarized as follows:

1. The clinical entity described as subacute thyroiditis has been proved by biopsy to be giant cell or pseudotuberculous thyroiditis.

2. Subacute thyroiditis, struma lymphomatosa, and Riedel's struma are separate clinical entities and probably are etiologically unrelated to one another, or at least do not represent various stages of the same disease.

3. The fact that subacute thyroiditis is almost always associated with pain and tenderness and that these symptoms rarely occur in the other types argues against the possibility that subacute thyroiditis represents an early stage of the more chronic processes. The tendency to spontaneous recovery in

subacute thyroiditis and its prompt and dramatic response to x-ray treatment also argue against this possibility.

4. The fact that Riedel's struma is more often unilateral and struma lymphomatosa usually involves the entire thyroid, and the frequent presence of adenomas in Riedel's struma and their infrequent occurrence in struma lymphomatosa, are arguments against the theory that struma lymphomatosa is an early stage of Riedel's struma. It is inconceivable that the fibrosis of Riedel's struma could regress and become struma lymphomatosa.

5. Although the etiology of these diseases is unknown it is possible that subacute thyroiditis is the result of a virus infection and that persistence of symptoms and evidence of inflammation in the thyroid is due to a foreign body reaction to colloid.

6. Struma lymphomatosa appears to be a systemic disease, possibly of the deficiency type, and further study of its relationship to achlorhydria, anemia, generalized lymphoid hyperplasia, and possibly to vitamin or other deficiencies is indicated. Many of these patients are not well before or after operation, and the hypometabolism and associated symptoms may not be specifically corrected by feeding desiccated thyroid. Roentgen therapy may cause prompt and complete subsidence of the enlargement of the thyroid in some cases of struma lymphomatosa, but does not alter the symptoms of systemic disease.

7. Riedel's thyroiditis appears to be a proliferative fibrosis usually centering about a degenerating adenoma. Although the role of this adenoma cannot be proved, it is possible that some change in the adenoma sets off a fibrous tissue reaction resembling that seen in a keloid. Removal of the core containing the adenoma appears to promote subsidence of the reaction.

8. X-ray is the treatment of choice for subacute thyroiditis and thyroidectomy is rarely if ever indicated. Thiouracil may be of value.

9. When the diagnosis of struma lymphomatosa is made before operation x-ray should be given a trial. If struma lymphomatosa is recognized at the time of operation a very conservative resection of both lobes of the thyroid is recommended.

The morbidity of radical resection is high and persistent hypometabolism is common when most of the gland is removed.

10. In Riedel's struma x-ray is of little or no value, and operation is apt to be difficult. It is unwise, unnecessary, and often dangerous to attempt to remove the entire lobe. If the onion-like concentric laminations in the fibrous tissue surrounding the central degenerating adenoma can be found, these avascular planes can be followed by blunt dissection and the core of the lobe shelled out without disturbing its capsule. Following this procedure the symptoms are relieved and there is no further proliferation of fibrous tissue.

Bibliography

1. Graham, A.: Struma lymphomatosa (Hashimoto). Tr. Am. A. Study Goiter, 222–251, 1940.
2. Graham, A., and McCullagh, E. P.: Atrophy and fibrosis associated with lymphoid tissue in thyroid; struma lymphomatosa (Hashimoto). Arch. Surg. *22:* 548–567 (April) 1931.
3. Joll, C. A.: Pathology, diagnosis, and treatment of Hashimoto's disease (struma lymphomatosa). Brit. J. Surg. *27:* 351–389 (Oct.) 1939.
4. King, B. T., and Rosellini, L. J.: Treatment of acute thyroiditis with thiouracil; preliminary report. J. A. M. A. *129:* 267–268 (Sept. 22) 1945.
5. McClintock, J. C., and Wright, A. W.: Riedel's struma and struma lymphomatosa (Hashimoto); comparative study. Ann. Surg. *106:* 11–32 (July) 1937.
6. Schilling, J. A.: Struma lymphomatosa, struma fibrosa and thyroiditis. Surg., Gynec. & Obst. *81:* 533–550 (Nov.) 1945.

CONCLUSION

Disease of the thyroid gland can be treated effectively by thyroidectomy, by drugs, by roentgen therapy, and by the administration of radioactive iodine. The protagonists of each method of treatment may attempt to extend its use beyond its zone of effectiveness. If they do, there will be unfavorable reactions and discredit will be reflected on them and on their methods.

Sufficient time has not as yet elapsed to evaluate the end results of therapy or to establish rules to govern the treatment of thyroid disease. Until the modern therapeutic measures have passed the test of time, we must continue to rely on conventional forms of treatment, but in so doing we should not close our eyes to progress nor continue to use methods which entail a greater risk when safer forms of therapy are available.

Since few of us are trained in the combined fields of internal medicine, roentgen therapy, nuclear physics, and surgery, and since all of these methods now hold important places in the treatment of thyroid disease, it is more important than ever that the physician should be well grounded in their potentialities and that he should adapt treatment to the requirements of the individual patient.

Today this individualization can best be provided by a skillful team of specialists who work together, cooperatively, to study the diagnosis and treatment of diseases of the thyroid gland. Through the efforts of such teams, working carefully, analyzing their results critically, and following their patients continually, there will emerge a clear comprehension of what can be accomplished by modern methods of treatment.

INDEX

65-1

66-1

67-41

71

72-1

73-1