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The wide variation in the secretory activities of the thyroid gland in different persons is reflected in the many disease processes now recognized as having their origin in disturbances of the gland's anatomic structure. The contributions (variously estimated from 8,000 to 10,000) devoted to the experimental, clinical and pathologic aspects of the problem of goiter have brought its solution nearer. In general, there is now recognized the specific rôle of the thyroid gland as a regulator of metabolism (catabolism, in particular) in proportion to the output of its hormone and the responsiveness of the tissues to the hormone. There are recognized two definite clinical manifestations, hyposecretion and hypersecretion. There is also evidence of the possible production of a perverted secretion. The former two possible functions have given rise to the many interesting clinical phenomena which have been associated with the variable pathologic changes in the thyroid gland.

Knowledge of the thyroid gland in hypersecretion of its hormone has grown insidiously from the imaginative records of the early physicians, who had no knowledge of its structure or function, to the present more accurate observations.

Early considerations of the clinical manifestations of hyperthyroidism had to do with the effect of thyroid enlargements on respiration. The only comments on the changes in the gland were those casually made in connection with the more accentuated early forms of therapy. Although Paracelsus (sixteenth century) definitely established the relationship between endemic goiter and cretinism, definite knowledge of the thyroid dates from the descriptions of it by Vesalius (1543) and Thomas Wharton (1656) and its later classification as a ductless gland by Haller (1776).

While there are many clinical accounts of the nature and evidences of swellings of the neck in association with cretinism or early unnamed myxedema, there is a striking absence of observations of the clinical manifestations which are now known to indicate hyperthyroidism. That such conditions existed is unquestionable, but the failure to observe some of the symptoms is not so easily understood. In testimony of their

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existence in former times, Van Leersum [1] pointed to the characteristic types in some of the paintings of the old Flemish, Dutch and German masters, who often reproduced their models too accurately to hide their physical defects. Bilateral or unilateral symmetrical swellings of the thyroid gland with staring eyes and widened palpebral fissures and lean figures were often vividly portrayed.

To Parry [2] belongs the credit of the association of palpitation of the heart with enlargement of the thyroid. An excerpt from his writing reads as follows: "There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed in that connection by medical writers. The malady to which I allude is enlargement of the thyroid gland. The first case of this coincidence which I witnessed was that of Grace B., a married woman, aged thirty-seven, in the month of August, 1786." Parry's full report indicates that he studied three instances of primary hyperthyroidism and two of so-called secondary hyperthyroidism (in women, aged 40 and 50). He described the glands as large, extending half way up the sternocleidomastoid muscles and lying anterior to the pulsating carotid arteries. One of the gland disorders started as a nodule on the right side, but soon spread over the rest of the gland. The records of these few instances and the meager descriptions of the thyroid glands in them constitute the basis of the present enormous superstructure of clinical, pathologic, experimental and etiologic studies concerning its disturbances.

During the seventy years that followed, innumerable clinical observations were made, among which are those of Graves (1835) and Basedow (1840), who pointed out certain definite characteristic symptoms, so that later the condition was designated, by their names, Graves' or Basedow's disease. During this time, the pathologic anatomy of the thyroid received little attention. Surgical removal, although practiced on animals (Schiff, 1859), when attempted on human beings, ended with disastrous results. Watson [3] is given credit for having done the first surgical removal in a case of exophthalmic goiter, a feat that required daring, since surgical treatment of any form of goiter at that time was condemned because of the serious consequences. Schill (1879) reviewed thirty-four articles in the French, German and English literature. He quoted Briere as stating that extirpation of goiter was carried out twenty-nine times during the period from 1785 to 1845; eleven of the

1. Van Leersum: Arch. internat. pour l'histoire de la méd. a la geog. méd. **29**:282, 1925.
2. Parry, C. H.: Collections from the Unpublished Medical Writings, London, Underwood, 1825, vol. 2, p. 3.
3. Watson: Edinburgh M. J. **19**:252, 1875.

patients died. Between 1845 and 1871, forty-four cases of operation were reported on; twelve of the patients died. Kicher reported a mortality of 19 per cent. In other clinics, the mortality was as high as 40 per cent (Susskind). The total number of such excisions to 1876 was 162. In most of the reports of instances in which operation was done, only brief mention is made of the pathologic nature of the gland, and the notations were largely the result of preoperative clinical observations. Graves,[4] discussing the disturbances in the thyroid gland in three instances, said that "they (the thyroid glands) are considerably larger than natural." He spoke of a "sudden interstitial effusion of blood into the thyroid," which he regarded as "slightly analogous in structure to the tissues called erectile." He preferred to view the changes as hypertrophies. Among the subsequent descriptive terms occurring in the literature, two probably referred to the hypersecreting thyroid gland, namely, parenchymatous goiter and vascular goiter. This dearth of distinctive study of the anatomic changes in the thyroid was probably due to the confusion resulting from the many opinions as to the etiology summed up by Klose and Helwig [5] as follows:

1. The constitutional theory (von Buschan): There was thought to be a secondary involvement of the thyroid gland.

2. The bulbar theory: The seat of the trouble was thought to be in the medulla oblongata and midbrain.

3. The central theory: Cortical lesions were held responsible.

4. The theory of hyperthyroidism and dysthyroidism: The occurrence of an increased or decreased thyroid secretion was suggested.

5. The theory of hypothyroidism: The thyroid was not thought to be a gland of internal secretion but a filter for the blood poisons; its failure of function led to auto-intoxication.

6. The theory of polyglandular disease: The entire endocrine system was considered to be damaged.

7. The sympathetic theory: The disturbance was considered to affect the sympathetic nervous system.

Such theories had their adherents who industriously defended them and accordingly directed their attention to the pathologic anatomy of the organs and tissues concerned. The pathologic anatomy of thyroid enlargements, in general, and those changes underlying exophthalmic goiter, in particular, were touched on only in scattered statements included in clinical dissertations in which the etiology, symptomatology and therapy received the most attention. Pathologic classifications were largely individual concepts, often specifically including the therapy recommended. One of these by Leveque (1872), recorded by Schill,[6] is

4. Graves: Clinical Lectures, Dublin, Fannin & Company, 1848, p. 150.
5. Klose and Helwig: Klin. Wchnschr. **2**:627, 1923.
6. Schill: Schmidt's Jahrb. **182**:177, 1879.

of interest because of the evidence contained therein of the early use of iodine. Leveque's classification was as follows: "1. Parenchymatous goiter—Iodine internally and externally, iodine injections. 2. Fibrose goiter—Iodine injections, hair setons. 3. Colloid goiter—Iodine internally and externally, hair setons. 4. Cystic goiter—Puncture, drainage, hair setons. 5. Vascular goiter—Chloride of iron injections."

A greater impetus was given the study of the changes in the thyroid (1) by such experiences as that of Kocher (1883),[7] in which he removed the entire organ in exophthalmic goiter and found it to be vital, the removal resulting in "cachexia thyreopriva"; (2) by the experimental prevention of such a condition by the use of thyroid grafts or the administration of thyroid substances (Schiff); (3) by the theory definitely advanced by Möbius [8] that "Graves' disease is an intoxication of the body by a morbid activity of the thyroid gland."

Clinical and pathologic studies now began to include more detailed descriptions of the anatomic changes in the thyroid gland, the former discussions of which were often incidental to dissertations on the pathologic anatomy of other organs and tissues believed at that time to be primarily basic in the production of the symptoms of exophthalmic goiter. In the light of the contribution of Möbius, various gross characteristics of the morbid anatomy were pointed out. Clark [9] spoke of a diffuse primary hypertrophy followed by a shrinking of the gland after death. He described the gland as firm, vascular and fleshy. Bogrow [10] and Baldwin,[11] who made similar observations, also concluded that there was a primary hypertrophy followed by a secondary atrophy. Such diffuse enlargements were confirmed in a general discussion lead by Murray [12] and others.[12] Askanazy,[13] Booth,[14] and Dinkler [15] pointed to the greater frequency of enlargement and involvement of the right lobe, a condition which had been observed many times before in earlier accounts. Hämig [16] discussed instances of massive involvement with diffuse accumulations of colloid. Other similar observations of colloid states were recorded in numerous surgical and postmortem studies of the glands. Notable among such observations is that quoted by Simmonds,[17] who said that while deficiency of colloid of the thyroid

7. Kocher: Arch. f. klin. Chir. **29**:254, 1883.
8. Möbius: Centralbl. f. Nervenh. u. Psychiat. **10**:25, 1887.
9. Clark: Bristol Med.-Chir. J. **5**:17, 1887.
10. Bogrow: Neurol. Centralbl. **14**:13, 1895.
11. Baldwin: Lancet **1**:145, 1895.
12. Murray: Brit. M. J. **2**:893, 1896.
13. Askanazy: Arch. f. klin. Med. **1**:118, 1898.
14. Booth: New York M. Rec. **54**:217, 1898.
15. Dinkler: Arch. f. Psychiat. **33**:2, 1900.
16. Hämig: Arch. f. klin. Chir. **55**:1, 1897.
17. Simmonds: Schmidt's Jahrb. **234**:134, 1892.

gland was the rule, not infrequently it was of normal or increased colloid content. These conclusions were in opposition to the views by Farner,[18] Müller,[19] Edmunds,[20] Kraus,[21] Sellerier [22] and Haskovec.[23] These authors were in agreement with the prevailing conception, namely, that the thyroid of "exophthalmic goiter" manifests itself as a compact, fleshy, vascular, granular, colloid-deficient gland, usually with a diffuse involvement. In addition to such changes nodules and cysts were reported found in the glands in scattered instances.

Microscopic changes varied with the gross observations. In general, it was observed that there was a widening out of the acini with a marked tendency to papillary formation, a columnar type of epithelium, a diminution in the colloid, a relative reduction in the supportive connective tissue, an infiltration with round cells and an increased vascularity with engorgement. Those who observed a richness of colloid contended that this substance predominated. Simmonds,[17] who opposed this latter view, stated that he observed a change in the staining of the colloid in two thirds of his cases, a papillomatous hyperplasia in half of them and desquamation in one fourth. He concluded that the irregularity was functional and not bound to any anatomic type. Hezel [24] pointed out that the process could not be considered hyperplastic, but must be viewed as adenomatous. The vascularity, the infiltrations with round cells and the necrotic areas appeared to him as an inflammatory process. Ehrich [25] observed a spotty formation of mucin in newly formed acini. Horsley [26] noted the formation of secretory vacuoles in the epithelial cells. In those glands in which he observed nodular and cystic changes, he found deposits of lime salts and fibrosis.

Möbius,[27] in his monograph on "Die Basedowische Krankheit," summarized his observations on the pathologic anatomy of the thyroid previous to 1900 as follows: "It appears that Basedow's symptoms may be observed in all types of goiter, large and small, hard and soft, with and without cysts and probably in malignant tumors of the gland." He remarked further that if a normal gland existed prior to the onset of the disease, a soft goiter of moderate size, usually larger on the right than on the left side, resulted. The other gross and microscopic changes he regarded as preexisting structures to which the changes induced by

18. Farner: Arch. f. path. Anat. **143**:509, 1896.
19. Müller: Beitr. z. path. Anat. u. z. allg. Path. **19**:127, 1896.
20. Edmunds: J. Path. & Bact. **3**:488, 1894.
21. Kraus: Buffalo M. J. **35**:793, 1896.
22. Sellerier: Thèse de Paris **255**:138, 1897.
23. Haskovec: Schmidt's Jahrb. **258**:127, 1898.
24. Hezel: Deutsche Ztschr. f. Nervenh. **4**:4, 1893.
25. Ehrich: Beitr. z. klin. Chir. **28**:1, 1900.
26. Horsley: Brit. M. J. **2**:1623, 1896.
27. Möbius: Specielle Path. u. Therap., Nothnagel **22**:18, 1896.

exophthalmic goiter were added. During the next twelve years painstaking experimental, clinical and anatomic studies of goiter, in general, tended firmly to establish the basic rôle of the thyroid in hyperthyroidism. Adherents of the "neurogenic theory" of the causation of exophthalmic goiter continued occasionally to advance pathologic evidence in support of their convictions, but their dissertations failed to stem the tide of studies concerning the relationship of disorders of the thyroid to clinical phenomena associated with its hypersecretion. A greater attempt was made to analyze the different clinical types and to correlate them with pathologic changes in the thyroid. Kocher [28] divided the instances (seventy-nine) in which operation was performed in the clinic of Kocher into the following groups: thirty-seven, high grade exophthalmic goiter; twenty-two, definite exophthalmic goiter with some symptoms missing; fourteen, strumae vasculosae; two, pseudo-exophthalmic goiter, and four, unclassified. In all of these instances the glands were enlarged. The older ones were more firm. Variable types of structure with no marked colloid or nodular types were found grossly and microscopically. Murray,[29] in citing his observations in a number of instances, mentioned four in which hyperthyroidism occurred in the presence of unilateral enlargement with adenoma or cystadenoma.

Histologic studies of the various types of glands in hyperthyroidism now began to be especially emphasized, since up to this time many of the gross characteristics had been more widely observed. Erdheim [30] reviewed and analyzed the more important studies and quoted the following authors and their concepts: (1) Brissand, a thyroid affected but without specific change; (2) Müller, specific cell hyperplasia and stroma, but still a colloid struma; (3) Farner, long follicles, papillary growth and cylindric epithelium; (4) Hämig, parenchymatous hyperplasia, solid cell masses, enlarged follicles and a colloid type in which the typical hyperplasia could not occur; (5) Askanazy, Hämig's effect of colloid, desquamation of cells and an excessive accumulation of connective tissue that shut off the lymphatic drainage and forced the "unripe poisonous thyromucin into blood vessels"; (6) Ehrich, an adherent of the vasoneural theory—a papillary structure to be regarded, as a phenomenon of coalescence, and (7) Langhans, irregularity of epithelium as the most important observation, possibly an increase, decrease or modification of colloid and probably a chemical alteration of secretion. Erdheim in a detailed careful study of a number of glands laid stress on the necessity of differentiating the young from the old cells by a method involving the staining of fat granules with osmium tetroxide, a

28. Kocher, Albert: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **9**:1, 1902.
29. Murray: Lancet **2**:1194, 1902.
30. Erdheim: Beitr. z. path. Anat. u. z. allg. Path. **33**:158, 1903.

technic which he had previously applied in differentiating adenoma from adenocarcinoma. He concluded (1) that in definite exophthalmic goiter there is a lively development of new formations, (2) that the new follicles may be large with papillae or small with flattened walls, (3) that many of the small cell masses are old and represent follicles that have degenerated through desquamation, (4) that different types of cells may be found in other types of struma, but in exophthalmic goiter the cells are young as determined by the granules, (5) that in addition to these typical changes follicles in which the colloid has degenerated and cysts may occur and (6) that the presence of fat cells in the supportive stroma is physiologic and not alone a matter of nutrition. He thought that the retrogressive changes probably indicate that the increased activity is superimposed on previous disturbances of the thyroid.

Wilson [31] in a clincopathologic study of 294 instances (operations and autopsies) divided them into two series with four groups in each. In the first series, he included all those types that were regarded as having the initial disturbance in the thyroid, as follows:

1. Eleven cases. The patients were young women with symptoms of from two months' to two years' duration. The thyroid glands were hard and granular and of an average weight of about 30 Gm. The cut surfaces were dry, granular and vascular. Microscopically, the chief characteristics seen in all of them were an increased number of cells with reduplication and a small amount of noneosin-staining secretion.

2. Nine cases. The patients were females, and all presented the classic symptoms. The glands weighed, on the average, about 53 Gm., and were hard, nodular and granular. Microscopically, the chief changes were papillary formations, infolding, large interalveolar increase of parenchyma and large amounts of noneosin-staining substance.

3. Fourteen cases. The patients were females and had had the symptoms for from three to thirty years. The essential microscopic characteristics were large intra-alveolar increase of parenchyma with a greater number of cells in a single layer, reduplication of layers and a large amount of thin secretion.

4. Thirty-four cases. All of these were regarded as in the second and third clinical stages. The essential histologic changes were an increase of stroma, an old intra-alveolar increase of parenchyma, the remains of infolding and a large amount of eosin-staining secretion.

In the second series, secondary changes in the gland were observed. Wilson concluded that the symptoms of exophthalmic goiter are asso-

31. Wilson: Am. J. M. Sc. **136**:851, 1908.

ciated with an increased absorption of an increased secretion; that the larger the number of functioning cells, the greater the secretion; that the more fluid the secretion, the more readily is it absorbed; that dense colloid is probably no evidence of present secretion but the complement of the absorbed portion, and further, that there was evidence of blocked absorption.

Shepherd and Duval,[32] in a study of fifty-nine cases, concluded that no etiologic changes could be regarded as specific for any special type of disease of the thyroid gland. Beck [33] presented another view stating that in simple goiter there is an abnormal increase of normal thyroid tissue and that hypertrophy may be either nodular, diffuse, parenchymatous, colloid, fibrous or vascular. He explained the increased activity on the basis of multiplication of the follicles, an increase of their contents and an associated increase in their vascularity.

Simmonds,[34] in a study of 100 instances of exophthalmic goiter, commented on the minute structural changes as follows: The colloid was diminished in two thirds of the specimens and normal or increased in the remainder. Follicular papillary epithelial hyperplasia and polymorphism of the alveoli were found in one half of the number. The presence of this change he regarded as diagnostic, the absence as of no significance. Desquamation of the epithelium was present in one fourth of the specimens, but this also occurred in acute infections. The hyperplasia of the lymphoid follicles (in 80 per cent of the cases) was a true response to a pathologic secretion; it was not of the inflammatory type. In the 80 per cent of the instances in which it was found, 84 per cent of the patients had symptoms of typical exophthalmic goiter while the other 16 per cent presented an atypical symptomatology. Simmonds further concluded that exophthalmic goiter is a symptom complex with no fixed pathologic picture in the thyroid gland.

While these careful observations were analytic, they did not satisfy the constant demand for a more accurately utilizable classification. Marine and Lenhart [35] attempted this in an interpretation of the structural changes in the hyperplasias of the thyroid. These authors divided such conditions into primary and secondary manifestations, as follows:

Primary (seventeen cases): (*A*) Developmental Stage: Grossly, in the classic type, the gland was larger, softer and a brighter red. Microscopically, it showed a lessening of the stainable colloid, vacuolization resulting in a granular débris and the formation of high cuboidal epithelium. Later, the gland became gray-red and finally

32. Shepherd and Duval: Tr. Am. Surg. A. **27**:56, 1909.
33. Beck: New York M. J. **91**:937, 1910.
34. Simmonds: Deutsche med. Wchnschr. **37**:2164, 1911.
35. Marine and Lenhardt: Pathological Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**:265 (Sept.) 1911.

changed from soft gray-red to grayish opaque, with infolding and increase of connective tissue as the cytologic changes. The glands remained symmetrical and rarely exceeded 200 Gm. in weight. (*B*) Involutionary Recovery or Colloid Stage: The gross and microscopic changes consisted of a reversal of those observed in group A. (*C*) The Stage of Exhaustion or Premature Atrophy: Grossly, the gland was smaller and firmer to the touch, granular and of a reddish opacity. The vascular increase remained. The increase of stroma was evident with false lobulation, but colloid was not seen. Microscopically, the acini were pressed by the increase in the connective tissue, with cell masses included. The epithelium was of a uniform high columnar type with a failure to form follicles. Desquamation, hyperchromatic nuclei and mitotic figures were also noted. In comment on the general changes in primary hyperplasia, Marine and Lenhardt pointed out that "the thyroid undergoes exceedingly rapid changes within the limits of health and disease, and further that excessive hyperplasia with hypersecretion unchecked will lead to cell death and in the end-stage to myxedema, and (in children) to developing cretinism with the clinical replacement of the symptoms of exophthalmic goiter by those of myxedema."

In the group of the secondary hyperplasias (twenty-six cases) were placed the active hyperplasias that were thought to have developed from a colloid gland. The essential anatomic changes were similar to those of the primary hyperplasias. Another group presented evidence of hemorrhage, degenerations, tumors and cystic formations, all of which the authors concluded, may modify the adjacent tissues. The stage of exhaustion was similar to that of the first stage in the primary hyperplasia. The pathologic changes described by Marine and Lenhardt were similar to those mentioned briefly by Kocher,[36] who attempted to correlate the exact clinical symptomatology with the cytologic changes and the iodine content of the gland.

Plummer [37] began to evaluate the mass of data that had accumulated, and from studies of his own concluded that exophthalmic goiter is a definite clinical complex associated with a hyperplasia of the thyroid gland that is proportionate to the degree of toxicity (toxic hyperplastic), and that it should be sharply differentiated from the constitutional states that may develop with nonhyperplastic goiter. Wilson [38] corroborated the opinion of Plummer in a detailed study of the thyroid in these different conditions. He also pointed out that many mild cases of toxic goiter reported in the literature have apparently been classed as simple goiter. Wilson further mentioned two divisions of such milder types, namely, class I, hypertrophies, hyperplasias and

36. Kocher, A.: Arch. f. klin. Chir. **95**:1007, 1911.
37. Plummer: Am. J. M. Sc. **146**:790, 1913.
38. Wilson: Tr. A. Am. Phys. **28**:576, 1913.

regenerations (79 per cent); and class II, fetal and colloid adenomas, adenomatoses and simple colloid goiter (21 per cent). The degree of toxicity could be determined, according to Wilson, from the structural changes with 80 per cent accuracy. Thus, in the numerous records of these investigations there were being slowly evolved criteria of the basic changes in hypersecreting or malsecreting thyroid glands in persons with variable symptoms.

Warthin,[39] in a recent report on 976 resected glands, 30 glands taken at autopsy from patients who had died following operation for exophthalmic goiter and 1,000 thyroid glands from autopsies on other persons, called attention to the existence of lymphoid tissue in connection with the many different structural changes of the thyroid gland in exophthalmic goiter. He concluded that the thymicolymphatic constitution underlies every case of exophthalmic goiter.

When one reflects on the great number of articles that have contributed to knowledge of the pathologic anatomy of the thyroid associated with its hyperactivity, one finds that there has developed a rather definite clinical picture and concept of the gross and microscopic aspects of the so-called classic type of thyroid in exophthalmic goiter. There is a uniformity of supporting evidence that: (1) the gland may vary in size from a very slight to a moderate degree; (2) it is symmetrically enlarged, with the possibility of the right lobe being somewhat larger than the left; (3) there is little accentuation of the lobular markings; (4) the capsule and supportive stroma are little, if at all, increased, (5) the structure of the gland may be vascular or ischemic, if the hyperplasia is marked, (6) the colloid is not grossly visible, (7) the color ranges from pinkish to opaque gray, depending on the intensity of the hyperplasia and the relative vascularity of the gland and (8) it is fleshy and moderately firm. Microscopically, there is observed: (1) a patchy increase in the fibrous connective tissue of the supportive stroma, (2) engorgement of the arteries and veins and dilatation of the lymphatic channels, (3) a variable infiltration with round cells, (4) polymorphism of the alveoli, (5) hyperplasia of the epithelium and hypertrophy with variable infolding and (6) diminution of the colloid with variation in its character. Although there have been many conflicts of opinion as to the significance and value of these different gross and microscopic manifestations, there is an obvious unanimity of the understanding of this specific response of the thyroid in the excess fabrication of its essential substance.

In addition, there has also been evolved another mass of convincing evidence that the thyroid gland does not always respond to stimuli in

39. Warthin: Ann. Int. Med. **2**:553, 1928.

this typical classic manner. The citations from the literature to this point indicate that normally the thyroid has a fluctuating physiologic response, the imprints of which may be left in the form of accidental structural modifications that react differently to subsequent stimuli. Under such condtions, a markedly variable clincal and structural response might be expected. Almost paralleling the records of classic examples of exophthalmic goiter are those of atypical manifestations. Interesting studies had been made, and more were to follow in the next thirteen years.

The recognition by Oswald (1899, 1908, 1909) that the activity of the thyroid is confined to its iodine-containing colloid, thyroglobulin, eventually led to the discovery of thyroxin by Kendall (1914). Following this, pertinent observations were made by Plummer,[40] whose presentation of the clinical differentiation between exophthalmic goiter and adenoma with hyperthyroidism served as a stimulus to further segregation of clinical types and the study of the pathologic anatomy of the thyroid gland underlying them. Plummer recorded the following facts as important: 1. There is a previous enlargement in cases of adenoma of the thyroid. 2. The time elapsing between the enlargement and the onset is fourteen and a half years in instances with adenoma and only nine tenths of a year in cases of exophthalmic goiter. 3. Exophthalmos is absent in hyperthyroidism from adenoma. 4. Hypertension and myocardial disease is more frequent in cases of adenoma. 5. Seventy-seven per cent of the patients with adenoma are more than 40 years of age, while those with exophthalmic goiter average 35 years of age. 6. The basal metabolic rate drops rapidly after the removal of an adenoma and slowly after the removal of the thyroid tissue in exophthalmic goiter.

In 1916, Goetsch,[41] who regared adenoma as a new growth of benign nature with colloid, cystic and fetal types, studied these types with a view to establishing their rôle in the production of toxic symptoms Employing the technic of Bensley,[42] he observed that the adenomas contained more mitochondria than could be found in the surrounding tissue; and as further evidence of their ability to hypersecrete, he recorded the abatement of symptoms following their surgical removal. Lahey [43] agreed with Goetsch, concluding that while nearly all the cells of the gland took part in the activity of the primary hyperthyroidism, only those in the adenoma were active in secondary hyperthyroidism. In the succeeding years, much clinical and pathologic evidence of the

40. Plummer: Clinical and Pathologic Relationships of Hyperplastic and Nonhyperplastic Goiter, J. A. M. A. **61**:650 (Aug. 30) 1913.
41. Goetsch: Bull. Johns Hopkins Hosp. **27**:129, 1916.
42. Bensley: Am. J. Anat. **19**:37, 1916.
43. Lahey: Internat. Clinics **4**:65, 1917.

rôle of adenoma was recorded in the literature. Jackson [44] observed instances of toxicity with multiple adenoma in the glands. Wilson [45] discussed "nodular goiters" with and without symptoms of hyperthyroidism. He divided them into two groups according to the basal metabolic rate. Shepard [46] was of the opinion that the pathologist is unable to distinguish between an adenoma causing hyperthyroidism and one which is inactive. Hertzler [47] looked on the occurrence of adenoma as an incident in the changing structure of the gland as it progresses through the period of adolescence. He concluded that the whole gland is diseased. Rienhoff [48] in a study of involution or regressive changes divided them into spontaneous involutions and hyperinvolutions. He observed the formation of nodules in regressions of the glands of exophthalmic goiter, and further pointed out that "areas of hyperinvolution correspond clinically and histologically to the so-called colloid adenomas, cystadenomas, fetal and colloid or mixed adenomas and colloid cysts." I [49] observed conditions in adenoma similar to those found by Hertzler and Rienhoff. More recently, Rienhoff and Lewis [50] analyzed 109 instances of nodular goiter with symptoms of hyperthyroidism in comparison with the changes in the remissions of exophthalmic goiters undergoing treatment with iodine. They pointed out that there is a striking similarity in structure between the iodine-treated glands and nodular goiter. They further concluded that "the nodules or involutional bodies are not neoplasms in any sense of the word but are merely regressive sequelae of a previous hypertrophy and hyperplasia of the parenchyma." They further stated that there is no proof of the existence of a hypersecreting neoplasm. Hertzler [51] held similar views; namely, that the diseases of the thyroid gland must be viewed as a continous process. Thus the nature and origin of these benign so-called adenomas have been discussed at length from the standpoint of the conflicting views of Wolfler,[52] who regarded them as originating in interacinar embryonic cell rests, and that of Virchow, who considered them (except fetal

44. Jackson: Wisconsin M. J. **21**:461, 1923.
45. Wilson: Am. J. M. Sc. **165**:738, 1923.
46. Shepard: California State J. M. **21**:16, 1923.
47. Hertzler: Endocrinology **10**:175, 1926.
48. Rienhoff: Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter and Their Relation to the Origin of Certain of the So-Called Adenomas, Arch. Surg. **13**:391 (Sept.) 1926.
49. Menne, F. R.: Northwest Med. **26**:304, 1927.
50. Rienhoff and Lewis: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79 (Jan.) 1928.
51. Hertzler: Pathogenesis of Goiter Considered as One Continuous Disease Process, Arch. Surg. **16**:61 (Jan.) 1928.
52. Wolfler: Arch. Chir. **29**:1, 1883.

adenomas) solitary or multiple nodular accumulations originating from a preexisting thyroid pattern. Cline,[53] in a study of 600 instances, concluded that the structural evidence observed by him substantiated the concept of Virchow. Their ability to produce an excess of hormone has never been conclusively proved. Many of the studies seem to indicate that while they may become active and hypersecrete, there is usually enough evidence in the surrounding structure of the gland as a whole to explain the symptoms occurring in a given instance.

During the time that attention was fixed on the importance of nodule formation, allied microscopic structural changes were being analyzed as to their significance in hypersecretion. In 1922, Goetsch [54] called attention to a focal interstitial formation of new acini, which he designated as adenomatosis, and pointed to its being a factor in mild hyperthyroidism. Helwig,[55] in a well illustrated study, pointed to the existence of small, disseminated hyperplasias in the form of interalveolar and intra-alveolar collections of acini with characteristic cellular changes as being responsible for the production of "hyperthyroidisms of the lighter grades." Helwig [56] further traced the steps of development from a simple colloid goiter to a typical exophthalmic type. Holst [57] made similar observations, concluding that changes in primary hyperthyroidism begin as a local proliferation. This further complicated the attempts to establish a definite structural change in the thyroid gland that may be associated with a given clinical picture. One is forced back to the necessity of applying the gross and microscopic criteria of the activity of the thyroid in classic exophthalmic goiter to the many intricate complexities of structure that present themselves for solution. A résumé of the literature leads one to the conclusion that specific clinical classifications of the types of hyperthyroidism are as futile as detailed classifications of the types of nephritis, when one tries to make the whole thyroid gland conform in structure to a fixed set of physiologic irregularities in different persons.

Although there have been conflicting interpretations of the thyroid in health and disease, there are outstanding facts of common observation. It is generally agreed that the gland varies markedly in size and shape and that clinically the picture ranges from cretinism and myxedema to hypersecretion of dysfunction as the case may be. We [58] have been able to group the surgically removed portions or entire glands

53. Cline: Am. J. Path. **1**:235, 1925.
54. Goetsch: Endocrinology **6**:59, 1922.
55. Helwig: Beitr. z. klin. Chir. **125**:75, 1922.
56. Helwig: Deutsche med. Wchnschr. **48**:420, 1922.
57. Holst: Acta. chir. Scandinav. **4**:191, 1923.
58. Menne, F. R.; Joyce, and Von Hungen: Thyroid Disturbances: Clinicopathologic Study of Three Hundred Instances, Arch. Surg. **13**:329 (Sept.) 1926.

according to their gross pathologic characteristics and predominating microscopic pathologic structures as follows:

I. Diffuse parenchymatous hyperplasia—marked increased activity
  (1) Gross observations: Gland compact, vascular or ischemic, grayish to pinkish white and colloid-free
  (2) Microscopic observations:
    (*a*) Hyperplasia and hypertrophy of epithelium
    (*b*) Peripheral or general vacuolization of colloid
    (*c*) Dilatation of lymph channels and engorgement of blood vessels
    (*d*) Variable increase in the supporting stroma with or without round-cell infiltration

II. Disseminated adenomatous hyperplasia—normal or moderately increased activity or no activity
  (1) Gross observations: Gland diffusely reddish-brown without noticeable nodularity or accentuation of lobular markings; a variable amount of colloid and pinkish to yellowish gray opacities
  (2) Microscopic observations:
    (*a*) Focal changes similar to those in group I
    (*b*) Normal or colloid-distended alveoli
    (*c*) Focal hyperplasia and hypertrophy of epithelium
    (*d*) Interalveolar hillocks or intra-alveolar papillomatous projections
    (*e*) Focal collections of round cells or pseudolymphnodes
    (*f*) Focally increased vascularity and dilated lymph channels
    (*g*) Focal fibrous increase of connective tissue

III. Nodular adenomatous hyperplasia—subnormal, normal or moderately increased activity
  (1) Gross observations: Variable nodular accentuation of the lobular markings with or without excessive storage of colloid cystic degeneration, hemorrhage, scarring or deposit of lime salt. The color usually varies with the regressive changes
  (2) Microscopic observations:
    (*a*) Focal changes similar to those found in groups I and II and compensatory
    (*b*) Characteristic retrogressive changes
    (*c*) Areas of adenomatosis

IV. Solitary adenoma
  (1) Gross observations: Adenoma variable in size, circumscribed, solitary or multiple, grayish-white to dark reddish-brown, solid and cystic or colloid-filled. Regressive changes may be present.
  (2) Microscopic observations:
    (*a*) All stages of fetal types of alveoli
    (*b*) Peripheral formation of pseudocapsule with round cell infiltration and compressed alveoli
    (*c*) Focal hyperactive areas in adjoining parenchyma
    (*d*) Adjacent areas of adenomatosis

While the gross division of the portions of the thyroid removed is rather easily affected according to this outline, there are numerous instances of the shading of one group into another. Glands of border line nature may, for the sake of study, be relegated to the group

according to the dominancy of the classifying characteristics. More detailed separations of types of disturbances seem futile.

In the microscopic analysis, it is important to establish histologic criteria of activity or rest. One thing is certain; namely, that the histologic appearance of the gland in group I (diffuse parenchymatous hyperplasia, so-called classic exophthalmic goiter) is just as definite as are the gross and clinical manifestations associated with it. This is conceded to be an entity in all respects. One may therefore safely assume that the microscopic pattern found here is that resulting from the production and delivery of thyroid hormone or its by-products into the lymphatics or veins. There is evidence to show that cellular hypertrophy, hyperplasia, peripheral vacuolization of colloid, dilated lymph channels and veins and the resulting alveolar distortion occur in the order named and are natural steps in the mechanism or function of any ductless gland and that they are accompanied by an increased blood supply to the part. Prolonged activity probably leads to the necessity for more supportive stroma, and the appearance of special inflammatory absorption reactions consisting of collections of lymph cells. Finally, destruction with areas of adenomatosis or a gradual reversal of the process occurs.

Any pathologic classification from a practical point of view is of value only so far as it may be readily fitted into a specific clinical concept. It has been of interest to note that there are many difficulties in such an assorting of thyroid diseases, and that the situation approaches futility when there is an attempt made to give each detail in the morbid anatomy a distinctive entity. Until more exact physiologic knowledge is at hand, the clinician and the pathologist must content themselves with a comparison of the evidences of disease in the patient and the anomalies of thyroid design as seen in the laboratory. The object in presenting this grouping is to show the extreme range of pathologic structure of the thyroid gland that one may find associated with the production of substances leading to so-called hyperthyroidism. In the case of every type represented, the clinical evidences of hyperthyroidism were found. The greater number of instances of classic types were found in the first two groups, but in all the groups were glands of patients who presented all of the typical symptoms of exophthalmic goiter. All gradations from the milder to the more severe forms of hyperthyroidism were found occurring as the result of the types of glands considered.

It seems from the literature that careful cytologic study of any given gland of a patient with clinical evidence of hypersecretion of the thyroid results in the disclosure of minute structural changes adequate to explain the degree of toxicity. Such specific microscopic foci may be entirely masked by the gross retrogressive structural changes of the gland at the time it is removed for study. It furthermore appears

from the conclusions of numerous other investigators that the general trend of opinion conforms to this.

THE INFLUENCE OF IODINE ON HYPERSECRETION OF THE THYROID GLAND

After more than a century of familiarity with the isolation and identification of iodine (Coindet, 1820) and a growing knowledge of its natural distribution in plant and animal life, its agency in the physiology of the latter, and of man in particular, is as yet not thoroughly understood.

In the accounts of medical practices of many centuries past are records of the use of iodine-containing substances in many ailments and especially in goiterous enlargements of the neck. Its use in the latter condition gradually became rationalized (1) by the determination of the presence of iodine as a natural constituent of the thyroid gland (Baumann, 1895), (2) by the experiments of Marine and Lenhardt, who protected animals (dogs and fish) from goiterous enlargements by the addition of the required amount of iodine to their food, (3) by the further experiments of these two authors [59] on regeneration and hyperplasia in the thyroid as influenced by iodine, (4) by the isolation and identification of thyroxin as the active principle of the thyroid (Kendall, 1914) and (5) by the observations of Plummer and Boothby concerning its clinical use in hyperactivity. To these might be added many other similar experiments and studies all of which pointed to the specific rôle of iodine in the physiology of the thyroid in health and disease.

While these important advances relative to the identification of iodine as a positive and necessary factor in thyroid functioning were developed, many clinical observations were also made with a view to a better understanding of the empiric use of iodine in thyroid irregularities. As a remedial agent in so-called goiter, iodine had been used in its crude form (ashes of sponge or seaweed) for many thousands of years. The purification of iodine and its compounds led to more accurate dosage and the development of various means of administration. The results were not wholly satisfactory because of the lack of control of clinical conditions and the inability of early clinicians accurately to differentiate the different types of thyroid disease. But from the time of the establishment of exophthalmic goiter (1786) as an entity, it was considered unwise to use iodine in the therapy of this condition. Occasionally, however, on account of erroneous diagnoses or by accident, iodine was administered and beneficial results were noted.

59. Marine and Lenhardt: Relation of Iodin to the Structure of Human Thyroids, Arch. Int. Med. **4**:440 (Nov.) 1909.

Trousseau [60] (1863), by mistake, gave tincture of iodine instead of tincture of digitalis to a patient with a supposed cardiac irregularity, which was probably secondary to hyperthyroidism. Improvement of the patient was noted and recurrence of the symptoms was observed when the correction was made. Numerous other instances of the beneficial uses of iodine in so-called exophthalmic goiter were recorded, but in general the results were bad, and in many of the large clinics of Europe the use of iodine in this disease fell into disrepute. But surgical removal in primary hyperthyroidism gave a mortality rate so high that frantic efforts were constantly being made to better the technic and to find further aids in the therapy. The introduction of rest in bed, the isolation of clinical types, the use of soporifics and preliminary pole ligations helped appreciably to lower the mortality rate. In the meantime the effect of partial surgical removal on the remaining gland stump was studied by Wagner,[61] Horsley [62] and Halstead,[63] who found that reconstructive hyperplasia and hypertrophy occurred. This observation led to a further understanding of what surgical removal accomplished besides the mass removal of offending parenchyma. It also opened the way for a study of the additional effect of iodine as a therapeutic adjunct.

During the succeeding years many attempts were made to use iodine in instances of hypersecretion, but its effects were too variable and often too dangerous. Its ultimate efficacy was to be dependent on further observations. Kocher [64] referred to the marked reduction of the amount of iodine associated with deficiency of colloid in the glands with marked hyperplasia in hyperthyroidism. Later Marine [65] pointed out that in 137 cases of exophthalmic goiter in which operation or autopsy had been performed, no specific anatomic changes were found; that the iodine content varied directly with the degree of active epithelial hyperplasia; that the administration of iodine in the simple hyperplasias of the thyroid in man and animals is followed in from three to five weeks by a progressive involution of the hyperplasia to its colloid stage. These experiences were confirmed by Kocher and others, who began to observe the effect of the feeding of iodine to exophthalmic patients as having a result that would substantiate this particular influence of iodine. Lowey and Zoudek [66] found that the use of iodine in primary

60. Trousseau: Clinical Lectures, translated by Bazire, London, New Sydenham Society, 1868, vol. 1, p. 587.
61. Wagner: Wien. med. Bl. **7**:771, 1884.
62. Horsley: Lancet **2**:1163, 1886.
63. Halstead: Johns Hopkins Hosp. Rep. **1**:373, 1898.
64. Kocher: Arch. f. klin. Chir. **95**:1007, 1911.
65. Marine: Anatomic and Physiologic Effects of Iodin on the Thyroid Gland of Exophthalmic Goiter, J. A. M. A. **59**:325 (Aug. 3) 1912.
66. Lowey and Zoudek: Deutsche med. Wchnschr. **47**:1387, 1921.

hyperthyroidism tended to bring the basal metabolic rate back to a normal level. Plummer, having in mind the possible toxicity of incompletely iodinized thyroxin and the variations in the symptomatology of the clinical types, suggested that the administration of a compound solution of iodine in instances of primary hyperthyroidism might be of value. Subsequently, Plummer and Boothby [67] published the beneficial results of its use in selected cases. Similar reports by others began to appear. Starr and Segall,[68] in a study of forty-two cases, made additional observations. They determined that the rate of detoxification (based on the reduction per diem in the basal metabolic rate) was 3.7 points, a rate similar to that obtained by Means and Aub [69] with subtotal thyroidectomy alone. They further pointed out that in 48 per cent of these cases, the administration of iodine had the same effect on the basal metabolic rate as the removal of five sixths of the gland; that iodine did not produce permanency of remission, recurrence being the rule, and that the return of intoxication resulted in a much higher basal metabolic rate. They therefore concluded that no gap should be allowed between the therapy employing iodine and the operation. This conclusion was concurred in by Chute,[70] who regarded the "optimal time" for thyroidectomy to be within a period of from two to three weeks after the treatment with iodine was started. During this time he observed the most marked clinical improvements and the greatest drop in the basal metabolic rate. He regarded the operation within such a time limit as safe, and also stressed the fact that the toxicity recurring after cessation of the treatment with iodine is greater than before its use, if surgical removal is not promptly made. He further concluded that in the severe cases iodine reduced the necessity of pole ligations from 51 to 13 per cent, but that iodine, even though administered over a long period of time, does not cure exophthalmic goiter. Petren [71] regarded iodine as having a life-saving action. He also noted that the symptoms reappeared after cessation of the treatment and recommended the use of roentgen rays and ligation as additional measures.

Marie [72] concluded that the results of the use of iodine testify only that a disproportion exists between the iodine content and the requirement of the organism at the time rather than a deficiency of iodine. Marine [73] later called attention to the use of iodine in too large

67. Plummer and Boothby: J. Iowa M. Soc. **14**:66, 1924.
68. Starr and Segall: The Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924.
69. Means and Aub: A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917.
70. Clute: The Effect of Compound Solution of Iodin and Rest in Surgery of Exophthalmic Goiter, J. A. M. A. **86**:105 (Jan. 9) 1926.
71. Petren: Ugesk. f. Laeger. **88**:363, 1926; abstr., J. A. M. A. **87**:72, 1926.
72. Marie: Presse méd. **34**:580, 1926.
73. Marine: Ann. Clin. Med. **5**:942, 1927.

amounts (compound solution of iodine contains 125 mg. of iodine per cubic centimeters). It was suggested by him that smaller amounts more nearly physiologic (1 mg. daily) should be given. He spoke of the preoperative measure of "heroic doses" as dangerous, from which much harm had occurred and would continue to occur. Marine regarded the beneficial effects of iodine in exophthalmic goiter as limited and its injurious effects as serious. He also stated that these injurious effects had increased during the last three years and were more serious than the disturbances noted as a result of the preventive use of various iodine-containing substances. Marine explained the effect of iodine on the basis of a probable storage of colloid which holds back secretion. He stated that when secretion is released, it is reestablished with full force and yields larger amounts, the gland becoming larger and more solid. Helwig's [74] views were in agreement with those of Marine. He concluded that the feeding of iodine called forth an enlargement of the follicles and a thickening of the colloid, and stated that in his experience the severest cases of exophthalmic goiter were encountered after the administration of iodine.

Sager [75] again called attention to the necessity of differentiating the types of hyperthyroidism before beginning the use of iodine, on the basis of Plummer's views. He quoted Plummer as regarding the action of iodine as due to one of three possibilities: (1) complete iodinization of thyroxin in the tissues (possible but improbable); (2) complete iodinization of thyroxin in the thyroid (most probable); (3) blocking of the discharge of the hormone.

More definite observations on the structural changes in the thyroid now began to appear (Cattell,[76] Warthin,[77] Giordano,[78] Kaffler,[79] Marine,[80] Helwig,[81] Sager,[75] Rienhoff and Lewis,[50] Menne, Joyce and Stewart [82]). All these studies agree that the essential changes induced by iodine consist of a regression of activities with an accumulation of colloid, a reduction in the degree of hyperplasia and hypertrophy of the epithelium and a decrease in the vascularity. Grossly, the glands tend to become larger, on the average, than untreated glands. The capsule and supportive stroma are not appreciably altered unless considerable

74. Helwig: Klin. Wchnschr. **5**:2356, 1927.
75. Sager: Exophthalmic Goiter: Pathologic Changes as a Result of the Administration of Iodine (Lugol's Solution), Arch. Surg. **15**:878 (Dec.) 1927.
76. Cattell: S. Clin. N. Amer. **6**:597, 1926.
77. Warthin: Ann. Clin. Med. **4**:686, 1926.
78. Giordano, A. S.: Histologic Changes Following Administration of Iodine in Exophthalmic Goiter, Arch. Path. **1**:881 (June) 1926.
79. Kaffler: München. med. Wchnschr. **73**:1400, 1926.
80. Marine: Ann. Clin. Med. **5**:942, 1927.
81. Helwig: Klin. Wchnschr. **5**:2356, 1927.
82. Menne, Joyce and Stewart: Ann. Int. Med. **1**:912, 1928.

time elapses during the therapy. Colloid is visible, and spotty, yellowish gray to pinkish gray opaque areas of hyperplasia may be seen. These changes are not unlike the involutional changes of untreated glands or of the types of disseminated adenomatus hyperplasias associated with hypersecretion. Although clinicians have made an attempt to utilize iodine only in nodule-free glands, occasionally nodules were found in the specimens of glands examined by us. Microscopically, the essential changes noted vary somewhat with the type of disease of the individual gland. In general, there occurs a progressive development of intracinar colloid, an ironing out of the papillary infoldings, a marked reduction in the hyperplasia and hyperthrophy of the epithelium and the development of more uniformity in the sizes of the alveoli. As a rule, the longer iodine is administered, the greater is the accumulation of colloid. But over-iodinization in the presence of the continuance of the etiologic factors of the disease not infrequently results in areas of hyperplasia and hypertrophy that break through the colloid resistance, and such areas may then hypersecrete with renewed energy. Because of this limited effect of iodine on the progression of the disease, surgical removal of a large portion of the gland in the hope of a normal rebuilding is still practiced. While the reversion in the pathologic changes of the thyroid gland induced by iodine is valuable from the standpoint of therapy, and throws light on the mechanism of internal secretion in health and in disease, the relationship of iodine to the etiology is still obscure.

SUMMARY

The earlier classifications of the pathologic anatomy of the thyroid consisted of extensive lists of anatomic terms indicating different degenerative or retrogressive processes. Such changes were often regarded as disease entities with which certain clinical phenomena could be associated. While there was this confusion in the general knowledge of thyroid irregularities, there was, on the other hand, a more definite concept of the pathologic anatomy of the thyroid in exophthalmic goiter. It is evident from the early literature that the thyroid in such instances usually retains its symmetry, is firm, vascular, free from false lobulation and scant in colloid. Microscopic studies generally agreed on the existence of a patchy increase in the supportive stroma, engorgement of the blood vessels, infiltration with round cells, marked hyperplasia and hypertrophy of the epithelium associated with alveolar distortion and reduction and modification of the colloid. This was the consensus concerning the changes in the gland in hypersecretion.

Observations of atypical gland structure associated with certain if not all the symptoms of hypersecretion gradually began to be recorded. These thyroid glands lacked symmetry; the disturbance was in either one of the lobes, the isthmus, or in the isthmus and one lobe. The pathologic changes were markedly variable. In some, the capsule and supportive stroma was particularly increased (interstitial thyroiditis); in others, the anatomic pattern was retained, but spotty pinkish gray areas could be seen in a background moderately rich in colloid. Still others showed a formation of pseudolobules, while others contained solitary or multiple adenomas in various stages of development or retrogression. The recognition of such a wide range of anatomic changes in the thyroid gland and their association with varying grades of hyperactivity served to narrow the division between the definiteness of the structure of the gland in hyperthyroidism, and the many other indefinitely understood structural deformities associated with its diseases. There developed a recognition of the possibility of oversecretion by focal areas often grossly hidden by major distorting pathologic processes in the thyroid.

Solitary adenoma in many of the thyroid glands occurring with symptoms of hyperthyroidism led to the conclusion that such nodules (solitary or multiple) might be responsible for the excessive or atypical production of hormone. Concerning this there developed a conflict of views (1) as to whether such nodules are neoplasms, (2) as to their ability to secrete and (3) as to their effect on the surrounding parenchyma. Glands containing nodules (adenoma?) often presented changes varying from simple unmodified colloid-filled acini to disseminated or diffuse parenchymatous hyperplasias. Accordingly, there has not been advanced any conclusive proof that such nodules are responsible for the toxic symptoms.

The therapeutic influence of iodine on the thyroid gland has been limited to such changes as it may produce in the so-called primary hyperthyroidism. Following its use, the thyroid retains its symmetry, it enlarges somewhat because of the accumulation of colloid, the vascularity is diminished, the hyperplastic areas have a spotty distribution and the colloid become visible. Microscopically, the changes are similar to those that were described previous to the use of iodine as belonging to hyperthyroidism in which disseminated foci of hypertrophy and hyperplasia were found. It has been pointed out that the changes induced by iodine are probably similar to the natural regressive processes of variable activities of thyroid gland in health and in disease. In instances in which patients were erroneously treated on the basis of having nodule-free glands, when one or more nodules really existed, no noteworthy changes were observed within the nodules. But in such cases the characteristic changes induced by iodine were observed in the surrounding affected parenchyma.

A résumé of the many views as to the pathologic anatomic modifications of the thyroid gland associated with modified activity or hyper-

secretion tends to lead to the conclusion that, in addition to the classic changes of primary, fulminating exophthalmic goiter, there are many other grades. It is further apparent that such changes as may be directly concerned with an excessive or imperfect fabrication of hormone may lie hidden or be incompletely evident because of previously formed minor or gross distortions of structure that are contributory to, but not responsible for, the malfunctioning of the thyroid.