October 29, 1964

NON-TOXIC GOITER

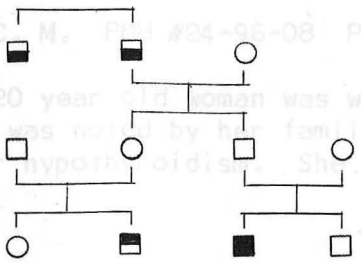
Case #1. [redacted] Euthyroid Goiter, probably due to abnormal iodoprotein

This 15 year old girl was noted at the age of 14 to have a mass in the neck. At no time was there tenderness, nervousness, weakness, heat intolerance, or weight loss. There were no eye signs, and P. E. revealed dry skin, a normal pulse, normal reflexes, no tremor, and a diffusely enlarged thyroid gland without tenderness, bruit, or nodules. Initial workup revealed I^{131} uptakes of 66 and 58.5%, PBI's of 10.5, 11.4, and 10.0, BEI's of 4.3, 4.7, and 3.4, and cholesterols of 162, 138, and 126. She was placed on l-thyroxine, and after three months of therapy she had an I^{131} uptake of 11%, a PBI of 6.9 µg%, and a BEI of 5.5. During the spring of 1964 the thyroid was discontinued for repeat testing, and after three months off therapy the PBI was again 10.7 and the BEI 3.3. She was again placed on l-thyroxine, and when last seen on [redacted]-64 the thyroid was almost impalpable.

Case #2. [redacted] Pendred's Syndrome

This 34 year old negro man has had a moderate impairment of hearing since birth (audiograms reveal this to be a sensory neurological defect). At the age of 18 he developed a goiter and was admitted to [redacted] where he was thought on clinical grounds (nervousness and weight loss with normal BMR and resting pulses) to have hyperthyroidism. A thyroidectomy was performed (1950). He apparently did well until about 1½ years ago when he began to develop stiffness of the joints, lethargy, hoarseness, and dyspnea on exertion. PE revealed gross myxedema with a dull affect, dry, scaly skin, myxedematous reflexes, edema, and cardiomegaly. Initial studies revealed an I^{131} uptake of 2% and a PBI of 10 µg%. There was a markedly enlarged heart without evidence of pericardial effusion by ice water infusion or CO_2 injection. The VP was 13; the CT was 36 sec, and EKG revealed ischemic changes. He was started on small doses of l-thyroxine, increasing to 0.15 mg/day before discharge.

On an outpatient basis the dosage of l-thyroxine has been increased to 0.3 mgm/day. He has lost a total of about 30 pounds in weight, and all his symptoms including the dyspnea have disappeared. The last PBI obtained ([redacted], 1964) was 4.2. He still had cardiomegaly and EKG evidence of lateral ischemia when seen in July. The family history is as follows:



Key ◧ deafness
◨ goiter
■ goiter and deafness

Case #3. [redacted] Goiter Responsive to Thyroxine

This 26 year old [redacted] noted the presence of a goiter while taking physical diagnosis in the spring of 1963. After becoming aware of the goiter he also noted the onset of mild nervousness and dysphagia, symptoms which disappeared after the completion of final exams. When first seen in [redacted] of 1963 his physical examination was completely normal except for a diffuse, smooth goiter, approximately 3-4 X normal size. The PBI was 7.7 and 7.5 with a BEI of 5.7. The I^{131} uptake was 5% in 6 hours and 10% in 24 hours. It was felt that this represented a colloid goiter; because of the possibility that this might represent the recovery phase of acute thyroiditis, however, it was decided to observe him for six months. In [redacted] of 1964 the thyroid had not changed in size; he was still euthyroid on physical examination. The repeat PBI was 6.8 and BEI was 4.1. He was started on l-thyroxin, 0.2 mgm/day. By [redacted] of 1964 only the thyroid isthmus was palpable and by [redacted] of 1964 no thyroid tissue was palpable whatsoever. He has remained well and still has normal PBI (7.5 µg%).

Case #4. [redacted] Carcinoma of the Thyroid

This 42 year old woman was noted by relatives to have developed a mass in the right side of her neck in [redacted] of 1962. The mass continued to enlarge, and in [redacted] of 1964 she developed intermittent difficulty in swallowing solids and subsequently liquids as well. She was subsequently admitted to the Medicine Service for a diagnostic workup. P. E. revealed a firm 1½ X 5 cm firm, irregular immovable mass in the right side of the thyroid without fixation to the skin. Barium swallow revealed an indentation in the esophagus in the area of the right side of the thyroid, and scintiscan revealed that the mass did not concentrate I^{131}. The PBI was 6.4, and the I^{131} uptake was 14.5%. In view of these findings she was transferred to surgery, where on operation the tumor mass was found to be invading the right sternohyoid muscle and to have encompassed the right recurrent laryngeal nerve. The pathologic diagnosis was papillary and follicular adenocarcinoma with capsular and vascular invasion and extension into the soft tissue. The right laryngeal nerve was saved, and following excision of the thyroid she was treated with 6000 r to the area of the thyroid bed. She has subsequently done well and shows no evidence at the present time of recurrence.

Case #5. [redacted] Nodular Goiter

This 25 year old woman was worked up in the outpatient clinic in 1962 for a series of complaints which were thought to represent an anxiety reaction. During this evaluation she was noted to have a diffusely enlarged thyroid gland with a somewhat larger left lobe, without any clinical evidence of hypo or hyperthyroidism. The PBI was 6.0 µg%, and the I^{131} uptake was 31%. During a hospitalization here in [redacted] of 1963 for mumps meningoencephalitis she was noted to have two large supraclavicular nodes on the left near the thyroid isthmus. At that time the scan was entirely normal in size and configuration. The I^{131} uptake was 25%, and the PBI was 5.5 µg%. She was subsequently reevaluated in the medicine clinic where the nodes were noticed to persist, and she was subsequently referred to the surgery service where a biopsy revealed only nodular thyroid tissue in the area thought to represent lymph nodes.

Case #6. [redacted] Postoperative Hypoparathyroidism

This 20 year old woman was well until [redacted] of 1962 when during a post partum period she was noted by her family to have developed a goiter without signs or symptoms of hyper or hypothyroidism. She was seen by a physician who told the family that it

might be malignant and who subsequently performed a total thyroidectomy. The histological diagnosis was Hashimoto's thyroiditis. Four days after surgery ([redacted]-62) she began to complain of "drawing in her hands" and was noted to have a positive Chvostek. Calcium and Vitamin D were started, and by [redacted]62 the Chvostek was no longer positive. The Vitamin D and calcium were continued, and she awakened her husband one morning in late November with twitching, a bleeding mouth, and subsequent stupor. About 4 weeks later she was noted by her family to have a generalized convulsion. A third seizure was precipitated in the EEG Lab by photic stimulation. She was subsequently referred to [redacted] in [redacted] of 1963 and admitted to the Neurology Service. P. E. was entirely normal. She had Calciums of 7.3, 8.7, and 8.0, P of 5.9, 5.7, 5.2, and a PBI of 2.5. She was thought to have postsurgical hypothyroidism and hypoparathyroidism and idiopathic epilepsy and was discharged on l-thyroxine 0.1 mgm/day, calcium lactate 2 gms tid, Vitamin D 50,000 units qod, and 100 mgm dilantin tid.

Over a period of 18 months she has been taken off all anticonvulsive drugs, and she has had no seizures and now has a normal EEG. She has been maintained on l-thyroxine (now 0.2 mgm/day) and varying amounts of calcium lactate and Vitamin D. During a subsequent pregnancy she had very low Calciums recorded (7.1 and 6.8) but has had no further episodes of tetany.

Case #7. [redacted] [redacted] Postoperative Hypoparathyroidism

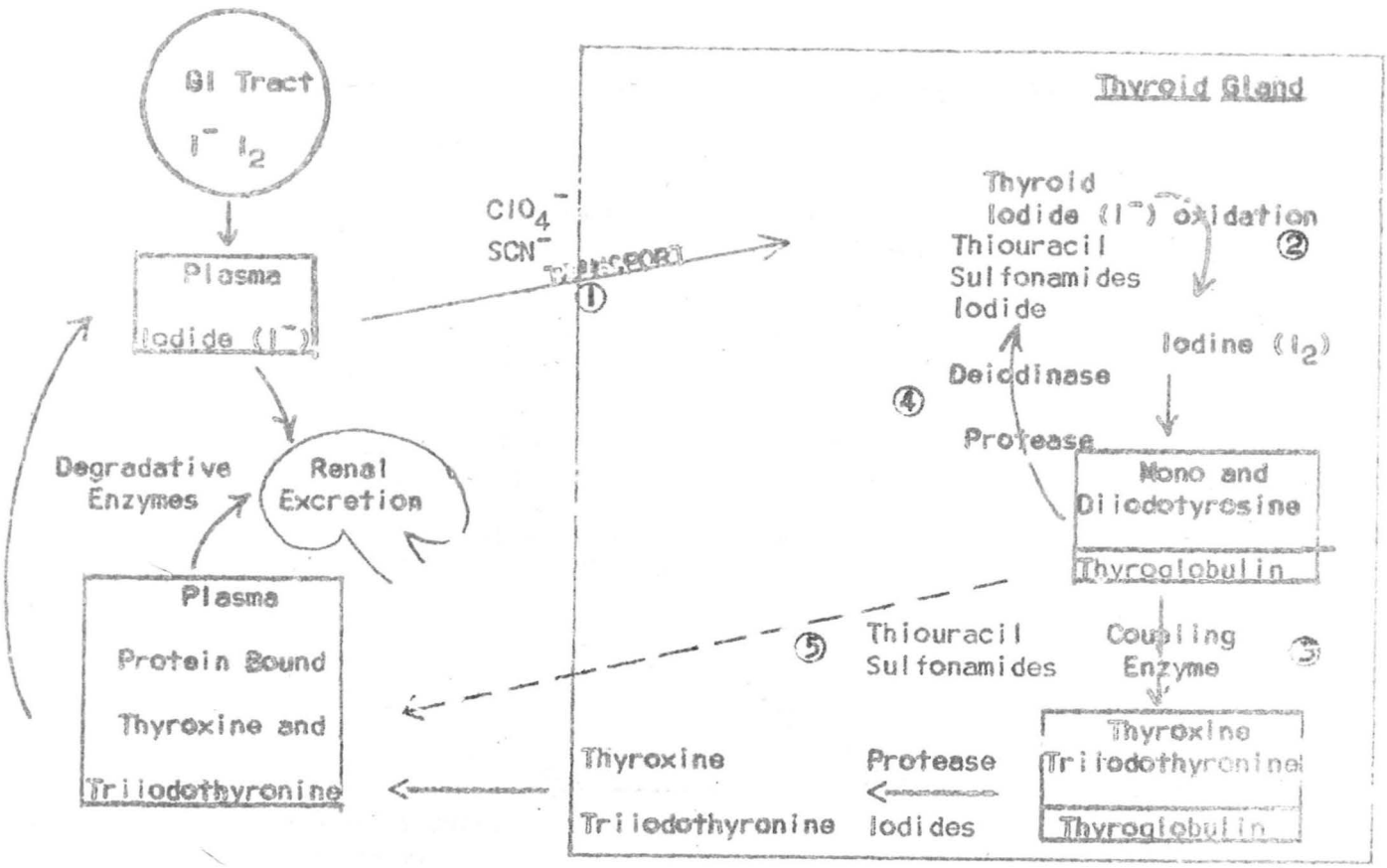
This 20 year old woman was well until three years ago when she noticed a lump in her throat unassociated with other symptoms. During the third trimester of pregnancy about a year ago the mass began to enlarge, again unassociated with other symptoms. She was evaluated following delivery at a local osteopathic hospital where she was thought to have "toxic adenoma of the thyroid". A complete thyroidectomy was performed; the pathological report was normal thyroid tissue with focal areas of increased lymphocytes suggestive of chronic thyroiditis. She was started on thyroid and prophylactic Vitamin D and calcium after surgery. One month later she began to note tingling of the fingers and to have intermittent episodes of tetany for which she was hospitalized on at least three occasions for treatment with IV calcium. She subsequently became pregnant again, the tingling worsened, and she was referred to [redacted] in [redacted] of 1964. At the time of referral she was on 0.9 mgm l-thyroxine per day, and the PBI was 15.5 µg%, although there were no overt signs of hyperthyroidism. She had a positive Chvostek and a Ca of 8.0, and she is now in the process of being controlled on calcium, Vitamin D, and a smaller dose of l-thyroxine.

KNOWN GENETIC CAUSES OF NODULAR GOITER

GROUP	TYPE OF ABNORMALITY	POSTULATED DEFECT	CLINICAL STATUS	TYPE OF INHERITANCE	DIAGNOSIS
1	Trapping Defect	Defect in either energy or carrier for transport	Hypothyroid	Recessive	I^{131} uptake=0 I^{131} uptake after TSH=0 Respond to iodide administration in large doses.
2	Oxidation and Organification†	Lack of peroxidase	Hypothyroid	Recessive	I^{131} uptake ↑ Precipitous fall after SCN^-
		Lack of iodinase	Usually euthyroid with deafness (Pendred's syndrome)	Intermediate	I^{131} uptake ↑ Definite fall after SCN^-
3	Coupling Defect	Either lack of "coupling" enzyme or abnormal thyroglobulin	Usually euthyroid	Intermediate	I^{131} uptake ↑ No fall after SCN^-
4	Dehalogenase Defect	Lack of ability to dehalogenate MIT and DIT*	Usually euthyroid	Intermediate	I^{131} uptake ↑ with rapid loss from gland. No fall after SCN^-. MIT and DIT present in blood and urine. Respond to iodide in large doses.
5	Abnormal Iodoprotein†	Perhaps hypertrophy of a normal pathway or because protein is permitted to enter and leave cell.	Usually euthyroid	Intermediate or Dominant	I^{131} uptake ↑ PBI normal to high. BEI relatively low in relation to PBI.

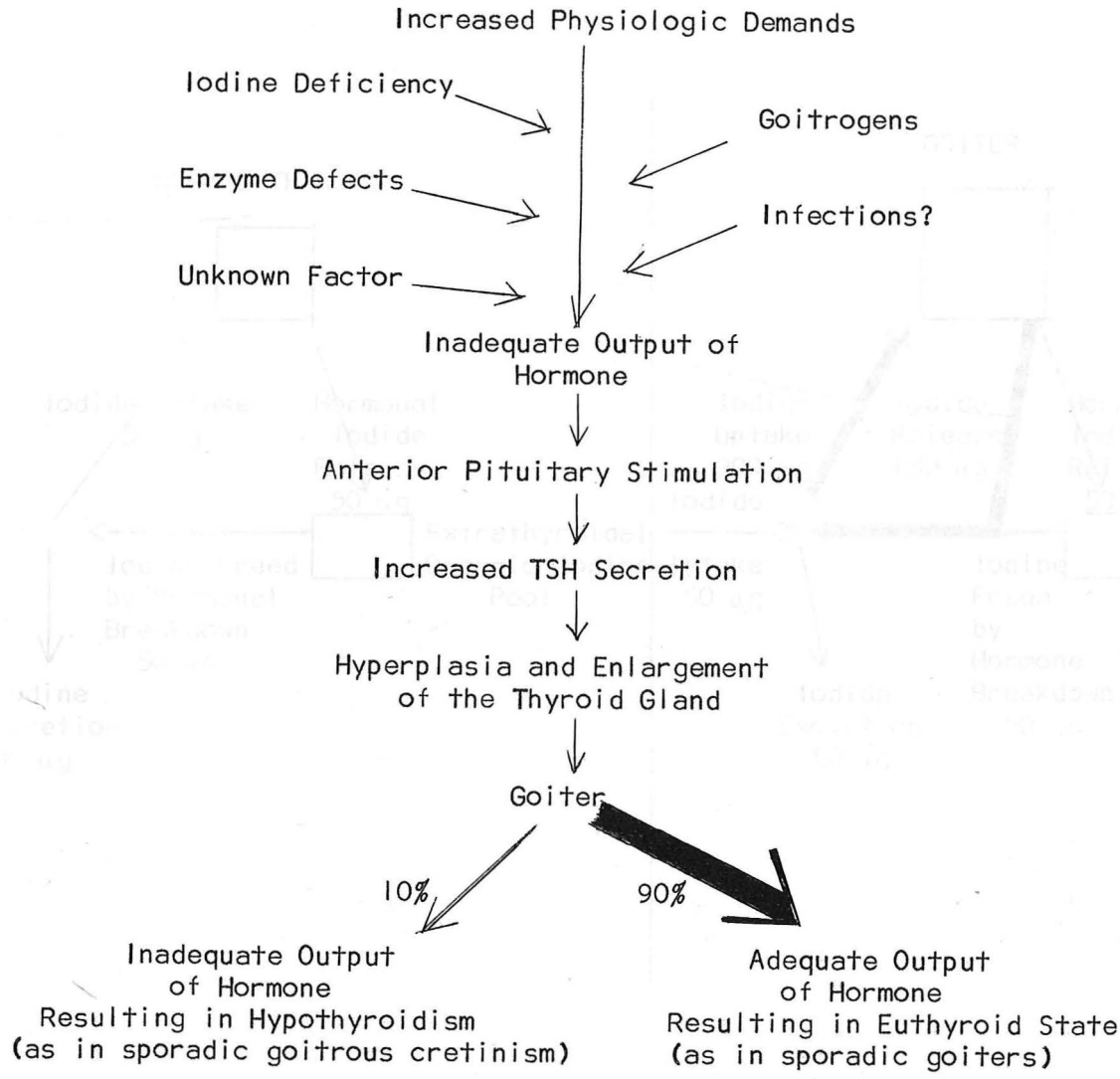
* The only one of the five groups in which the specific enzyme deficit has been defined.
† The two defects most commonly found in sporadic goiter.

SCHEMATIC REPRESENTATION OF THE KNOWN
GENETIC CAUSES OF NODULAR GOITER

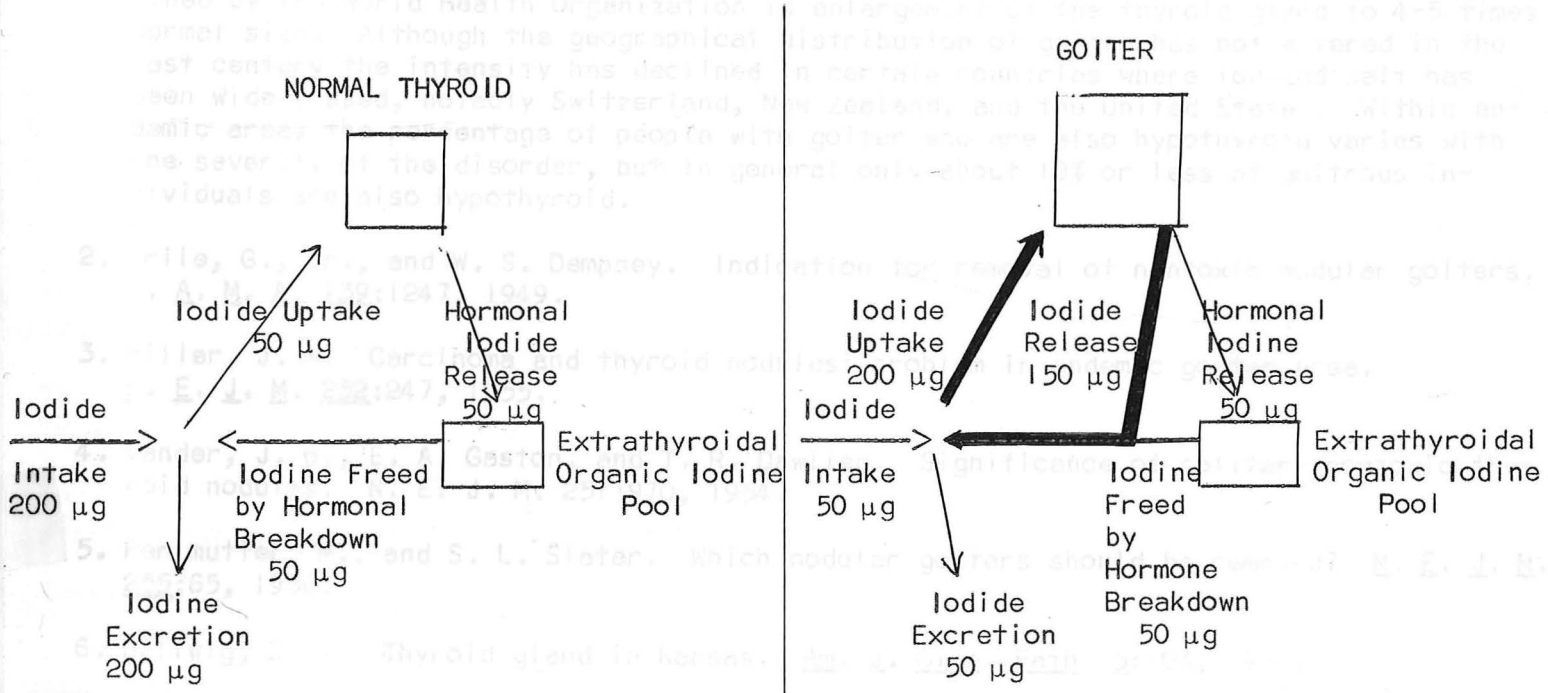


The sites of the five known types of genetic defects are shown in red, and the sites of action of the principal types of anti-thyroid drugs are shown in blue.

PATHOGENESIS OF GOITER



EFFECT OF INCREASED TSH SECRETION ON IODINE METABOLISM



REFERENCES

DEFINITION AND INCIDENCE

1. Kelly, F. C., and W. W. Snedden. Prevalence and geographical distribution of endemic goitre. Ch. in Endemic Goitre, a World Health Organization Monograph, 1960, p. 27.

As of 1960 200 million people in the world were estimated to have goiter, which as defined by the World Health Organization is enlargement of the thyroid gland to 4-5 times normal size. Although the geographical distribution of goiter has not altered in the past century the intensity has declined in certain countries where iodized salt has been widely used, notably Switzerland, New Zealand, and the United States. Within endemic areas the percentage of people with goiter who are also hypothyroid varies with the severity of the disorder, but in general only about 10% or less of goitrous individuals are also hypothyroid.

2. Crile, G., Jr., and W. S. Dempsey. Indication for removal of nontoxic nodular goiters. J. A. M. A. 139:1247, 1949.

3. Miller, J. M. Carcinoma and thyroid nodules: problem in endemic goiter area. N. E. J. M. 252:247, 1955.

4. Vander, J. B., E. A. Gaston, and T. R. Dawlier. Significance of solitary nontoxic thyroid nodules. N. E. J. M. 251:970, 1954.

5. Perlmutter, M., and S. L. Slater. Which nodular goiters should be removed? N. E. J. M. 255:65, 1956.

6. Hellwig, C. A. Thyroid gland in Kansas. Am. J. Clin. Path. 5:103, 1935.

7. Schlesinger, M. J., S. L. Cargill, and I. H. Saxe. Studies in nodular goiter: incidence of thyroid nodules in routine necropsies in nongoitrous region. J. A. M. A. 110: 1638, 1938.

8. Hull, O. H. Critical analysis of two hundred and twenty-one thyroid glands: study of thyroid glands obtained at necropsy in Colorado. Arch. Path. 59:1270, 1955.

Schlesinger, et al (Ref. 7) arbitrarily defined nodular goiter as any gland containing at least one palpable nodule, that is a nodule 1 cm in diameter or greater. Subsequent surveys in this country by the U. S. Public Health Service and others have continued to use this criterion. The surveys listed above including clinical examinations of large numbers of normal individuals and the pathological examination of thyroid glands in varying parts of the U. S. all report strikingly similar results. From 4-8% of examined individuals have asymptomatic nodular goiter; of these 60% are clinically solitary and 40% are multinodular or diffuse. In the autopsy series, 8-12% of individuals have theoretically palpable nodules, whereas the incidence of nodules of all sizes is actually 62%.

9. Mortensen, J. D., L. B. Woolner, and W. A. Bennett. Gross and microscopic findings in clinically normal thyroid glands. J. Clin. Endocrinol. 15:1270, 1955.

Furthermore, with advancing age nodularity increases so that by the 9th decade 100% of all thyroid glands have one or more nodules. Consequently, it is clear that the frequency of goiter is a matter of definition, and persons with palpable nodules or glands represent the extreme end of a normal continuim.

NATURAL HISTORY AND PATHOLOGY

10. Kilpatrick, S. R., and G. M. Wilson. Simple non-toxic goiter. Ch. in The Thyroid Gland, Vol. 2, ed. by R. Pitt-Rivers and W. R. Trotter, Washington: Butterworth, Inc. 1964, p. 88.

11. DeSmet, M. P. Pathological anatomy of endemic goitre. Ch. in Endemic Goiter, a World Health Organization Monograph, 1960, p. 315.

12. Stanbury, J. B. Non-toxic goiter, in panel discussion "Thyroid Diseases in Children and Adults", Bul. N. Y. Aca. Med. 34:39, 1958.

This is a lifelong disease becoming apparent first at adolescence as adolescent goiter, progressing into middle life when euthyroid nodular goiter is a common finding. In later life many of the patients with the most profound degree of nodular goiter develop toxic nodular goiter.

13. Taylor, S. The size of follicles in non-toxic goitre. Lancet I, Jan. 26, 1952, p. 175.

14. Taylor, S. The evolution of nodular goiter. J. Lab. Clin. Endocrinol. 13:1232, 1953.

15. Taylor, S. Physiologic considerations in the genesis and management of nodular goiter. Am. J. Med. 20:698, 1956.

16. Taylor, S. Genesis of the thyroid nodule. Brit. Med. Bul. 16:102, 1960.

17. Johnson, N. The blood-supply of the human thyroid gland under normal and abnormal conditions. Brit. J. Surgery 42:587, 1955.

Using autoradiographic techniques Taylor has described 5 stages in the development of nodular goiter: 1.) diffuse enlargement and homogeneous hyperplasia, 2.) the development of micro inactive and active areas, 3.) the enlargement of inactive lobules to form nodules, 4.) enlargement of the nodules to become cystic and inactive, 5.) the nodules become more numerous with varying amounts of hemorrhage, necrosis, cystic degeneration, fibrosis and calcification. Within this schema the asymptomatic nodular glands in all elderly individuals described in reference 9 can be looked upon as not progressing beyond stage 3, or stated in another way stages 1-3 are normal stages and stages 4 and 5 are the pathological state.

18. Pitt-Rivers, R., D. Hubble, and W. H. Hoathen. A chromatographic study of thyroidal iodine metabolism in nontoxic nodular goiter. J. Clin. Endocrinol. 17:1313, 1957.

One of the few biochemical studies of nodules in which the thyroxine content was found to be low and the ratio of MIT:DIT was found to be high.

19. Smith, J. F. The pathology of the thyroid in the syndrome of sporadic goitre and congenital deafness. Quart. J. Med. 29:297, 1960.

In goiters due to known metabolic defects the pathology resembles that described above with particularly prominent epithelial proliferation. At present it appears that the various forms of TSH mediated enlargement are impossible to distinguish morphologically. The more severe the hypothyroidism, however, the more extreme the degree of cellular pleomorphism and, in general, the larger the gland.

ETIOLOGY

Genetic Defects - General

20. Fraser, G. R. A genetical study of goitre. Ann. Hum. Genet. (London) 26:335, 1963.

As the result of detailed family investigation of 31 unselected men who had non-toxic goiter it was found that 6 or approximately 20 per cent were due to simple genetic defects. Genetic determinants of a more complex nature were not assessed in this study. The incidence of such familial association is probably much less frequent in women.

21. Stanbury, J. B. Familial goiter. Ch. in The Metabolic Basis of Inherited Disease, Ed. by J. B. Stanbury, J. B. Wyngaardes, and D. S. Frederickson. New York: McGraw-Hill Book Co., 1960, p. 273.

22. McGirr, E. M. Sporadic goitrous cretinism. Brit. Med. Bul. 19:113, 1960.

23. Blizzard, R. M. Inherited defects of thyroid hormone synthesis and metabolism. Metabolism 9:232, 1960.

24. Stanbury, J. B. The metabolic basis for certain disorders of the thyroid gland. Am. J. Clin. Nutrition 9:669, 1961.

25. McGirr, E. M. Sporadic goiter due to dyshormonogenesis. Ch. in Clinical Endocrinology 1, Ed. by E. B. Astwood. New York: Grune and Stratton, 1960, p. 133.

26. Stanbury, J. B. The metabolic errors in certain types of familial goiter. Recent Prog. Hormone Res. 19:547, 1963.

27. Murray, I. P. C., and E. M. McGirr. Iodine metabolism in thyroid dysfunction. Ch. in The Thyroid Gland, Vol. 2, Ed. by R. Pitt-Rivers and W. R. Trotter. Washington: Butterworth, Inc., 1964, p. 39.

General reviews of the types of metabolic blocks which can cause goiter. The last two of these references are both lucid and very complete.

Genetic Defects - Trapping Defect

28. Federman, D., J. Robbins, and J. E. Rall. Some observations on cretinism and its treatment. N. E. J. M. 259:610, 1958.

29. Stanbury, J. B., and E. M. Chapman. Congenital hypothyroidism with goitre. Absence of an iodide-concentrating mechanism. Lancet 1: 1162, 1960.

Whereas the thyroid can maintain a 40:1 concentration of iodide in relation to the plasma (120:1 under TSH stimulation) the blood to thyroid ratio is 1:1 in this condition. Furthermore, this inability to concentrate is also present in the parotids, mammary glands, and GI tract of affected individuals. The defect can be overcome by giving enough dietary iodine so that the thyroid concentration is sufficient to support thyroxine synthesis. The heterozygotes (parents) are completely normal.

Genetic Defects - Defect in Oxidation and/or Organification of Iodine

30. Haddad, H. M., and J. B. Sidbury, Jr. Defect of the iodinating system in congenital goitrous cretinism: report of a case with biochemical studies. J. Clin. Endocrinol. 19:1446, 1959.

31. Parker, R. H., and W. H. Beierwaltes. Inheritance of defective organification of iodine in familial goitrous cretinism. J. Clin. Endocrinol. 21:21, 1961.

In the most severe form of organification defects cretinism is quite common. Stanbury believes that this form is due to absence of thyroidal peroxidase.

32. Leszynsky, H. E. Genetic studies in familial goitrous cretinism. Acta endocrinologica 46:103, 1964.

A report of a family with a deficit in organification in which hyperthyroidism occurred in two members who were supposedly heterozygotes.

33. Fraser, G. R., M. E. Morgan, and W. R. Trotter. The syndrome of sporadic goitre and congenital deafness. Quart. J. Med. 23:279, 1960.

34. Trotter, W. R. The association of deafness with thyroid dysfunction. Brit. Med. Bul. 16:92, 1960.

35. Thould, A. K., and E. F. Scowes. The syndrome of congenital deafness and simple goitre. Advances in Thyroid Research, 1961, p. 22.

The association of goiter (now known to be due to an organification defect) with deaf mutism was originally described by Pendred and subsequently by Brain. The organification defect is incomplete, and most individuals are euthyroid.

36. Costa, A., F. Cotlingo, G. M. Ferraris, G. Fregola, and F. Morocio. Comparisons between endemic goiter, cretinism, deaf mutism, and sporadic goiter, cretinism, and deaf-mutism. Advances in Thyroid Research, 1961, p. 289.

37. Baschieri, L., G. Benedetti, F. deLuca, and M. Negri. Evaluation and limitations of the perchlorate test in the study of thyroid function. J. Clin. Endocrinol. 23:786, 1963.

The use and limitations of the perchlorate discharge test are emphasized in these two papers. Furthermore, the complexity of the relation between deafness and the organification defect is emphasized by the finding that a high percentage of congenital deaf mutes without goiter have positive perchlorate discharge tests.

38. Ramalingaswami, V. Endemic goitre. Ch. in The Thyroid Gland, Vol. 2, Ed. by R. Pitt-Rivers and W. R. Trotter. Washington: Butterworths, 1960, p. 71.

Furthermore, there is some relationship between iodine deficiency, endemic cretinism, and endemic deaf-mutism, particularly in severely affected areas (the Alps, Himalayas, and the Andes). Trotter (Ref. 34) also reviews this subject including the evidence that the incidence of deaf-mutism fell in Switzerland from 1.7/1000 births to 0.4/1000 births after the introduction of iodine prophylaxis.

Genetic Defects - Coupling Defect

39. Stanbury, J. B., K. Ohela, and R. Pitt-Rivers. The metabolism of iodine in 2 goitrous cretins compared with that in 2 patients receiving methimazole. J. Clin. Endocrinol. 15:54, 1955.

40. Stanbury, J. B., G. Riccabora, and M. A. Janssen. Iodotyrosyl coupling defect in congenital hypothyroidism with goitre. Lancet I:917, 1963.

41. Morris, J. H. Defective coupling of iodotyrosine in familial goiters. Arch. Int. Med. 114:417, 1964.

This defect which is inherited as either an intermediate or a dominant is characterized by a high ^{131}I uptake which is not discharged for up to a week. There is a negative reaction to SCL or perchlorate. Because the dehalogenase is intact no MIT or DIT is excreted, and the only radioactive substances in blood are a small amount of T_4 and I.

Genetic Defects - Dehalogenase Defect

42. Stanbury, J. B., J. W. A. Meijer, and A. A. H. Kassenaar. The metabolism of iodotyrosines. II. The metabolism of mono- and di-iodotyrosine in certain patients with familial goiter. J. Clin. Endocrinol. 16:840, 1956.

43. Choufoer, J. C., A. A. H. Kassenaar, and A. Querido. The syndrome of congenital hypothyroidism with defective dehalogenation of iodotyrosines. Further observation and a discussion of the pathophysiology. J. Clin. Endocrinol. 20:983, 1960.

Not only are MIT and DIT excreted in blood and in urine, but since so much iodide is lost by this route the patients become iodine deficient on a normal iodine intake, and in the instance described above, administering an excess of iodine results in a regression of the goiter.

Genetic Defects - Abnormal Iodoprotein

44. DeGroot, L. J., and J. B. Stanbury. The syndrome of congenital goiter with butonal-insoluble serum iodine. Am. J. Med. 27:586, 1959.

45. Lissitzky, S., J. L. Codoccioni, G. Cortouzou, and S. Monte. Eumetabolic goitrous adult with iodoprealbumin in thyroid tissue and blood. J. Clin. Endocrinol. 24:305, 1960.

46. Dowling, J. T., S. H. Ingbar, and N. Freinkel. Abnormal iodoproteins in the blood of eumetabolic goitrous adults. J. Clin. Endocrinol. 21:1390, 1961.

47. Greenspan, F. S., J. M. Lowenstein, P. Spilken, and S. Craig. Abnormal iodoprotein in non-toxic goiter. N. E. J. M. 269:830, 1963.

48. Kuhn, A., S. R. Cogan, and S. Berger. Circulating iodoprotein in two patients with autonomous thyroid nodules. J. Clin. Endocrinol. Met. 22:1, 1962.

As many as half of random patients with diffusely enlarged glands may have a large component of circulating iodoprotein, in most cases an albumin-like protein. Since it is not butonal extractable there may be large discrepancies between the PBI and

BEI. As emphasized by Ref. 45, however, the PBI-BEI discrepancy is unreliable in that it may not be significant in individuals who do have circulating iodoproteins. Apparently, this is due to the fact that in some individuals the abnormal protein or peptide is much smaller than 4S and may extract.

49. Robbins, J., J. Wolff, and J. E. Rall. Iodoproteins in normal and abnormal human thyroid tissue and in normal sheep thyroid. Endocrinology 64:37, 1959.

50. DeGroot, L. J., and E. Corvalho. Studies of proteins of normal and diseased thyroid glands. J. Clin. Endocrinol. 20:21, 1960.

51. Beckers, C., and M. deVisscher. Thyroid proteins in endemic goiter. Metabolism 10: 695, 1961.

52. Stanbury, J. B., and M. A. Janssen. The iodinated albumin-like component of the plasma of thyrotoxic patients. J. Clin. Endocrinol. 22:978, 1962.

53. Hjort, T. Thyroglobulin in serum. Acta Med. Scand. 174:137, 1963.

54. Chavarria, C., G. Munos-Ferreira, G. Guevarra, J. J. Rupp, and K. E. Paschkis. Butonal-insoluble iodinated compound in the plasma of a goitrous cretin. J. Clin. Endocrinol. 20:894, 1960.

55. Lobo, L. C. G., M. M. daSilva, F. B. Hargreaves, and A. M. Couceiro. Thyroidal iodoproteins in endemic cretins. J. Clin. Endocrinol. 24:285, 1964.

An iodoprotein is also found in the blood of patients with thyroid cancer, Hashimoto's thyroiditis, subacute thyroiditis, endemic goiter, Graves' disease, and in very small quantities in normal individuals. Therefore, it may represent only a "leakage" phenomenon occurring under the impact of TSH rather than a primary defect.

Goitrogens

56. Clements, F. W. Naturally occurring goitrogens. Brit. Med. Bul. 16:133, 1960.

57. Roche, J., and S. Lissitzky. Etiology of endemic goiter. Ch. in Endemic Goitre, a World Health Organization Monograph, 1960, p. 351.

Also see Ref. 38.
With one exception (seasonal goiter in children in Tasmania) there is no definite evidence that naturally occurring goitrogens are ingested in sufficient quantity in the human diet to cause goiter. This is clearly not true in domestic animals, and whether low grade ingestion over many years could result in nodularity in human goiter is not known.

Drugs

58. Paley, K. R., E. S. Sobel, and R. S. Yalow. Some aspects of thyroidal iodine metabolism in a case of iodine-induced hypothyroidism. J. Clin. Endocrinol. 18:79, 1958.

59. Paris, J., W. M. McConahey, C. A. Owen, Jr., L. B. Woolner, and R. C. Bohn. Iodide goiter. J. Clin. Endocrinol. 20:57, 1960.

Also see Ref. 15.
In addition to iodides, the commonest drug-induced goiter in this country, a variety of other drugs including phenylbutazone and Vitamin A, BAL, sulfonamides, perchlorate, cobalt, PAS, and resorcinol can cause goiter on occasion. As in all instances of blocked organic iodination, the thiocyanate test becomes positive in iodine induced goiter.

Infections

60. Hintze, G., P. Fortelius, and J. Railo. Epidemic thyroiditis. Acta endocrinologica 45:381, 1964.

61. Harden, R. McG., W. D. Alexander, and M. T. Harrison. Non-toxic goitre in males. Brit. Med. J. 1:1419, 1964.

62. Black, M. A., R. C. Horn, Jr., and J. M. Miller. Unilateral thyroid nodules with lymphocytic thyroiditis: surgical problems and management. Arch. Surg. 87:280, 1963.

These publications emphasize that both subacute and Hashimoto's thyroiditis can present as asymptomatic, euthyroid goiter. Indeed Hashimoto's disease may account for 20 per cent or more of non-toxic goiters according to Ref. 60 and can present as both single nodules and as multinodular goiter (62).

Iodine Deficiency

63. Greenwald, I. Endemic Goiter: Heredity, Deficiency, Intoxication, or Infection. Ch. in Clinical Endocrinology, Ed. by E. B. Astwood. New York: Grune and Stratton, 1960, p. 123.

64. Anonymous. Goiter and iodine deficiency. Nutrition Reviews 22:169, 1964.

Despite claims to the contrary iodine deficiency is widely accepted as the major cause of endemic goiter throughout the world.

65. Stanbury, J. B., G. L. Brownell, D. S. Riggs, H. Perinetti, J. Itoiz, and E. B. del Castillo. Endemic Goiter, The Adaptation of Man to Iodine Deficiency. Cambridge: Harvard University Press, 1954.

66. Roche, M., F. deVenanzi, J. Vera, E. Coll, M. Spinetti-Benti, J. Mendez-Martinez, A. Gerardi, and J. Forero. Endemic goiter in Venezuela studied with I^{131}. J. Clin. Endocrinol. 17:99, 1957.

67. Ramalingaswami, V., T. A. V. Subramanian, and M. G. Deo. The aetiology of Himalayan endemic goiter. Lancet 1:791, April 15, 1961.

68. Lomberg, B. A., P. Wohlberg, O. Wegelius, G. Hellstrom, and P. I. Forsius. Iodine metabolism of endemic goiter on the Aland islands (Finland). J. Clin. Endocrinol. 18:991, 1958.

69. deVisscher, M., C. Beckers, H. G. van den Schrieck, M. deSmet, A. M. Ermans, H. Golperin, and P. A. Bastenie. Endemic goiter in the Uele region. I. General aspects and functional studies. J. Clin. Endocrinol. 21:175, 1961.

In general the characteristics of thyroid function in iodine deficiency can be summarized as follows: increased I^{131} uptake, PBI may be normal, slightly low, or elevated (see Ref. 54 and 55), thiocyanate and perchlorate flush tests usually negative, I^{131} uptake returns to normal when I^{127} is administered.

70. Ermans, A. M., J. E. Dumont, and P. A. Bastenie. Thyroid function in a goiter endemic. I. Impairment of hormone synthesis and secretion in the goitrous gland. J. Clin. Endocrinol. 23:539, 1963.

71. Ermans, A. M., J. E. Dumont, and P. A. Bastenie. Thyroid function in a goitrous endemic. II. Nonhormonal iodine escape from the goitrous gland. J. Clin. Endocrinol. 23:550, 1963.

The last apparent discrepancy in explaining endemic goiter as due to iodine deficiency - namely the fact that the total iodine content in the gland may be increased in the face of iodine deficiency - has been explained by these studies. Some iodine deficient patients, presumably due to the massively increased TSH secretion, have a profound discharge of inorganic iodide from the gland so that the gland becomes much less efficient and a goiter can perpetuate itself.

72. Parker, R. H., and W. H. Beierwalles. Elevated serum protein-bound iodine values with dietary iodine deficiency. J. Clin. Endocrinol. 22:19, 1962.

Since the iodization of salt in this country is voluntary, there is no way of knowing whether varying degrees of iodine deficiency may contribute to some cases of goiter in the old goiter belt. This is a recent report of an epidemic in a state school in Michigan where iodized salt was not used. This possibility should at least be kept in mind, although it is probably rare. In Great Britain, where salt is not iodized a large percentage of goiter is thought to be due to iodine deficiency (See Ref. 15, 16, and 61).

73. Lowenstein, F. W. Principles and problems of endemic goitre control. Ch. in Endemic Goitre, a World Health Organization Monograph, 1960, p. 443.

74. deMoerloose, J. Legislation on iodine prophylaxis. Ch. in Endemic Goitre, a World Health Organization Monograph, 1960, p. 453.

Actually, in only seven countries of the world is the iodization of salt compulsory by law (Canada, Columbia, Costa Rica, Guatemala, Panama, Paraguay, and Yugoslavia) throughout the entire country. In some countries (Brazil, Bulgaria, Hungary, Mexico, Peru) its use is mandatory in goitrous areas only, and in some other countries (Switzerland, U. S. A., New Zealand) its use is widespread and almost universal but not compulsory. In Austria and the United Kingdom apparently only about 5% of the population uses iodized salt.

TREATMENT

75. Greer, Monte A. The effect of endogenous thyroid activity of feeding dessicated thyroid to normal human subjects. N. E. J. M. 244:385, 1951.

76. Johnston, M. W., A. H. Squires, and R. F. Farquharson. The effect of prolonged administration of thyroid. Ann. Int. Med. 35:1008, 1951.

No matter how long thyroid is ingested by normal people the thyroid gland returns to normal function within a few weeks after its use is discontinued.

77. Astwood, E. B., C. E. Cassidy, and G. D. Aurbach. Treatment of goiter and thyroid nodules with thyroid. J. A. M. A. 174:459, 1960.

78. Astwood, E. B., and C. E. Cassidy. Treatment of simple goiter and thyroid nodules with thyroid hormone. Ch. in Clinical Endocrinology I, Ed. by E. B. Astwood. New York: Grune and Stratton, 1960, p. 152.

79. Astwood, E. B. Management of thyroid disorders. J. A. M. A. 186:585, 1963.

The Astwood papers review the old European literature from the 1890's which showed that dessicated thyroid is an excellent form of therapy for endemic goiter. They went on to show that sporadic goiter responds just as well - about 30% excellent response, 30% moderate response, and 30% no response. If one takes special care that each gland is suppressed, treats for adequate periods of time, and considers those patients who have had goiter for less than 10 years as many as 91% have good to complete response. A very surprising finding was that if the thyroid is discontinued in patients who have responded, in about 41% the goiter will not recur.

80. Schneeberg, N. G., I. J. Stahl, G. Maldia, and H. Menduke. Regression of goiter by whole thyroid on triiodothyronine. Metabolism 11:1054, 1962.

This is a typical paper in which Astwood's data has not been confirmed. In this series only 39% had any response whatsoever to thyroid therapy. It is striking that in no other published series has the care been taken as did Astwood to ensure the suppression of each gland.

81. Elgee, Neil J. Goitrous tracheal compression successfully treated medically. J. A. M. A. 183:819, 1963.

An example of the regression of an enormous goiter on thyroid therapy.

82. Bergfelt, G., and L. Risholm. Postoperative thyroid hormone in nontoxic goitre. Acta Chir. Scand. 126:531, 1963.

This paper emphasizes that postoperative thyroid therapy decreases the recurrences from nontoxic goiter; 0 of 86 patients who received thyroxine had a recurrence whereas 10% of those who received no thyroxine had recurrences.

83. Hales, I. B., J. Myhill, T. H. Oddie, and M. Croydon. Quantitative observations with the triiodothyronine suppression test of thyroid function. J. Clin. Endocrinol. 21: 189, 1961.

84. Friis, T. Effect of l-triiodothyronine on thyroid gland and its clinical application (Triiodothyronine Suppression Test). Acta Med. Scandinav. 173:569, 1963.

These two papers explain why some people with non-toxic goiter do not respond to thyroid therapy. Of the euthyroid patients who do not respond to 150 µg of TIT per day, most have non-toxic goiters. The triiodothyronine test should be considered definitive only if the patient suppresses. A negative test is not so meaningful since about 20% of clinically euthyroid people with non-toxic goiters do not suppress. These findings confirm the impression of Astwood that the dosage for each patient should be titrated individually.

85. Miller, J. M., R. C. Horn, and M. A. Block. Evolution of toxic nodular goiter. Arch. Int. Med. 113:72, 1964.

The autonomous thyroid nodule is probably a transition stage between TSH dependent goiter and toxic nodular goiter. Even so, the vast majority of autonomous nodules probably never progress to the toxic stage.

86. Cortell, Ruth. The effect of thyroxine on the response of the thyroid gland to thyrotropic hormone. Endocrinol. 35:488, 1944.

87. Ecklund, R., and R. Ryan. Suppression of release of radioactive iodine as a test of thyroid function. J. Clin. Endocrinol. 22:26, 1962.

Thyroid has been reported to have two different effects on thyroid function: 1.) to decrease the sensitivity of the thyroid to TSH (unconfirmed and thought to be unimportant), 2.) to decrease the secretion of TSH (the significant effect). As is emphasized in Ref. 87 decreased TSH secretion has two effects - decreased I^{131} uptake and decreased release of thyroxine from the gland. The latter function may have the most usefulness ultimately in the TSH suppression test.

THE CANCER PROBLEM

88. Cole, W. H., D. P. Slaughter, and L. J. Rossiter. Potential dangers of nontoxic nodular goiter. J. A. M. A. 127:883, 1945.

A statement of the extreme view that non-toxic nodular goiter is a premalignant lesion and should routinely be removed as prophylaxis against cancer.

89. VandenLaan, W. P. The occurrence of carcinoma of the thyroid gland in autopsy material. N. E. J. M. 237:231, 1947.

90. Mustacchi, P., and S. J. Cutler. Some observations on the incidence of thyroid cancer in the United States. N. E. J. M. 255:889, 1956.

Both in autopsy material and in cumulative risk statistics carcinoma of the thyroid as a cause of death is extraordinarily rare - the cumulative risk figure being 1.5 to 4 per 100,000 population, depending on the area of the country.

91. Mortensen, J. D., W. A. Bennett, and L. B. Woolner. Surgical Forum 5:659, 1954.

In 1000 consecutive autopsies at the Mayo Clinic the rate of incidence of thyroid cancer was almost the same in clinically normal thyroid glands as in clinically suspect and surgically removed nodular thyroid glands (around 4%).

92. Zimmerman, L. M., and D. H. Wagner. Reglation of nodular goiter to thyroid carcinoma. Ch. in Clinical Endocrinology I, Ed. by E. B. Astwood. New York: Grune and Stratton, 1960, p. 160.

There are probably three reasons for the increased diagnosis of carcinoma of the thyroid - 1.) an increase in the number of malignancies as a whole, 2.) an increased exposure to ionizing radiation in the area of the neck in childhood, and 3.) an apparent increase probably due to routine detailed histological examination of the thyroid and to the complexities of the histological diagnosis of malignancy in this tissue. At the Mayo Clinic at least what is now recognized as metastatic papillary carcinoma was previously called "lateral abberrant thyroid".

93. Woolner, L. B., M. L. Lemmon, O. H. Beahrs, B. M. Black, and F. R. Keating. Occult papillary carcinoma of the thyroid gland: a study of 140 cases observed in a 30-year period. J. Clin. Endocrinol. 20:89, 1960.

Of 140 small papillary thyroid carcinomas discovered for the most part during other surgery at the Mayo Clinic, 58 had nodal metastases and 82 had none. Of these patients followed for 3-32 years not one in either category has died of cancer of the thyroid and not one has evidence of other metastasis.

94. Hirabayashi, R. N., and S. Lindsay. Carcinoma of the thyroid gland: A statistical study of 390 patients. J. Clin. Endocrinol. 21:1596, 1961.

Of 390 patients with carcinoma of the thyroid of all types only 19% die of the disease. Furthermore, when broken down further only 11% of patients with papillary carcinoma die of the disease whereas 33% of patients with follicular and 76% of patients with anaplastic carcinoma die - the latter two are less common lesions.

95. Robinson, E., and A. Hochman. The treatment of thyroid carcinoma. Cancer 15:1130, 1962.

96. Crile, G. Papillary carcinoma of the thyroid. Ch. in Clinical Endocrinol. I, Ed. by E. B. Astwood. New York: Grune and Stratton, 1960, p. 168.

Of the various forms of therapy for carcinoma of the thyroid only two forms of therapy can be shown to prolong survival - dessicated thyroid therapy in papillary adenocarcinoma, and I^{131} in those rare tumors which concentrate I^{131}. Crile emphasizes furthermore that the worst of all possible events in carcinoma of the thyroid is the development of hypothyroidism which must be carefully prevented.

97. Sokal, J. E. The problem of malignancy in nodular goiter - recapitulation and a challenge. J. A. M. A. 170:405, 1959.

98. Sokal, J. E. The incidence of thyroid cancer and the problem of malignancy in nodular goiter. Ch. in Clinical Endocrinology I. Ed. by E. B. Astwood. New York: Grune and Stratton, 1960, p. 168.

99. Shimaoka, K., J. Badillo, J. E. Sokal, and F. C. Marchetta. Clinical differentiation between thyroid cancer and benign goiter. J. A. M. A. 181:179, 1962.

100. Bowers, O. M., and J. B. Vander. Thyroid nodules and thyroid malignancy. Ann. Int. Med. 57:245, 1962.

Furthermore, the clinical differentiation between carcinoma of the thyroid and benign goiter can be made with considerable accuracy without in any way endangering patients.

101. Becker, F. O., P. G. Economou, and T. B. Schwartz. The occurrence of carcinoma in "hot" thyroid nodules. Ann. Int. Med. 58:877, 1963.

102. Shimaoka, K., and J. E. Sokal. Differentiation of benign and malignant nodules by scintiscan. Arch. Int. Med. 114:36, 1964.

The above reports emphasize the rarity with which carcinomas concentrate I^{131}. A cold nodule does not mean carcinoma, however, since only a small fraction of these have even the histological criteria for malignancy.

103. Veith, F. J., J. R. Brooks, W. P. Grigsby, and H. A. Selenkow. The nodular thyroid gland and cancer. N. E. J. M. 270:431, 1964.

A view of the conservative approach generally in agreement with that of Sokal now taken by the Department of Surgery at the Brigham.

104. Means, J. H., L. J. deGroot, and J. B. Stanbury. The Thyroid and Its Diseases, 3rd Ed. New York: McGraw-Hill Book Co., 1963.

A reminder that although the concept of thyroidectomy for cancer prophylaxis is no longer supportable, there are other indications for surgery of non-toxic goiter.

105. Jones, K. H., and P. Fourman. Prevalence of parathyroid insufficiency after thyroidectomy. Lancet II:121, July 20, 1963.

A recent reminder that total thyroidectomy is not a benign procedure. In one hospital even when the inferior thyroid arteries were preserved 28% of patients had partial hypoparathyroidism subsequently as judged by an EDTH provocative test.