

## Chapter 17. Multinodular Goiter

The normal thyroid gland is a fairly homogenous structure, but nodules often form within its substance. These nodules may be only the growth and fusion of localized colloid-filled follicles, or more or less discrete adenomas, or cysts. Nodules larger than 1 cm may be detected clinically by palpation. Careful examination discloses their presence in at least 4% of the general population. Nodules less than 1 cm in diameter and not clinically detectable unless located on the surface of the gland, are much more frequent. The terms adenomatous goiter, nontoxic nodular goiter, and colloid nodular goiter are used interchangeably as descriptive terms when a multinodular goiter is found.

### INCIDENCE

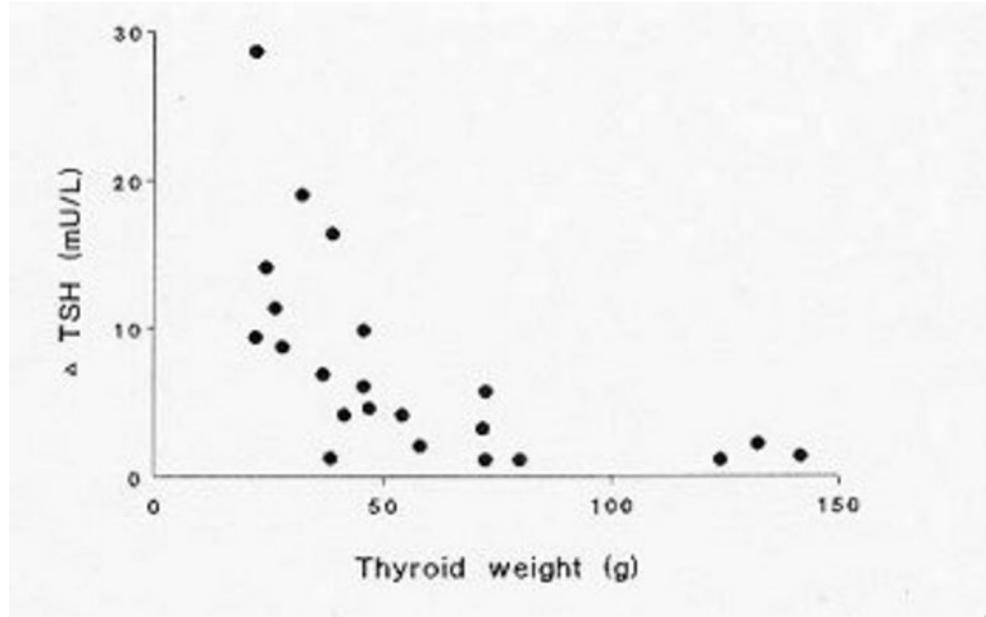
The incidence of goiter, diffuse and nodular, is very much dependent on the status of iodine intake of the population. In areas of iodine deficiency, goiter prevalence may be very high and especially in goiters of longstanding, multinodularity develops frequently (see Chapter 20). The incidence of multinodular goiter in areas with sufficient iodine intake has been documented in several reports. In a comprehensive population survey of 2,749 persons in northern England, Tunbridge et al.<sup>1</sup> found obvious goiters in 6.9% with a female/male ratio of 13:1. Single and multiple thyroid nodules were found in 0.8% of men and 5.3% of women, with an increased frequency in women over 45 years of age. Routine autopsy surveys and the use of sensitive imaging techniques produces a much higher incidence. In three reports nodularity was found in 30% to 60% of subjects in autopsy studies, and in 16% to 67% in prospective studies of randomly selected subjects on ultrasound.<sup>2</sup> In Framingham the prevalence of multinodular goiter as found in a population study of 5234 persons over 60 years was 1%.<sup>3</sup> Recent results from Singapore shows a prevalence of 2.8%.<sup>4</sup> In an evaluation in 2,829 subjects, living in southwestern Utah and Nevada (USA between 31 and 38 years) of age, 2.3% had non-toxic goiter, including, 18 single nodules, 3 cysts, 38 colloid goiters and 7 without a histological diagnosis. No mention was made of multinodular goiters, although some might have been present in the colloid and unidentified group.<sup>5</sup> In general, in iodine sufficient countries the prevalence of multinodular goiter is not higher than 4%.<sup>6</sup>

### CAUSE

The first comprehensive theory about the development of multinodular goiter was proposed by David Marine and studied further by Selwyn Taylor, and can be considered one of the classics in this field. Nodular goiter may be the result of any chronic low-grade, intermittent stimulus to thyroid hyperplasia. Supporting evidence for this view is circumstantial. David Marine first developed the concept, that in response to iodide deficiency, the thyroid first goes through a period of hyperplasia as a consequence of the resulting TSH stimulation, but eventually, possibly because of iodide depletion or a decreased requirement for thyroid hormone, enters a resting phase characterized by colloid storage and the histologic picture of a colloid goiter. Marine believed that repetition of these two phases of the cycle would eventually result in the formation of nontoxic multinodular goiter.<sup>8</sup> Studies by Taylor of thyroid glands removed at surgery led him to believe that the initial lesion is diffuse hyperplasia, but that with time discrete nodules develop.<sup>9</sup>

By the time the goiter is well developed, serum TSH levels and TSH production rates are usually normal or even suppressed.<sup>10</sup> For example, Dige-Petersen and Hummer evaluated basal and TRH-stimulated serum TSH levels in 15 patients with diffuse goiter and 47 patients with nodular goiter.<sup>11</sup> They found impairment of TRH-induced TSH release in 27% of the patients with nodular goiter, suggesting thyroid autonomy, but in only 1 of the 15 with diffuse goiter. Smeulers et al. <sup>22</sup>, studied clinically euthyroid women with multinodular goiter and found that there was an inverse

relationship between the increment of TSH after administration of TRH, and size of the thyroid gland (Figure 17-1). It was also found that, while being still within the normal range, the mean serum T3 concentration of the group with impaired TSH secretion was significantly higher than the normal mean, whereas the mean value of serum T4 level was not elevated.<sup>12</sup> These and other (1) results<sup>12</sup> are consistent with the hypothesis that a diffuse goiter may precede the development of nodules. They are also consistent with the clinical observation that, with time, autonomy may occur, with suppression of TSH release, even though such goiters were originally TSH dependent.



**Figure 1. Relationship of TSH (after 400 m g TRH i.v.) and thyroid weight (g) in 22 women with clinically euthyroid multinodular goiter (with permission ref. 12).**

Comprehensive reviews about insights into the evolution of multinodular goiter have been published by Studer et al.<sup>13-16</sup> An adapted summary of the major factors that are discussed by these authors is presented in Table 17-1 and will be referred to in the discussion that follows.

**Table 1. Factors That May Be Involved in the Evolution of Multinodular Goiter.**

<i>Primary factors</i>
<ul style="list-style-type: none"> <li>• Functional heterogeneity of normal follicular cells, cause unknown, possibly genetic and acquisition of new inheritable qualities by replicating epithelial cells</li> <li>• Subsequent functional and structural abnormalities in growing goiters</li> </ul>
<i>Secondary factors (Stimuli to New Follicle Generation)</i>

- TSH (induced by, e.g., iodine deficiency, goitrogens, inborn errors of thyroid hormone synthesis)
- Other thyroid-stimulating factors

## PRIMARY FACTORS

Genetic heterogeneity of normal follicular cells and acquisition of new inheritable qualities by replicating epithelial cells.

It has been shown that cells of many organs, including the thyroid gland, are often polyclonal, rather than monoclonal of origin. Also from a functional aspect it appears that through developmental processes the thyroid epithelial cells forming a follicle are functionally polyclonal and possess widely differing qualities regarding the different biochemical steps leading to growth and to thyroid hormone synthesis like e.g. iodine uptake (i.e. transport), thyroglobulin production and iodination, iodotyrosine coupling, endocytosis and dehalogenation. As a consequence there is some heterogeneity of growth and function within a thyroid and even within a follicle (Fig. 17-2). Studer et al 16a demonstrated the existence of monoclonal and polyclonal nodules in the same multinodular gland. They analyzed 25 nodules from 9 multinodular goiters and found 9 to be polyclonal and 16 monoclonal. Three goiters contained only polyclonal nodules and 3 contained only monoclonal nodules. In 3 goiters poly- and monoclonal nodules coexisted in the same gland.

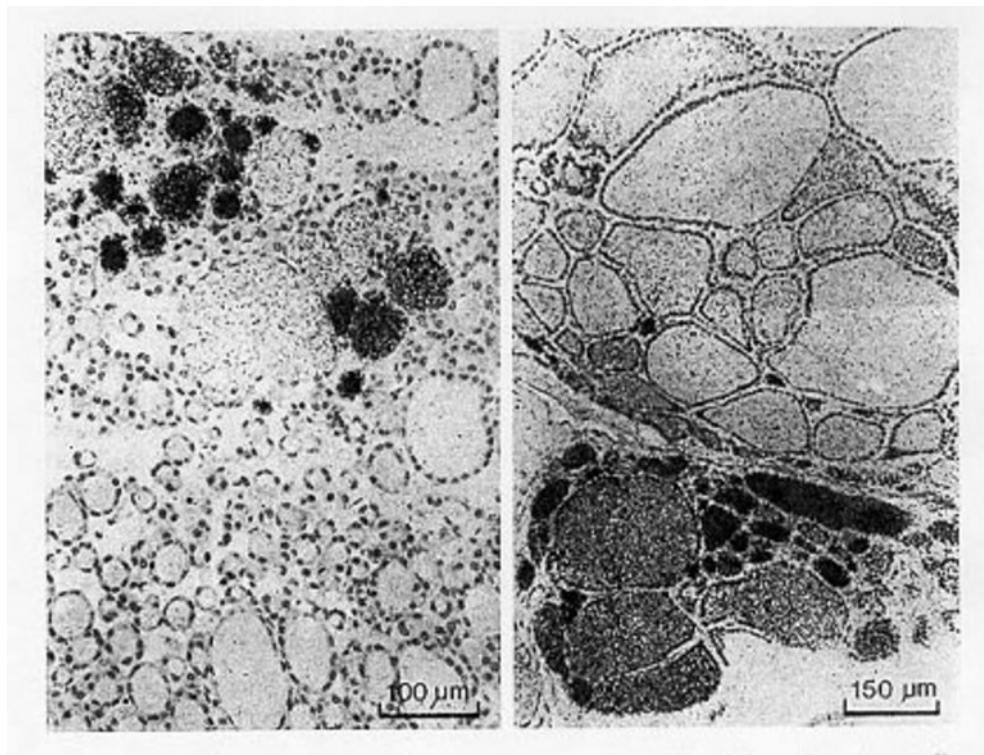


Figure 2. Heterogeneity of morphology and function in a human multinodular goiter. Autoradiographs of two different areas of a typical multinodular euthyroid human goiter excised after administration of radioiodine tracer to the patient. There

**are enormous differences of size, shape and function among the individual follicles of the same goiter. Note also that there is no correlation between the size or any other morphological hallmark of a single follicle and its iodine uptake. (with permission ref. 15).**

Newly generated cells may acquire qualities not previously present in mother cells. These qualities could subsequently be passed on to further generations of cells. A possible example of this process is the acquired abnormal growth pattern that is reproduced when a tissue sample is transplanted into a nude mouse.<sup>16b</sup> Other examples are acquired variable responsiveness to TSH.<sup>13</sup> These changes may be related to mutations in oncogenes such as ras, or others which do not produce malignancy per se, but that can alter growth and function. An example of acquisition of genetic qualities is the identification in the last few years of constitutively activating somatic mutations not only in solitary toxic adenoma, but also in hyperfunctioning nodules of toxic multinodular goiters. So far these mutations in MNG have only been found in the TSH-receptor (TSHR) gene, and not in the Gs-alpha gene. Different somatic mutations are found in exon 9 and 10 of the TSHR gene and the majority of mutations that are present in toxic adenomas are also found in toxic nodules in multinodular goiter. Sometimes different toxic nodules in the same multinodular gland harbor different mutations.<sup>16c,d</sup> An important fact is the finding of a germline mutation of codon 727 of the TSHR gene that is specifically associated with MNTG (16e). Also evidence was found for linkage of familial euthyroid goiter to the recently identified locus for familial multinodular nontoxic goiter (MNG-1) on chromosome 14q<sup>16f</sup>. Perhaps MNTG constitutes a heterogeneous group consisting of MNG due to multiple autonomously functioning nodules generated by somatic mutations of the TSHR (and Gs-alpha?) gene, and MNG caused by a germline mutation(s) of this gene. TSH-R mutations have also been detected in microscopically hot areas in thyroids of patients living in an iodine deficient region<sup>17</sup>. Three dominant MNG loci have been identified in familial MNG, i.e. MNG1, 2 and 3. In MNG1 a major locus was identified on chromosome 14q by a genomic search on a single large Canadian family with 18 cases of nontoxic multinodular goiter. Although the gene for TSHR is located on this chromosome, it was excluded as a candidate gene. In the analysis of an Italian three-generation pedigree with familial MNG2, including 10 affected females and 2 affected males, a novel MNG locus was searched for. Because no male-to-male transmission was present in the study pedigree, an X-linked autosomal dominant pattern of inheritance was hypothesized and confirmed. A significant LOD score was observed in the Xp22 region. A third locus, MNG3, for a dominant form of familial multinodular goiter was detected on 3q26.1-q26.3, in 2 independent Japanese families. This variant however was characterized by congenital hypothyroidism. For a review on the pathogenesis and genetics of multinodular goiter see ref (17b)

Subsequent functional and structural abnormalities in growing goiters

Follicles of second and following generations are less well formed and compartmentalization of key enzymes may become altered. Intercellular communication may become disrupted. As a consequence inter- and intrafollicular growth and function may become poorly integrated resulting in further heterogeneity.<sup>13,18</sup>

## SECONDARY FACTORS

The secondary factors discussed below stimulate thyroid cell growth and/or function and, because of differences in cellular responsiveness that are presumed to exist, aggravate the expression of heterogeneity which leads to further growth and focal autonomic function of the thyroid gland. Local necrosis, cyst formation sometimes with bleeding and fibrosis may be the anatomical end stage of such processes.<sup>13</sup> (see pathology)

## Iodine Deficiency

Stimulation of new follicle generation seems to be necessary in the formation of simple goiter. Evidence accumulated from many studies indicates that iodine deficiency or impairment of iodine metabolism by the thyroid gland, perhaps due to congenital biochemical defects, may be an important mechanism leading to increases in TSH secretion.<sup>18a</sup> Since in experimental animals the level of iodine per se may modulate the response of thyroid cells to TSH, this is an additional mechanism by which relatively small increases in serum TSH level may cause substantial effects on thyroid growth in iodine-deficient areas. Koutras et al.<sup>19</sup> found that the thyroidal iodine clearance of patients with nontoxic nodular goiter in Scotland was, on average, higher than that in normal persons (Fig. 17-3). This finding was interpreted as a reflection of a suboptimal iodine intake by such patients. Similar observations have been made in Belgium and France but not in the United States. When data published from various major cities in Western Europe, regarding thyroid volume and iodine excretion are put together,<sup>20</sup> an inverse relation is found between urinary iodine excretion and thyroid volume (Fig. 17-4). Physiologic stresses, such as pregnancy, may increase the need for iodine and require thyroid hypertrophy to increase iodine uptake that might otherwise satisfy minimal needs. An elevated renal clearance of iodine occurs during normal pregnancy.<sup>21,22</sup> It has been suggested that in some patients with endemic goiter there are similar increases in renal iodine losses.<sup>23,24</sup> Increased need for thyroxin during pregnancy may also lead to thyroid hypertrophy when iodine intake is limited. Iodide need in pregnancy is increased by increased iodide loss through the kidneys, but also because of significant transfer of thyroid hormone from the mother to the fetus.<sup>25</sup> Glinoeer and co-workers showed that, especially in areas of moderate iodine intake, thyroid volume increase is predominantly effected by a higher HCG serum concentration during the first trimester of pregnancy, and by a slightly elevated serum TSH level present at delivery.<sup>20</sup>

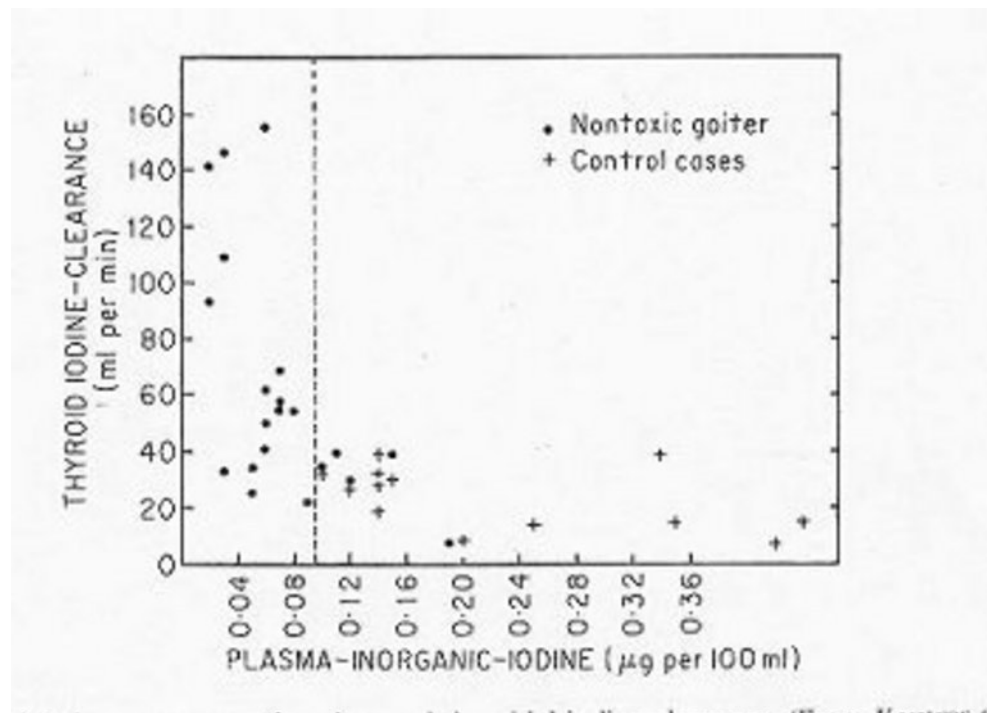


Figure 3. Relationship between nontoxic goiter and thyroidal iodine clearance (with permission ref. 19).

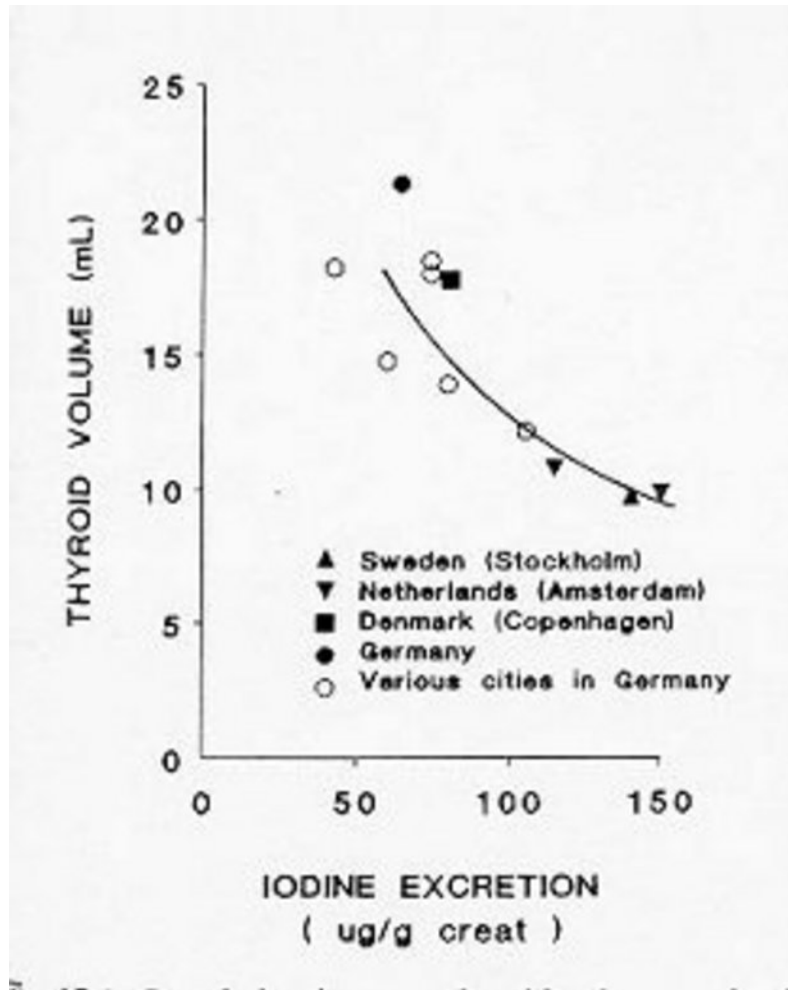


Figure 4. Correlation between thyroid volume and urinary iodine excretion in normal populations from various areas (with permission ref. 20).

### Dietary Goitrogens

Patients occasionally have thyroid enlargement either because of goitrogenic substances in their diet<sup>27</sup> or because of drugs that have been given for other conditions. Peltola<sup>28</sup> has shown this response experimentally by feeding rats minute doses of a natural goitrogen over many months. Similar results have been obtained by Langer<sup>29,30</sup> using combinations of the three most prevalent goitrogens contained in cabbage. The explanation for the effect of such substances is that the goitrogen is much more effective at the level of iodothyronine synthesis than at earlier steps in hormone production such as iodide trapping. Thus, the RAIU may be high, but with a block in hormone synthesis the stage would be set for the production of a goiter. This possibility remains to be proved in humans, but one might surmise that, if true, it would operate most effectively in a situation of borderline iodine supply. As discussed in Chapter 5, the goitrogen KSCN potentiates the effect of severe iodine deficiency in endemic areas of Africa.

### Inherited Defects in T4 Synthesis

An intriguing clue to the cause of nontoxic goiter in some patients is that it is familial. No particular pattern of inheritance has been found in these situations, although the

condition can often be traced through several generations. Occasionally, other members of the family may have Graves' disease. One might propose that patients with nontoxic goiter are heterozygous for genes that in the homozygous state may lead to clinically apparent hypothyroidism. Some investigators have evaluated iodide transport in patients with multinodular goiter and found it to be normal.<sup>31</sup> Parker and Beierwaltes<sup>32</sup> observed that many relatives of patients with defective iodine organification had goiter, but the results of iodine-binding studies were normal in these subjects. Some relatives of patients with the iodotyrosine halogenase defect have goiter and are euthyroid. In the latter instance, it has been possible to demonstrate that relatives have a deficiency in the deiodinating enzyme system, but this deficiency is not severe enough to cause hypothyroidism. Similar results were reported by McGirr.<sup>33</sup>

R.S., 42-Year-Old Man: Multinodular Goiter Produced by a Congenital Metabolic Defect.

The birth and early development of this clerk were entirely normal. His progress in school was slow, but he managed to complete trade school. A goiter was first noted at age 14; because of slowly increasing pressure symptoms, it necessitated a subtotal thyroidectomy 9 years later. The specimen showed hyperplasia and involution. By age 37 a goiter again was present. The patient ultimately sought help because of difficulty in passing a preemployment examination. His mother had a goiter, and one sister died at age 13 at operation for removal of a goiter. Two other siblings were well.

The patient appeared well developed and adequately nourished. The thyroid was four times the normal size, lobulated, and without a bruit or thrill. The patient's intelligence was less than average. His physical examination was otherwise normal. The RAIU was 60% at 2 hours and 82% at 24 hours. The PBI concentration in serum was 4.8 m g/dl (normal, 4-8 m g/dl).

A second subtotal thyroidectomy was performed. Slices from the specimen deiodinated MIT and DIT normally. The tissue was fractionated by centrifugation, and 99% of labeled iodine was found in the 1000,000 × g supernatant fraction. On ultracentrifugation, 51% of the protein was present as a 19.4 S component and 49% as a 4.3 S component. The latter fraction, which would contain lightweight proteins such as albumin, was much increased over normal values. On enzymatic digestion of the supernatant fraction (presumably containing TG), 40% of the <sup>131</sup>I, administered prior to surgery, was DIT; 21%, MIT; and 3%, iodothyronine. Twenty-one percent resisted hydrolysis. Electrophoresis of the supernatant fraction showed that <sup>131</sup>I was associated with a visible TG band, and in addition, a protein moving in the position of albumin, present in high concentration. This protein behaved immunologically as albumin. It was estimated that the thyroid contained approximately 5 g/dl of this iodinated albumin or albumin-like protein.

The pathologic diagnosis was multinodular goiter with multiple adenomas. Numerous adenomas of the fetal and embryonal type were interspersed with colloid nodules; the picture suggested prolonged stimulation of the thyroid gland.

After the second operation, the patient was maintained on thyroid hormone replacement and did well. There was no further recurrence of the goiter. This case illustrates the development of multinodular goiter in a patient with an inherited defect in thyroid hormone biosynthesis.

The appearance of the goiter by age 14, the strong familial tendency to thyroid disease, and the mental retardation, all suggested that this patient had a congenital goiter that may have been associated with hypothyroidism during early life. The tendency of the goiter to recur, as well as the histologic pattern of the second surgical specimen, supported the interpretation that the goiter grew in response to an abnormality in hormone synthesis. Metabolic compensation was apparently achieved during adult life by means of hypertrophy of the gland. The thyroid appeared to form and release into the serum an abnormal iodoprotein. This iodoprotein was metabolically inactive, and it indicated inefficient use of iodide by the thyroid. Formation of

this protein presumably was secondary to some metabolic block in hormone synthesis.

Despite the possibility that inherited defects are involved in some patients with multinodular goiter, most have been completely normal when examined specifically for such defects. Major problems of analysis are the low sensitivity to identify recessive states and the marked heterogeneity of function that exists within a single gland.<sup>13</sup> For example, Niepomniszcze and co-workers<sup>34</sup> evaluated peroxidase function in 13 patients with nontoxic multinodular goiter. Both "cold" and "warm" nodules were identified by scintiscanning before thyroidectomy. The iodide peroxidase activity of cold nodules was in general reduced, whereas in 10 warm nodules studied, 7 had normal activity and 3 decreased activity. Thus, one may conclude that the cold nodules of these multinodular glands, were peroxidase deficient. However, in the same glands, normal activity could be found in other nodules that were active in concentrating RAI. Heterogeneity of iodide organification was confirmed in the studies of Peter et al.<sup>35</sup> and summarized by Studer.<sup>36</sup> By autoradiography two types of cold follicles were found, namely those that failed to accumulate iodide because of deficient trapping and those that could transport iodide but could not organify it, suggesting failure of apical membrane peroxidase.<sup>37</sup> Three TSH dependent enzymic activities, i.e. peroxidase, NADPH-cytochrome-c reductase and monoamine oxidase, showed dissimilar activity within a single tissue sample and among different tissues of multinodular goiters<sup>37a</sup> As in multinodular goiter not only distinct nodules are discernable, but thyroid tissue is in general goitrous, it would seem reasonable to assume that some form of a partial biosynthetic abnormality is the most likely explanation for sporadic multinodular goiter. This concept appears to be borne out in the reported family in which goiter was associated with a mutation in the TG gene in the area of a "hormonogenic" thyroxin residue.<sup>38</sup> Apart from this phenomenon affecting the whole thyroid gland, somatic mutations of the TSH-R additionally cause growth and autonomous function of some nodules present in this type of goiter.

## Other Thyroid-Stimulating Factors

Other substances that could be involved in stimulating thyroid enlargement are epidermal growth factor (EGF) and insulin-like growth factors (IGF). EGF stimulates the proliferation of thyrocytes from sheep, dogs, pigs, calves, and humans.<sup>42</sup> While stimulating growth, EGF reduces trapping and organification of iodide, TSH receptor binding, and release of thyroglobulin, T3 and T4. On the other hand TSH may modulate EGF binding to thyroid cell membranes and thyroid hormone may stimulate EGF production and EGF receptor number.<sup>42</sup> In a study on adenomatous tissue, obtained from patients with multinodular goiter, it was found, by immunohistochemistry, that expression of EGF was increased.<sup>43</sup> IGF-2 interacts with trophic hormones to stimulate cell proliferation and differentiation in a variety of cell types. The interaction between TSH and IGF-2 is synergistic.<sup>44</sup> Increased IGF-I expression may contribute to goiter formation.<sup>45</sup> A similar synergistic effect may exist between IGF-I and TSH<sup>46</sup>. This synergism on DNA synthesis is mediated by complex interactions including the secretion of one or more autocrine amplification factors. Non-functioning nodules in patients with multinodular goiter contain the same IGF-1 receptors that are present in the normal adjacent extra-nodular follicles but are expressed in higher concentrations.<sup>47</sup> Fibroblast growth factor (FGF)- 1, stimulates colloid accumulation in thyroids of rats but only in the presence of TSH.<sup>48</sup> Expression of FGF-1 and -2 and FGF-receptor- 1 accompany thyroid hyperplasia and may play a role in development of multinodular goiter.<sup>48a</sup> Fancia et al.<sup>48b</sup> found that in goiters with aneuploid components growth rate was higher than when euploid components were present (48c.) Other factors promoting cell growth and differentiation have been identified in the past decade. These include cytokines, acetylcholine, norepinephrine, prostaglandins, substances of neural origin like vasoactive intestinal peptide, and substances of C-cell origin. It is however not known to what extent these compounds play a role in the genesis of multinodular goiter. These substances are discussed in Chapter 1 and

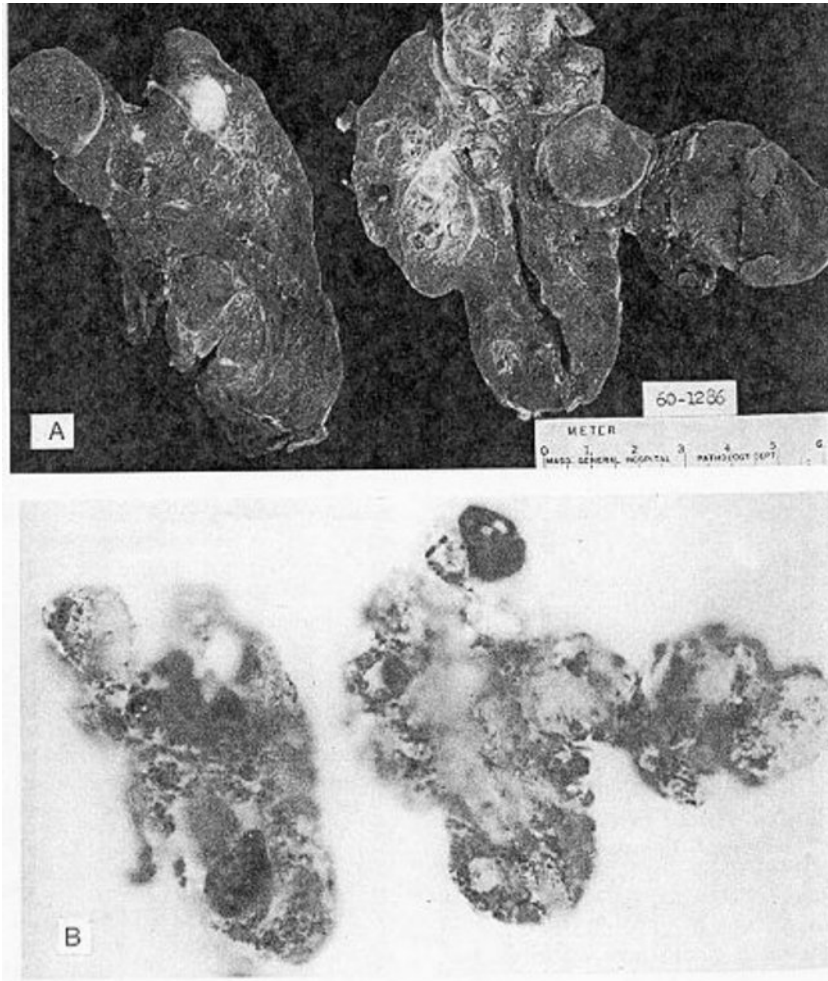
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The hypothesis that the development of thyroid autonomy is due to a gradual increase in the numbers of cells having relatively autonomous thyroid hormone synthesis is supported by the 27% prevalence of impaired TSH responses to TRH in patients with nodular goiter as opposed to such responses in only 1 of 15 patients with diffuse goiter.<sup>11</sup> Such partial autonomy may appear only with time and could possibly be prevented by TSH-suppressive therapy. The fact that it is possible to induce hyperthyroidism in some patients with multinodular goiters by administration of iodide suggests that certain of the nodules in the multinodular gland are autonomous but unable under normal iodine intake to concentrate sufficient quantities of iodide to cause hyperthyroidism.<sup>49</sup> Presumably iodide administration provides sufficient substrate for generation of excessive amounts of hormone, although it does not readily account for the long persistence of the hyperthyroidism in some of those cases.

Thus, there may be several etiologic factors in simple and nodular goiter, and some of these factors may act synergistically. The end result is a collection of heterogeneously functioning thyroid follicles, some of which may be autonomous and produce sufficient amounts of thyroid hormone to cause hyperthyroidism.

## **PATHOLOGY**

Although it is rare to obtain pathological examination of thyroid glands in the early phase of development of multinodular goiters, such glands should show areas of hyperplasia with considerable variation in follicle size. The more typical specimen coming to pathologists is the goiter that has developed a nodular consistency. Such goiters characteristically present a variegated appearance, with the normal homogeneous parenchymal structure deformed by the presence of nodules (Fig. 17-5a,b, below). The nodules may vary considerably in size (from a few millimeters to several centimeters); in outline (from sharp encapsulation in adenomas to poorly defined margination for ordinary nodules); and in architecture (from the solid follicular adenomas to the gelatinous, colloid-rich nodules or degenerative cystic structures). The graphic term Puddingstone goiter has been applied. Frequently the nodules have degenerated and a cyst has formed, with evidence of old or recent hemorrhage, and the cyst wall may have become calcified. Often there is extensive fibrosis, and calcium may also be deposited in these septae. Scattered between the nodules are areas of normal thyroid tissue, and often-focal areas of lymphocytic infiltration. Radioautography shows a variegated appearance, with RAI localized sometimes in the adenomas and sometimes in the paranodular tissue. Occasionally, most of the radioactivity is confined to a few nodules that seem to dominate the metabolic activity of the gland.



**Figure 5. (A) Cross section of multinodular goiter. (B) Gross radioautograph of the thyroid in part a. Observe the variation in  $^{131}\text{I}$  uptake in different areas.**

If careful sections are made of numerous areas, 4-17% of these glands removed at surgery will be found to harbor microscopic papillary carcinoma<sup>43,50-52</sup> The variable incidence can most likely be attributed to the different criteria used by the pathologists and the basis of selection of the patients for operation by their physicians. These factors are discussed below.

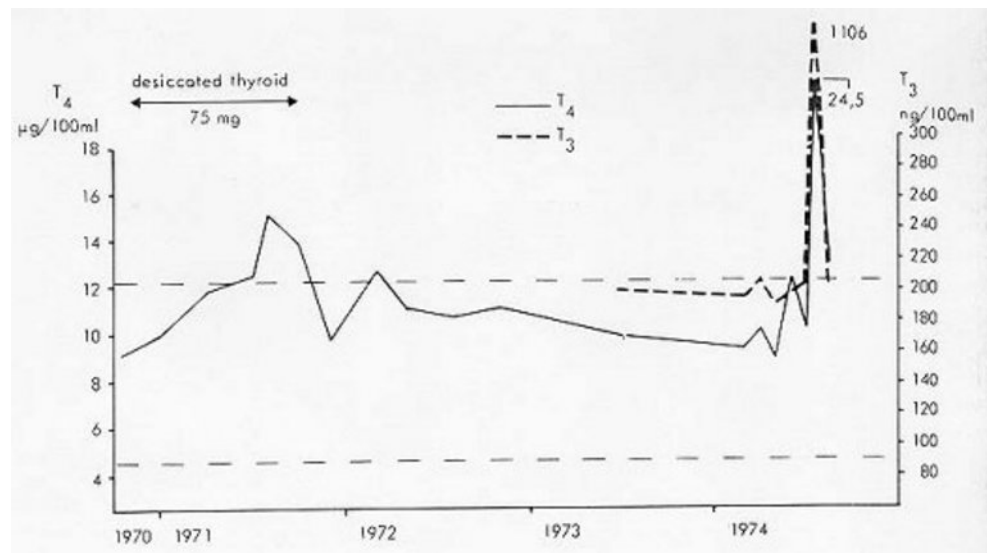
## NATURAL HISTORY OF THE DISEASE

Multinodular goiter is probably a lifelong condition that has its inception in adolescence or at puberty. Minimal diffuse enlargement of the thyroid gland is found in many teenage boys and girls, and is almost a physiologic response to the complex structural and hormonal changes occurring at this time. It usually regresses, but occasionally (much more commonly in girls) it persists and undergoes further growth during pregnancy. This course of events has not been documented as well as might be desired in sporadic nodular goiter, but it is the usual evolution in areas where mild endemic goiter is found.

Patients with multinodular goiter seek medical attention for many reasons. Perhaps most commonly they consult a physician because a lump has been discovered in the neck, or because a growth spurt has been observed in a goiter known to be present for a long time. Sometimes the increase in the size of the goiter will cause pressure symptoms, such as difficulty in swallowing, cough, respiratory distress, or the feel-

ing of a lump in the throat. Rarely, an area of particularly asymmetrical enlargement may impinge upon or stretch the recurrent laryngeal nerve. Commonly the goiter is discovered by a physician in the course of an examination for some other condition. An important scenario is for the patient to seek medical attention because of cardiac irregularities or congestive heart failure, which proves to be the result of slowly developing thyrotoxicosis. (The issue is discussed more fully later in this chapter). Many times the goiter grows gradually for a period of a few too many years, and then becomes stable with little tendency for further growth. It is rare for any noteworthy spontaneous reduction in the size of the thyroid gland to occur, but patients often describe fluctuations in the size of the goiters and the symptoms they give. These are usually subjective occurrences, and more often than not the physician is unable to corroborate the changes that the patient describes. On the other hand, it could be that changes in blood flow through the enlarged gland account for the symptoms.

Occasionally, a sudden increase in the size of the gland is associated with sharp pain and tenderness in one area. This event suggests hemorrhage into a nodular cyst of the goiter, which can be confirmed by ultrasound. Within 3-4 days the symptoms subside, and within 2-3 weeks the gland may revert to its previous dimensions. In such a situation, acute thyrotoxicosis may develop and subside spontaneously<sup>53,54</sup> (Figure 17-6).



**Figure 6. T4 and T3 levels in a patient with multinodular goiter. Desiccated thyroid was withdrawn because of thyrotoxic symptoms. Note high T3 and T4 peak values in mid 1974 due to acute hemorrhage in thyroid nodule (with permission ref. 53).**

Rarely, if ever, do the patients become hypothyroid and if they do, the diagnosis is more probably Hashimoto's thyroiditis than nodular goiter. In a study in clinically euthyroid subjects with multinodular goiter, 13 out of 22 had subnormal TSH release after TRH.<sup>12</sup> If the goiter is present for a long time, thyrotoxicosis develops in a large number of patients. In a series collected many years ago at the Mayo Clinic, 60% of patients with MNG over 60 were thyrotoxic.<sup>55</sup> The average duration of the goiter before the onset of thyrotoxicosis was 17 years; the longer the goiter had been present, the greater was the tendency for thyrotoxicosis to develop. This condition appears to occur because with the passage of time, autonomous function of the nodules develops. In a more recent study of patients with euthyroid multinodular goiter, thyroid function was autonomous in 64 and normal in 26. After a mean follow-up of 5.0 years (maximum 12 years) 18 patients with autonomous thyroid function became overtly hyperthyroid and in 6 patients with primarily normal thyroid function autonomy developed.<sup>56</sup> In Figure 17-7 (below) the typical course of thyroid function tests is il-

lustrated in a patient with multinodular goiter starting from complete euthyroidism on to overt thyrotoxicosis. Occasionally a single discrete nodule in the thyroid gland becomes sufficiently active to cause thyrotoxicosis and to suppress the activity of the rest of the gland (see Chapt.13). If these patients are given thyroid hormone, continued function of nodules can be demonstrated by radioiodine scanning techniques. Thus, these nodules have become independent of pituitary control. When patients with euthyroid multinodular goiter are frequently tested, it appears that in some of them occasional transient increases of serum T3 and/of T4 are seen<sup>57</sup> (Figure 17-8, below). The possibility that the abrupt development of hyperthyroidism may follow administration of large amounts of iodine to these patients has already been mentioned.<sup>49</sup>

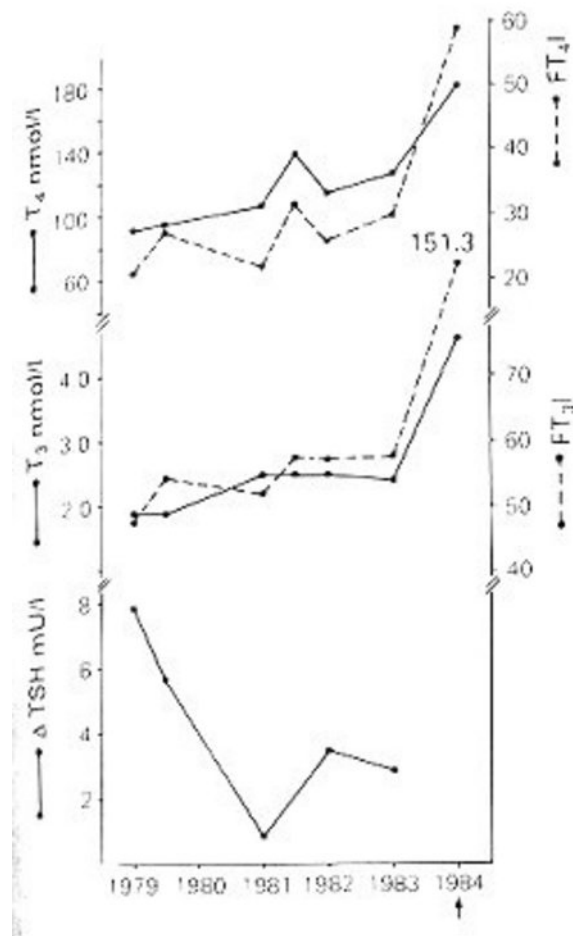


Figure 7. Course of thyroid function tests, including the increment of TSH in response to TRH in a patient who demonstrated the whole functional cycle from non-autonomy (1979), through autonomy (1981) up to overt hyperthyroidism (1984) (with permission ref. 56).

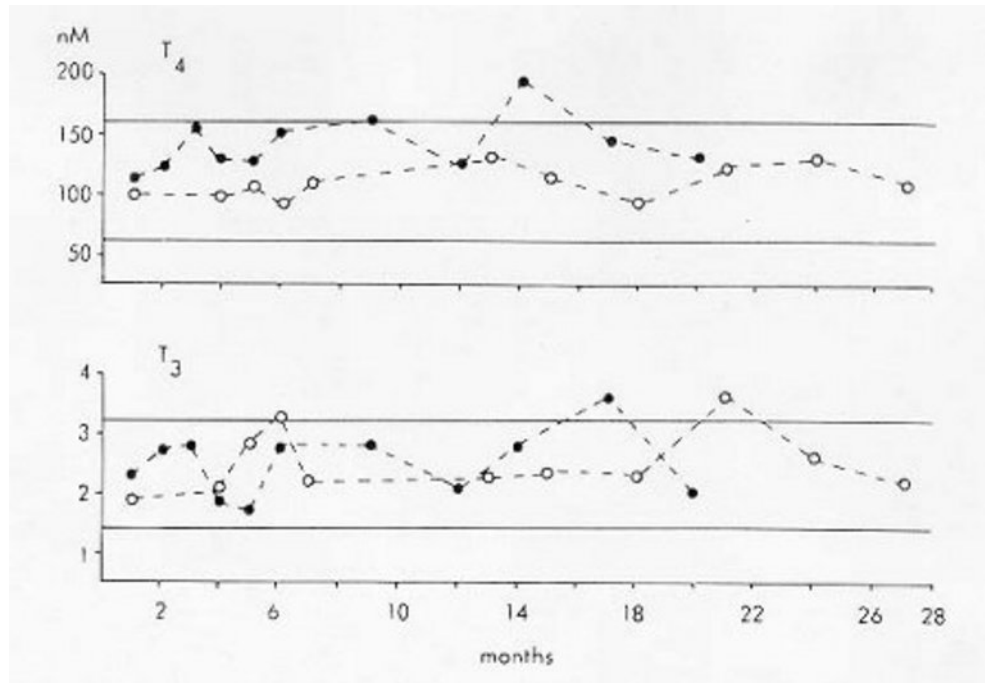


Figure 8. Serum T<sub>4</sub> and T<sub>3</sub> levels during a follow-up of 20 and 27 months in 2 patients ("---" and "—"), both aged 60 years, with euthyroid multinodular goiter. The continuous lines indicate 95 percent confidence limits of the normal range (with permission ref. 57).

Occasionally an invasive thyroid cancer develops in a multinodular goiter. This fact brings the discussion to one of the most serious problems relating to multinodular goiter, that of carcinoma.

## THE CARCINOMA PROBLEM

If surgical specimens of multinodular goiters are examined carefully, 4-17% are found to harbor a carcinoma.<sup>43,50-52</sup> These carcinomas vary widely in size and are typically of the papillary variety. Similar tumors are occasionally found in thyroid glands affected by Hashimoto's thyroiditis and in otherwise normal glands. Stoffer et al.<sup>58</sup> reported that 13% of the glands resected in thyroid operations for any reason contained papillary adenocarcinoma. In Japan, routine autopsies of patients who were not suspected of having thyroid disease and who had no known irradiation experience, 17% were found to have small carcinomas when careful serial sections of the thyroid glands were done.<sup>59</sup> If the figures of Stoffer et al, that were recently confirmed<sup>50</sup>, truly represent the prevalence of invasive carcinoma, one would certainly be forced to conclude that all multinodular goiters should be resected in order to prevent dissemination of malignant disease. However, it seems quite unlikely that all lesions that appear to satisfy the histological criteria for malignant neoplasia are potentially lethal. This view is strongly supported by the final report of the study on the significance of nodular goiter carried out by Vander et al.<sup>3</sup> in Framingham, Massachusetts. They followed for 15 years all 218 nontoxic thyroid nodules previously detected in a total population of approximately 5,000 persons. None of these lesions showed any clinical evidence of malignancy at the end of that time.

A strong case can be made for the view that there is only minimal risk from carcinoma in multinodular goiter. Sokal<sup>60,61</sup> has presented this argument in detail, and we can do no better than to borrow directly from his published analysis. The prevalence of clinical nodularity of the thyroid is at least 4%, or 40,000 per 1,000,000 population.<sup>2</sup> Use of a much higher figure can be justified by the autopsy studies described above.

Despite the high frequency of nodular goiter, only 36-60 thyroid tumors appear per 1,000,000 persons each year.<sup>62,63</sup> or by analysis of reported statistics on thyroid surgical specimens.<sup>61</sup> A recent national cancer survey in the United States found an incidence of 40 per 1,000,000.<sup>63</sup> Riccabona<sup>64</sup> published an overview of the incidence of thyroid cancer in 40 countries, both with and free of endemic goiter. The range of incidence varied between 7.5 and 56 per 1,000,000 persons each year. There is no increased goiter rate in endemic goiter areas. The prevalence of significant thyroid carcinoma at routine autopsy is less than 0.1%<sup>61,65,66</sup> and persons with this type of tumor are probably examined as frequently as are those with other forms of neoplasia. The United States mortality figures for thyroid carcinoma are constant at about 6 per 10-6 population each year. Riccabona also summarized death rates from thyroid cancer in non-endemic and in endemic countries.<sup>64</sup> For Austria this was 16 per 10-6 per year in 1952 and 10 per 10-6 per year in 1983. For Switzerland this was in 1952, 18 per 10-6 per year and in 1979, 9 per 10-6 per year. The death rate per year for the United States in 1979 was 3 per 10-6, for Israel in 1952 1 per 10-6 per year and for the UK 7 per 10-6 in 1963. Death rates from thyroid cancer in endemic goiter areas from regions in Austria, Yugoslavia, Finland and Israel were between 10 and 16 per 10-6 per year between 1980 and 1984.

Lastly, it should be recognized that meticulous examination of autopsy specimens from persons dying of nonthyroid disease may show small (less than 0.5 cm) papillary lesions in 4-24% of human thyroid glands.<sup>67-69</sup> A recent report of 1020 sequential autopsies revealed the presence of microscopic papillary carcinoma in 6%.<sup>66</sup> Although the prevalence of this type of lesion increases with age, there is no question that such lesions may be present even in younger persons. The proportion of these lesions that even become clinically apparent is unknown, but their presence in otherwise normal thyroid glands should be kept in mind when evaluating reports of similar prevalences of thyroid carcinoma in multinodular thyroid glands.

If 4% of patients with nodular goiter actually have thyroid carcinoma, the prevalence of tumor in the general population would be 1,600 per 1,000,000. It is remarkable that only about 25 of these 1,600 hypothetical tumors would become apparent each year, or that only about 10 would prove fatal. Thus, there appears to be a gross discrepancy between the mortality from thyroid carcinoma and its reported frequency in surgical specimens of multinodular goiters. Reasonable arguments can be mustered in an effort to reconcile the information. Perhaps the most important single factor is selection. Persons with nodular goiter who come to operation are not representative of the general population but are patients with clinically significant thyroid disease who have been selected by their physicians for thyroid surgery. One of the factors controlling the selection process is the suspicion of malignant tumor. In fact, the selection process is especially good, as reflected by the high recovery of malignant thyroid tumors in patients operated on with this presumptive diagnosis.<sup>70</sup> A second factor is that the histologic diagnosis of thyroid carcinoma may not correlate well with true invasiveness. It is impossible to prove this thesis, but pathologists agree that the criteria for judging malignancy are variable and that it is exceedingly difficult to predict with any degree of certainty the growth potential of a particular thyroid lesion.

Other arguments may be used to defend a conservative therapeutic position. In the first place, the tumors that are usually found in multinodular goiters are papillary tumors, and their degree of invasiveness is low. Indeed, the survival rate for intrathyroid papillary carcinoma is only slightly less than that for normal persons of the same age and sex.<sup>71</sup> Furthermore, prophylactic subtotal thyroidectomy is not a guarantee of protection from cancer arising in a nodular goiter, since the process is usually diffuse, and it may be assumed that abnormal tissue is left in the neck after operation. In fact, unless replacement therapy is given, partial thyroidectomy might be expected to induce a tremendous growth stimulus in the remaining gland. A further point is that thyroidectomy, even in the best of hands, carries its own risk and its own morbidity, with dimensions comparable to those of missing a small papillary carcinoma within a multinodular goiter. Obviously this last possibility does not apply when a focus of unusual induration or rapid growth rate is detected clinically.

## SIGNS, SYMPTOMS AND DIAGNOSIS

Many of the symptoms of multinodular goiter have already been described. They are chiefly due to the presence of an enlarging mass in the neck and its impingement upon the adjacent structures. There may be dysphagia, cough, and hoarseness. Paralysis of a recurrent laryngeal nerve may occur when the nerve is stretched taut across the surface of an expanding goiter, but this event is very unusual. When unilateral vocal cord paralysis is demonstrated, the presumptive diagnosis is cancer. Pressure on the superior sympathetic ganglions and nerves may produce a Horner's syndrome.

As the gland grows it characteristically enlarges the neck, but frequently the growth occurs in a downward direction, producing a substernal goiter. A history sometimes given by an older patient that a goiter once present in the neck has disappeared may mean that it has fallen down into the upper mediastinum, where its upper limits can be felt by careful deep palpation. Hemorrhage into this goiter can produce acute tracheal obstruction. Sometimes substernal goiters are attached only by a fibrous band to the goiter in the neck and extend downward to the arch of the aorta. They have even been observed as deep in the mediastinum as the diaphragm. Occasionally the skilled physician can detect a substernal goiter by percussion, particularly if there is a hint from tracheal deviation, or the presence of a nodular mass in the neck above the manubrial notch.

Symptoms suggesting constriction of the trachea are frequent, and displacement of the trachea is commonly found on physical examination. Roentgenographic examination is useful in defining the extent of tracheal deviation and compression. Compression is frequently seen but rarely is functionally significant. The authors have expected to find softened tracheal cartilage after the removal of some large goiters, but tracheomalacia has been observed only on the rarest occasion. Patients may be remarkably tolerant of nodular goiter even when the enlargement is striking. This finding is especially true in the endemic goiter areas of the world. On the other hand, when the facilities for removal are available, most patients like to be rid of their goiters.

It is generally agreed that, thyroid isotope or ultrasound scanning are of little or no use in the diagnosis of carcinoma in a multinodular goiter 17b. Two aspects are important in the differentiation from malignancy. First, the clinical presentation. If the goiter is of longstanding, showing little or no growth, absence of a dominant node, familial, while there is no neck irradiation in the past, especially in childhood, no hoarse voice, and no suspicious lymphnodes in the neck, there is little fear for carcinoma. The second point is that if suspicion is present FNA cytology may be helpful.

## HYPERTHYROIDISM IN THE NODULAR THYROID GLAND

A significant proportion of patients with nodular thyroid glands develop thyrotoxicosis, and this is directly related to the duration the goiter has been present. Possible explanations for this occurrence were discussed earlier. Typically, the thyrotoxicosis comes about so insidiously that the patient is often unaware of the symptoms.

The symptoms of thyrotoxicosis are those observed with other causes of thyroid hormone excess, and are discussed in Chapter 10. Emotional lability, heightened neuromuscular activity, altered integument, increased metabolic rate, cardiac irritability and tachycardia, and increased motility of the intestine are seen, as in Graves' disease, but infiltrative ophthalmopathy is absent. Toxic adenomatous goiter was first clearly distinguished from Graves' disease by H. S. Plummer and is sometimes known as Plummer's disease<sup>72</sup>.

Certain features are much more prominent than in Graves' disease, perhaps because the disease usually appears first in the fifth through seventh decades<sup>73</sup>. Congestive heart failure occurs, and is often resistant to the usual therapeutic measures. Recurrent or permanent atrial fibrillation, or recurrent episodes of atrial tachycardia may dominate the picture. In fact, thyrotoxicosis should be carefully excluded in any goitrous adult with congestive heart failure or tachyarrhythmia. Occasionally mus-

cle weakness is so severe that the patient is unable to climb stairs, or even to walk, when few other symptoms or signs of the disease have become manifest. Emotional lability is often unusually prominent in these patients. Depression, crying episodes, emotional fatigue, and irritability may lead one to conclude that the problem is that of an agitated depression. Frequently the symptoms are confusing because they are coincidental mixed with those of menopause. Although emotional problems may be caused by thyrotoxicosis, the contribution of the thyroid often cannot be defined until the patient has been rendered euthyroid.

Thyrotoxicosis in multinodular goiter can occur for other reasons than nodular autonomy. In the first place, any patient with long-standing diffuse hyperplasia of Graves' disease may develop nodules in the thyroid gland. On the other hand, the normal glandular elements between the nodules may become diffusely hyperplastic, as in any other gland. This condition would be Graves' disease in a multinodular goiter. If the circulating thyroid immunostimulator, typical of Graves' disease, is present in the serum, it would indicate the presence of autoimmune thyroid disease. Several clinical observations support a fundamental distinction between Graves' disease and Plummer's disease. Frequently the hyperactive tissue in the latter is confined to one or a few nodules, as demonstrated by isotopic scan. Exophthalmos is not present in toxic nodular goiter, unless there is concomitant Graves' disease, and these patients have a family background of thyrotoxicosis less frequently. Usually they are older, and thyrotoxicosis is milder and often exists for a long time without much symptoms, but responds much less readily to the administration of antithyroid drugs. Very few patients have recurrent thyrotoxicosis after surgery, and few become hypothyroid. There is a widespread clinical impression that all patients with multinodular goiter will develop thyrotoxicosis if given sufficient time.

Thyrotoxicosis can also develop because a single nodule in the thyroid has become overactive and independent of pituitary control. In as many as 46%, this condition may be T3 thyrotoxicosis<sup>74</sup>. Nodules causing hyperthyroidism are generally 3 cm or more in diameter. The function of the rest of the gland is suppressed due to the lack of circulating TSH.

## THERAPY FOR NONTOXIC NODULAR GOITER

If the enlargement of the gland is moderate, there are no symptoms and serum TSH is normal, therapy is not required. If there are symptoms due to pressure, if the patient is disturbed by the appearance of the goiter, if there is growth of one nodule, or possible toxicity develops, diagnostic measures and treatment are necessary. Attempts to reduce multinodular goiter by administering suppressive doses of thyroid hormone are usually little or not effective and carry the risk of inducing thyrotoxicosis if autonomy of thyroid function is already present. Although this form of treatment is still being used by about half of the clinicians in the USA and Europe<sup>76,76a</sup>, it is the opinion of this author that it is obsolete and dangerous for the elderly. However other physicians believe that thyroid hormone replacement in a dosage that does not induce hyperthyroidism can be used without difficulty, and may help prevent growth of a goiter over years.

Administration of <sup>131</sup>I in euthyroid or hyperthyroid multinodular goiter, to both decrease the size and to treat thyrotoxicosis is becoming more popular over the years because of its efficacy and safety, especially in Europe.<sup>80-84</sup> A substantial reduction in goiter size after one or more treatment doses, though not always complete, occurs in virtually all patients.<sup>85</sup> Hypothyroidism ensues in a substantial number of patients, varying from 25 percent after five years<sup>85,86</sup> to 100 percent after eight years<sup>83</sup> depending on the cumulative <sup>131</sup>I dose administered and the sensitivity of the thyroid to <sup>131</sup>I. After administering large doses of <sup>131</sup>I, temporary increases of thyroid hormone levels may complicate the clinical situation.<sup>87</sup> In the anticipation of such situations, administration of antithyroid drugs for several weeks before administration of <sup>131</sup>I and/or treatment with beta adrenergic blocking agents after <sup>131</sup>I administration should be considered. Also multiple small doses of 5-10 mCi <sup>131</sup>I (185-370 MBq)

may be administered. A very interesting side effect of this treatment, as noted below, is the induction of Graves' Disease in 5-10 percent of patients. This is presumed to be due to release of antigens, stimulating an immune response.

Even in the case of large goiters, causing substantial tracheal compression with concomitant airflow obstruction treatment with radioactive iodine can be very effective.<sup>87a,87b</sup> Huysmans et al.<sup>87a</sup>, treated 19 elderly patients (mean age 66.14 years) with a multinodular goiter with a mean thyroid volume of 296ml (range 108-1002 ml), with a single intravenous dose of <sup>131</sup>I, aimed at delivering 3.7Mbcq/g thyroid tissue. No exacerbation of compressive symptoms occurred. A mean percent of reduction in thyroid volume of 43% was noted after one year. After administering the same dose <sup>131</sup>I to patients with toxic- or nontoxic multinodular goiter, without substernal extension, no increase in thyroid volume was seen immediately after treatment.<sup>87c</sup> If felt necessary small multiple doses may be given. It is the opinion of this author and of others <sup>87d</sup> that in general radioactive treatment of euthyroid- or toxic MNG is the first choice of treatment. Prior administration of human recombinant TSH may reduce the dose RAI to be given <sup>87da</sup>. Stimulation with rhTSH before (<sup>131</sup>I) therapy not only hinders the decrease in the thyroid RAIU observed with conventional (<sup>131</sup>I) therapy but in fact also significantly enhances the absorbed thyroid dose (total change average + 74%). Whether this leads to a significant increase in goiter size reduction needs additional study<sup>87db</sup>.

Many physicians, especially in the United States, consider subtotal thyroidectomy to be an useful alternative therapy <sup>76</sup>, especially if a well qualified surgeon is available. Surgery offers a rapid reduction in goiter with minimal risk, provides an histologic diagnosis, typically leaves no mass, and of course provides no radiation exposure. Exploratory surgery should be performed in case of sudden growth of the goiter, bleeding leading to mechanical symptoms, when a firm nodule is present, suspicious enlarged lymph nodes are palpable, vocal cord paralysis is found, or in some cases when there is substernal extension of the goiter causing substantial trachea obstruction. The author believes that surgery is otherwise hardly needed, except possibly in younger patients when the dose of radioiodine to be given is high.<sup>84</sup> The authors do not endorse prophylactic surgery to prevent the occurrence of carcinoma.

After surgical removal of a nodular goiter, it seems theoretically sound to give the patient minimally replacement or suppressive doses of thyroid hormone to suppress TSH production and prevent regeneration of the goiter. However this form of therapy is controversial. Although in one report no recurrences were found during thyroid hormone administration <sup>87e</sup>, in more recent studies others found no difference between untreated and patients treated with thyroid hormone after operation <sup>87f,g,h</sup>. In one of these studies <sup>87h</sup> carried out over 9 years, no effect of T4 treatment after thyroidectomy was seen in 104 patients operated for non-toxic goiter (the recurrence rate was 9.5% with treatment compared with 11.3% in untreated patients). If re-growth occurs, early ablative treatment with <sup>131</sup>I should be considered.

There is no place for administration of iodide in sporadic multinodular goiter. It generally has little or no beneficial therapeutic effect, and in an occasional patient may be followed by a rise in plasma hormone concentration and symptoms of thyrotoxicosis.<sup>49,88</sup> This condition is the "jodbasedow" phenomenon, and is dependent on autonomy of function of some elements of the goiter. Its occurrence is not confined to regions of iodine deficiency and is seen on occasion wherever iodide is administered to patients with well-established multinodular goiter. This should be remembered when elderly patients, that may have MNG, are given radiographic contrast agents for IVP, CAT or other studies.

Multinodular goiters frequently recur after partial thyroidectomy. Solymosi and Gal reported their experience in treating such recurrent nodular goiters with percutaneous ethanol injections. Patients had on average three sessions with injections, with a total dose of around 0.88 ml of ethanol per ml of nodular volume, and their experience was that nodules shrank by more than 50% of the pretreatment volume. Some patients experienced burning pain, and one had temporary hoarseness. They believe this is an appropriate therapy for recurrent nodular goiter (88.1).

## THErapy FOR TOXIC NODULAR GOITER

Treatment of toxic nodular goiter with RAI is generally satisfactory and will cause a reversion to euthyroid or hypothyroid state. The dose of  $^{131}\text{I}$  may be calculated on the basis of uptake determinations and gland weight, as discussed in Chapter 11 on Graves' disease. Multinodular glands, toxic or not, are relatively resistant to  $^{131}\text{I}$ , and for this reason some therapists increase the standard dose by 20-50%. (This is done as part of the schedule given in Chapter 11 since dose is increased with weight). It is frequently seen that areas in the thyroid of low functional activity at the time of therapy, may become activated after destruction of the hyperfunctioning. Frequently doses are between 15 and 50 mCi (555 and 1850 MBq). Jensen et al.<sup>88a</sup> treated their patients with a mean dose of 37 mCi (1370 MBq) range 6.3-150 mCi (233-5550 MBq). After one year of follow-up 16% of patients were hypothyroid. Danaci et al.<sup>86</sup> treated multinodular toxic goiters with a fixed dose of 16.6 mCi (631 MBq)  $^{131}\text{I}$  and they reported a cumulative relapse rate of 39% at 5 years and a cumulative incidence of hypothyroidism of 24% at 5 years. In a large prospective study involving 130 consecutive patients with toxic multinodular goiter and a mean follow-up of 6 years, 92% of patients were cured after one or two treatments with  $^{131}\text{I}$ . Thyroid volume was reduced by a mean value of 43% and side effects were few. Patients were treated with a median dose of 10mCi (370 MBq) (86a). Some authors prefer to administer a standard dose of 400MBq to both patients with Graves' disease and toxic MNG. This patient-friendly and possibly cost-effective regimen proved to be very effective in curing hyperthyroidism 88b.

An acute increase in the severity of thyrotoxicosis after radioiodine treatment may occur due to damage of the thyroid cells and release of stored thyroid hormone. It may sometimes occur months later, due to induction of autoimmune hyperthyroidism with development of thyroid stimulating antibodies, especially in patients presenting with TPO antibodies.<sup>88c,88d</sup> Therapy with  $^{131}\text{I}$  usually reduces the gland to a cosmetically satisfactory size, but rarely to normal dimensions. Even in the case of toxic nodular goiters of large size many thyroidologists use  $^{131}\text{I}$  as the first choice of treatment. Careful pre-treatment with antithyroid drugs in these cases is imperative. Therapy can induce worsened thyrotoxicosis with cardiac problems, and death has been reported. If the patient is made euthyroid with antithyroid drugs prior to therapy, this is unlikely to happen. Alternatively multiple smaller doses may be given, or the RAI treatment can be followed promptly by administration of antithyroid drug and then KI, as detailed in Chapter 11. When using large doses, it is important to consider the radiation dose administered and potential effects on neck structures and the body.

Some physicians find that subtotal thyroidectomy is a useful alternative therapy, after preparation with antithyroid drugs and KI. Thyroidectomy is indicated if there is a question of carcinoma. The patient may then be prepared with an antithyroid drug administered until the euthyroid state is achieved. The degree of thyrotoxicosis in this group of patients is usually rather mild. Thus, it is permissible to prepare the patient simply by the administration of propranolol. Thyroid storm occurs only with the greatest rarity after surgical treatment of toxic nodular goiter. When, after operation, airway patency is significantly compromised because of tracheomalacia (an extreme rarity!), a tracheotomy tube is often inserted and left in place for several weeks until peritracheal scarring has produced a rigid airway. Alternatively, the trachea is sutured to surrounding tissues, or plastic rings are sutured to the outside of the trachea in order to provide support.

Unfortunately, many patients with toxic nodular goiter first come to the attention of the physician because of cardiac symptoms, such as palpitations due to atrial fibrillation or symptoms of congestive heart failure. These patients need cardio-specific and antithyroid medication simultaneously. After rendering the patient euthyroid and stabilization of the cardiac situation, radioiodine therapy is satisfactory in spite of a slow response in this type of patient.

## COLLOID OR DIFFUSE GOITER

Colloid goiter is histologically distinct from nontoxic nodular goiter, but it may be closely related etiologically. For this reason, it is discussed briefly at this point. It occurs occasionally as a diffuse enlargement of the thyroid gland in adolescent girls, and is especially frequent in this age group in endemic goiter areas. It occurs much less frequently in adults. Typically, the goiter is asymptomatic. It occasionally causes dysphagia or dyspnea, but it is rare for a colloid goiter to produce significant compression of the trachea or esophagus. The gland is usually symmetrically enlarged and feels soft or spongy.

On gross inspection the excised gland is reddish-tan or pale tan in color and homogeneous on the cut surface. On histologic section, the parenchyma is seen to be nonnodular and composed of uniform follicles filled with colloid. The follicles may be of normal size, in which case it must be considered that an increase in the number of normal follicles has produced the increased bulk of the gland, or the follicles may be uniformly distended to several times the usual diameter. Fibrosis and lymphocyte infiltration are not prominent.

The cause of the condition is unknown. In the past it has been ascribed to the intermediate phase of the Marine cycle i.e. between the hyperplastic stage and the multinodular (end) stage of the thyroid gland as described above. More recent studies in mice suggest that such goiters can be induced in animals by TSH without a prior hyperplastic phase.<sup>13,89</sup> The stimulus to TSH secretion in these patients may be an increased requirement for thyroid hormone, possible associated with puberty or pregnancy, a period of decreased iodide intake, or the presence within the thyroid of a biochemical lesion interfering with the normal synthesis of thyroid hormone.

The small colloid goiter of adolescent girls may disappear over 1-3 years. On the other hand, it may grow gradually and evolve into the nontoxic multinodular goiter found in adults.

A diagnosis of colloid goiter cannot be made with certainty without histologic confirmation. Thyroid function tests are variable, but the results are frequently normal. Antithyroid antibodies are absent if Hashimoto's thyroiditis is not present. Needle biopsy will confirm the diagnosis but is seldom warranted.

Reassurance that the lesion is not a malignant neoplasm, and that the thyroid is not overactive, is often the only therapy required. If the goiter is large, thyroid hormone may be given in an attempt to decrease its size. If one accepts the theory that the goiter has grown in response to a need for more thyroid hormone, it is logical to expect that exogenous thyroid hormone would cause it to decrease in size. Unfortunately, practice does not always bear out the theory. Only about 70%<sup>71</sup> of patients will respond with complete or partial regression of goiter. If there are significant pressure symptoms or if the goiter is a serious cosmetic problem, administration of <sup>131</sup>I or surgical resection may be indicated. Subsequent replacement therapy with T<sub>4</sub> will be then necessary.

## SUBSTERNAL AND ACQUIRED INTRATHORACIC GOITER

The terms substernal and intrathoracic goiter include instances in which there is a pronounced downward prolongation of the lower pole or poles of the thyroid gland or a downward growth of a nodule from the lower pole below the level of the manubrial notch. The original development site of the thyroid is presumed to be normal. It is an acquired rather than an embryological abnormality. Displacement of the thyroid through the thoracic strait changes the picture from one in which surgery is simple to one in which it is potentially difficult, and the symptoms may change from relatively slight to severe. The term substernal may be used for those goiters with the greatest diameter above the level of the sternal notch and intrathoracic for those in which it is below this notch.

## Cause

The downward prolongation of the thyroid is due to growth from the lower pole of either a single nodule or one of several nodules in a nodular goiter. When one remembers the anatomy of the thyroid, it is easy to see why at times the growth may be downward rather than anterior, where it is limited by the pretracheal muscles, or posterior or lateral, where it meets resistance from firm structures. The deeper layer of pretracheal muscles is inserted into the posterior part of the clavicle and sternum, and as the nodule slides up and down with deglutition and other movements of the neck, it is guided behind the bony structures of the cervical ring. For a varying length of time, generally a long period, the mass will descend into and come out of the thorax with perfect ease. After a time, more and more of the mass falls below the superior bony margin. The moment the nodule reaches a size that precludes its moving upward into the neck itself, it becomes a completely intrathoracic goiter and, because of its fixed position, is potentially more dangerous in case of sudden swelling from any cause. The size of the growth within the thorax may increase markedly. A tongue of tissue may extend behind the trachea and esophagus, and the lower level may be below the level of the aortic arch and even as far as the diaphragm. Although the lower pole is the usual starting point, it is possible for the growth to start from a lateral lobe and thus add to the difficulties of diagnosis because of the apparent freedom of the lower pole from any connection with the intrathoracic growth.

Substernal and intrathoracic goiters are typically found in older persons. A kyphosis, a stooped posture, and an increased anterior-posterior thoracic diameter no doubt promotes an intrathoracic position of the gland. By having the patient lie supine with a pillow under the shoulders, a large part of the gland may be delivered into the neck, and at surgery it is sometimes surprising how easily a large substernal goiter may be pulled out through the cervical inlet and removed without recourse to splitting of the sternum.

## Clinical Picture

The symptoms are most often due to mechanical factors, the result of pressure from the mass on surrounding structures. Thyrotoxicosis may also arise from such a gland. Often the first thing that bothers the patient is an obstruction to breathing when the head is in a particular position or when he or she is asleep and the head is lying at a fixed angle. Patients may give a history of attacks during the day or night during which they fear they will suffocate. Dyspnea may suddenly become severe during a respiratory infection and can lead to respiratory failure unless recognized. Bleeding into a cystic lesion is also a cause of sudden accentuation of obstructive symptoms. An irritable cough or slight hoarseness may occur. Difficulty in swallowing may develop so insidiously that the patient is not aware of the problem until it has assumed considerable proportions. Patients with large, strategically located masses may show a striking pattern of dilated veins over the upper chest. Very rarely a vena cava superior syndrome may ensue.

## Diagnosis

A patient with a substernal goiter may show tracheal deviation or evidence of dilated cervical or facial veins. The potential for venous obstruction may be made apparent by having the patient elevate the arms above the head. If external jugular vein dilatation is seen (Pemberton's sign), a significant obstruction to venous return is present due to the mass in the thoracic inlet. The roentgenogram will show a substernal tumor and often deviation of the trachea. Radioisotope scanning (with <sup>131</sup>I) is of much help in defining the limits as well as in identifying the nature of the mass. CT or MRI imaging may be necessary especially to distinguish a goiter from a vascular tumor or aneurysm.

## Treatment

The small, asymptomatic substernal goiter does not require therapy. If necessary, <sup>131</sup>I treatment can be applied. Surgery is hardly ever necessary, but if so (relatively young patient and or high dose radioiodine needed), these glands do not demand any change in anesthesia or special surgical treatment. Since their greatest diameter is above the level of the strait, they lift out easily and there is no greater danger of nerve damage than in routine thyroidectomy nor is there any increased risk of post-operative complications.

When the growth is lodged below the bony strait, the problem may be more serious. Tracheal intubation ensures the continuity of breathing if it should become necessary to exert pressure against the trachea during the surgical procedure. The blood supply of the mass comes from the regular sources of blood supply to the thyroid and is carried down into the thorax with the descent of the goiter. Consequently, the procedure is first to control the blood supply from above by tying the upper pole and the lateral vessels, and then to find the line of cleavage that will allow the mass to be separated from the bed in which it lies. Because the tracheal tube ensures an adequate supply of air, it is possible, in practically all cases, to deliver the growth with a finger lifting below and traction from above.

## SUMMARY

Perhaps the most common of all the disorders of the thyroid gland is multinodular goiter. Even in nonendemic regions it is clinically detected in about 4% of all adults beyond the age of 30. Pathologically it is much more frequent, the percentage of incidence being roughly the same as the age of the group examined. The disease is much more common in women than in men.

Multinodular goiter is thought to be the result of primarily two factors. The first factor is genetic heterogeneity of follicular cells with regard to function (i.e. thyroid hormone synthesis) and growth. The second factor is the acquisition of new qualities that were not present in mother cells and become inheritable during further replication. Mutations may occur in follicular cells leading to constitutively activated adenomas and to thyrotoxicosis. These factors may lead to loss of anatomical and functional integrity of the follicles and of the gland as a whole. These processes ultimately lead to goiter formation and are accelerated by stimulatory factors. These stimulatory factors may be TSH, brought about by events such as iodine deficiency, inborn errors of thyroid hormone synthesis, goitrogens or local tissue growth-regulating factors. These basic and secondary factors may cause the thyroid to grow and gradually evolve into an organ containing hyperplastic islands of normal glandular elements, together with nodules and cysts of varied histologic pattern.

Nodular goiter is most often detected simply as a mass in the neck, but at times an enlarging gland produces pressure symptoms on the trachea or esophagus. Occasionally tenderness and a sudden increase in size herald hemorrhage into a cyst. Thyrotoxicosis develops in a large proportion of these goiters after a few decades. Rare complications are paralysis of the recurrent laryngeal nerve, and pressure on the superior sympathetic ganglion causes a Horner's syndrome.

The diagnosis is based on the physical examination. Thyroid function test results are normal or disclose subclinical or overt hyperthyroidism. Thyroid autoantibodies are usually absent or low, excluding Hashimoto's thyroiditis. Imaging procedures may reveal distortion of the trachea, calcified cysts, or impingement of the goiter on the esophagus.

From 4 to 17% of multinodular thyroids removed at operation contain foci that on microscopic examination fulfill the criteria of malignant change. The infrequency of thyroid cancer as a cause of death clearly proves that the vast majority of these lesions are not lethal or even clinically active. One of the reasons for the high incidence of

cancer in surgical specimens is that patients with multinodular goiters were often selected for surgery because of a concern for carcinoma.

If a clinically and biochemically euthyroid multinodular goiter is small and produces no symptoms, treatment is not necessary. T4 given in an effort to shrink the gland or to prevent further growth may be unsuccessful and may cause thyrotoxic symptoms. This therapy is more likely to be effective if begun at an early age while the goiter is still diffuse than in older patients in whom certain nodules may have already become autonomous. If the clinically euthyroid goiter is unsightly, shows subclinical hyperthyroidism or is causing pressure symptoms, treatment with 131I is successful in virtually all cases but causes hypothyroidism at varying degree. Surgery is an acceptable alternative. The efficacy of T4 treatment after surgery, to prevent regrowth, is uncertain.

Overt toxic nodular goiter is usually treated with RAI. A gratifying reduction in the size of the goiter and control of the thyrotoxicosis may be expected. Hypothyroidism often ensues. Surgery is an alternative but usually not necessary treatment.

The term colloid goiter is applied to glands composed of uniformly distended follicles appearing as a diffuse enlargement of the thyroid gland. The condition is found almost exclusively in young women. With time and due to a number of primary and secondary factors it may gradually develop into a multinodular goiter which becomes increasingly prominent as the decades pass. Appropriate therapy, if required, is the timely administration of thyroid hormone, that may be continued for several years.

An intrathoracic goiter is usually an acquired rather than a developmental abnormality. It may come about in embryonic life by a carrying downward into the thorax of the developing thyroid anlage, or in adult life by protrusion of an enlarging thyroid through the superior thoracic inlet into the yielding mediastinal spaces. These lesions may produce pressure symptoms and may also be associated with hyperthyroidism. If too large for treatment with 131I, the appropriate therapy is resection of the goiter through the neck, if possible. Attachment of the intrathoracic goiter to the gland in the neck ordinarily proves the site of origin and provides a method for its easy surgical removal.

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