

## CURRENT METHODS OF DIAGNOSIS AND MANAGEMENT OF GOITER

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**G**OITER, for consideration in this report, will be discussed from the viewpoint of three types: nodular goiter, Graves' disease, and thyroiditis. The specific methods most useful today in the diagnosis and management of these are the subject of this paper.

### Nodular Goiter

*Diagnosis.* Nodular goiter is a disease of adult life, commonest in women about middle age or older. In a patient with multinodular goiter, hyperthyroidism may be suspected for many reasons; some of the commonest are unexplained loss in weight and poorly explained tachycardia or bouts of atrial fibrillation. A nodule, especially if it seems to be solitary, which is hard and growing, must seriously be suspected of malignancy. A radioiodine ( $I^{131}$ ) scan or scintigram is of some diagnostic value, though, as a rule, it fails to detect cold nodules that are 2 cm. or less in diameter. Larger inactive or cold nodules may show up clearly because on the scintigram they appear paler than the surrounding tissue or, in the case of hyperthyroidism from a toxic nodule itself, the appearance of the nodules on the scintigram will usually be darker than the surrounding tissue that may be relatively suppressed by the excess of thyroxine emanating from the nodule. A nodule that is producing hyperthyroidism is quite unlikely to be carcinoma.

If carcinoma is suspected and the nodule is cold, then there is a greater likelihood of the presence of carcinoma than there would be otherwise. It must not be assumed that the presence of hyperthyroidism excludes the presence of carcinoma. In rare instances hyperthyroidism arises from a malignant nodule and, even more rarely, active hyperthyroidism from metastatic thyroid nodules has been reported—only seven such cases are known.<sup>1</sup> A nodule in the thyroid gland of a child, or of a person less than 20 years of age, should be strongly suspected as being papillary carcinoma. However, when no thyroid nodule is palpable, papillary carcinoma is frequently diagnosed by a biopsy of enlarged lymph glands of the neck.

In making a diagnosis of hyperthyroidism in multinodular goiter it should be borne in mind that the radioiodine uptake is but slightly elevated in a large proportion of the cases. The uptake values frequently range between 50 and 60 percent of a tracer dose, and in many patients lower uptakes are found. The laboratory aids to diagnosis are also limited by the fact that the protein-bound iodine (PBI) is often only slightly elevated. A radioactive  $T_3$  red cell uptake of more than 22 percent is consistent with hyperthyroidism but may be due to a number of other conditions.

Its counterpart test employing absorptive resins may be used and may be more readily available.\*

*Treatment.* For a single hot nodule with hyperthyroidism, excision usually is recommended. Single cold nodules are removed if there is more than the slightest suspicion of carcinoma. Multinodular goiters if large and unsightly or causing pressure symptoms are usually treated surgically. In some patients with large multinodular goiters and hyperthyroidism, shrinkage to the point of almost complete clinical disappearance has occurred after large doses of  $I^{131}$ . If the goiter is not large, if there is no evidence of hyperthyroidism clinically, and if a reasonable number of dependable tests corroborate this status, surgery is not usually advised. Hyperthyroidism from a thyroid nodule occurs because of the autonomous action of the thyroid tissue within the nodule; for this reason thyroid hormone in doses that ordinarily are suppressive, almost never suppresses the  $I^{131}$  uptake of the nodule, but only of the normal surrounding thyroid tissue. It still may be worthwhile to try l-thyroxine (0.3 mg.) or desiccated thyroid (3 gm.) in doses slightly larger than the physiologic dose. When shrinkage of a multinodular goiter occurs it often is difficult to determine whether there is shrinkage due to decrease in the size of the nodules or whether the change is due to a decrease in mass of normal thyroid tissue, which on the basis of physiologic knowledge seems much more likely.

In patients with nodular goiter, when the presence of hyperthyroidism is doubtful but suspected, medical therapy can be given for one or two months, and the results will usually make the diagnosis evident. If hyperthyroidism exists, preparation with iodine alone or administration of iodine plus an antithyroid drug for a few weeks and surgical removal of the majority of thyroid tissue is usually considered by nearly all physicians to be the preferred treatment. If there is associated severe concurrent disease, or if threatened or actual cardiac decompensation is present,  $I^{131}$  therapy can be used to great advantage in toxic nodular goiter.<sup>2</sup> In our experience, the preferred dose is much greater than that needed in Graves' disease, even in consideration of the measured uptake. It may be that some cells in a state of low activity at the time of treatment may become active later, and it may be that the hyperactive nodule may contain enough colloid to separate the acinar cells by a greater distance than occurs in Graves' disease, resulting in less radiation to each cell from the  $I^{131}$  in the adjacent ones. We usually aim to give a dose that will leave at least 25 mc. of  $I^{131}$  in the goiter. When severe cardiac decompensation is uncontrollable, and is associated with hyperthyroidism with nodular goiter, we have given more than 70 mc. at a single dose, not only without damage but with excellent clinical results. By using such large doses the rate of recovery is greatly improved, and the necessity for multiple doses is significantly reduced (*Fig. 1*). Hypothyroidism almost never occurs in  $I^{131}$ -treated nodular goiter, since the normal thyroid tissue is suppressed and receives little irradiation. I doubt that such therapy ever

\*Examples: Abbott Laboratories; and T. B. I., Nuclear Consultants Corp.

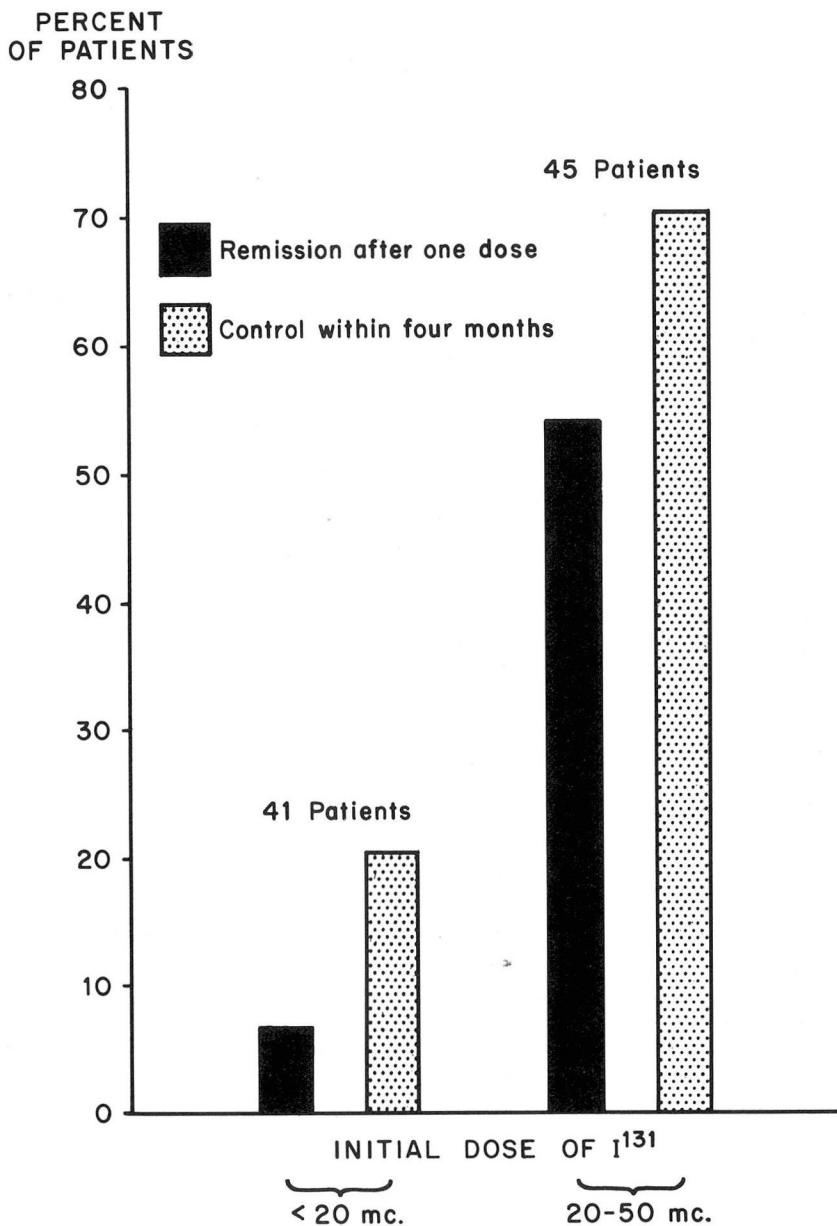


Fig. 1. Graph demonstrating the relatively small proportion of patients receiving doses of I<sup>131</sup> under 20 mc. who have complete remission of hyperthyroidism after a single dose or within four months as compared to those receiving larger doses.

causes thyroid crisis. Propylthiouracil or methimazole can be used to control the hyperthyroidism of nodular goiter; large doses may be needed and full control occurs slowly. Few physicians and few patients would be satisfied to continue such treatment indefinitely and, a further disadvantage is the fact that withdrawal of treatment in nodular goiter leads to recurrence of the hyperthyroidism in more than half of the patients.

### Graves' Disease

We consider Graves' disease to be a systemic disorder probably emanating from the nervous system, with excessive production of an abnormal type of thyroid stimulator,<sup>3</sup> often associated with exophthalmos though not necessarily so, the thyroid itself being diffusely affected. The hyperthyroidism per se, which is the effect of excess thyroxine or possibly to some extent triiodothyronine, is the same as in toxic nodular goiter, but Graves' disease has features not accounted for by hyperthyroidism.

Graves' disease with goiter, exophthalmos, tremor, tachycardia, and typical signs is, as a rule, one of the simplest diagnoses to make, yet it can also be obscure. When in doubt, one would hesitate to make the diagnosis of hyperthyroidism of Graves' disease unless the basal metabolic rate were elevated (over +15 percent) and the  $I^{131}$  thyroidal uptake more than 60 percent. It is apparently true that in an occasional instance the amount of protein-bound iodine is not high, and the basal metabolic rate is within the range ordinarily considered normal, yet hyperthyroidism is present and is associated with a rapid turnover rate of thyroxine. For similar reasons hyperthyroidism may be present when the 24-hour  $I^{131}$  uptake is only slightly elevated, though in some patients there may be a higher uptake at six hours than at 24 hours, and this elevation, if present, is excellent evidence of overactivity of the thyroid. In cases of doubt the triiodothyronine red cell uptake test may be valuable, especially when iodine contamination is interfering with other tests.

Frequently, exophthalmos is dissociated almost completely from hyperthyroidism as such, so far as one can determine from the patient's history, from any tests, or from long-term follow-up data. Thus, some patients have normal basal metabolic rates and normal levels of protein-bound iodine and  $I^{131}$  thyroidal uptake. Some, however, have high thyroidal uptakes of  $I^{131}$  though other tests may be normal. In some patients the feeding of desiccated thyroid or the administration of triiodothyronine, 100  $\mu$ g. daily for one week, shows little or no suppression of  $I^{131}$  uptake, just as would be the case in active hyperthyroidism. The overactive thyroid in nearly all instances has a high  $I^{131}$  uptake, and usually the turnover rate is not so rapid that the  $I^{131}$  is ineffective.

When exophthalmos of Graves' disease begins and there is no evident hyperthyroidism it is frequently misdiagnosed. Commonly the exophthalmos is mistaken for ocular allergy because of the chemosis and edema of the conjunctiva in the

absence of pus. Sometimes in the beginning it is unilateral, and an orbital tumor is suspected. Occasionally pain is the first symptom of exophthalmos of Graves' disease. Typically the lids bulge laterally, the upper lids bulging more than the lower. Subsequently the lids themselves appear swollen, though most of the swelling is from the bulging of infiltrated fatty tissue, which protrudes from the orbital cavity and extrudes between the muscle bands. This fatty tissue can often be seen as lumps beneath the lower lids when the patient looks upward. Some degree of lid retraction and lid lag commonly occurs, and frequently there is some degree of muscle paralysis, often only of the superior rectus. The cause of exophthalmos is not known. It is not due to thyroid-stimulating hormone (TSH). It never occurs in spontaneous myxedema, in which thyroid-stimulating hormone is excessive. It is said to occur in acromegaly, though I have never seen this. It occurs rarely in Cushing's syndrome.<sup>4-6</sup> It is associated in many instances with excess of the long-acting thyroid stimulator (LATS),<sup>3,7,8</sup> which exists in Graves' disease. Dr. J. Max McKenzie, of Montreal, has done assays for long-acting thyroid stimulator in some of our patients with exophthalmos, and from the assays we have found no demonstrable correlation between the concentration of this material in the blood serum and the rapidity with which the exophthalmos is advancing or with its severity. It seems likely that exophthalmos is intimately connected with the pituitary, and that it is not caused by TSH or by LATS. It may be produced by "exophthalmos producing substance," which Dobyns and Steelman<sup>9</sup> believe is separate from TSH, and can be extracted from the pituitary glands of animals. Excess of exophthalmos-producing factor, measured in the eyes of carp, has been reported to be present in patients with Cushing's syndrome and acromegaly.<sup>10</sup>

*Treatment of the hyperthyroidism of Graves' disease. Iodine.* With the array of useful measures of treatment for hyperthyroidism, iodine has little place in our armamentarium today. Thyroid crisis, which in 1930 was relatively common for reasons not well understood, now almost never occurs. When a crisis does occur it can be treated with Lugol's solution, in doses of 1 ml. twice daily. Larger doses are of no advantage. Potassium iodide tablets, 5 gr., twice daily, may be given; or if the patient is vomiting, sodium iodide can be given intravenously. Such therapy needs to be used in conjunction with other treatment. Sedation is usually tolerated in large doses; phenobarbital up to 5 or 6 gr. daily, morphine in large doses if necessary. Reserpine in doses as high as 2.5 mg. to 5 mg. injected intramuscularly every eight hours has caused remarkable improvement in persons with extremely severe thyrotoxicosis. Guanidine also has been used to advantage to counteract the hyperactivity of the sympathetic nervous system and thus counteracting the reflex release of epinephrine and norepinephrine.

Iodine in mild hyperthyroidism is apparently almost never followed by a lasting remission. Iodine is used by some physicians as an adjuvant therapy in the medical treatment of exophthalmos. This use is based on the concept that iodine inactivates

pituitary TSH. This is not well proved, and it is now established that TSH has little if anything to do with the production of exophthalmos.

*Antithyroid drugs.* The antithyroid drugs in commonest use in this country now are propylthiouracil and methimazole.\* One great advantage in using these drugs is that the thyroid gland is left intact. This seems to be a particular advantage in young women who are expecting to bear more children. It is also an advantage in children in whom some degree of hypothyroidism would be most likely to occur after other forms of therapy, and could conceivably be overlooked or not be well treated.

Some of the disadvantages of the antithyroid drugs are the necessity for long-continued use, and the dependence upon the patient for the systematic use of the drug, especially since these materials are active in single doses for only a matter of a few hours at a time. There are also toxic side effects, and treatment may need to be stopped because of such symptoms as a rash or joint pains; these effects occur in 1 or 2 percent of the patients. The only serious complication is agranulocytosis, which cannot be anticipated but, fortunately, is extremely rare with moderate doses of the drugs. All patients nevertheless need to be warned that the occurrence of fever, sore throat, and malaise may mean serious blood dyscrasia. This occurs only in about 0.1 percent of the patients treated and, fortunately, these almost always recover when given antibiotics and blood transfusions.

In children, hyperthyroidism is apt to disappear and to remain in remission, and thus propylthiouracil is particularly suitable for many instances of this disease in childhood. In older individuals, recurrence after drug therapy is common. It is particularly common in patients in whom hyperthyroidism has already recurred after surgery, as well as in those with large goiters. The situation in which propylthiouracil or methimazole is most useful is in the moderate hyperthyroidism of the Graves' disease type in which the goiter is not extremely large. Even then in highly selected cases the recurrence rate after a year of treatment is at least 25 percent.

The dose of propylthiouracil should be 300 mg. or more.<sup>11</sup> A few patients need 500 mg. and occasionally larger amounts to control the hyperthyroidism completely. Care should be taken to have the patient take the medication in three well-divided doses throughout the 24 hours. If methimazole is used, a comparable dosage would be from 30 to 100 mg. per day. After the hyperthyroidism is completely controlled one may follow several courses. The usual one is to decrease the dosage to as little as 100 mg. or even 50 mg. a day and to keep it at this level as long as the hyperthyroidism is in abeyance. This course frequently leads to loss of control of hyperthyroidism, and since the impression is strong that constant control for a long time is a factor of importance in obtaining a lasting remission, I prefer to continue at a thoroughly effective dosage. Also in order to suppress the pituitary as much as

\**Tapazole, Eli Lilly and Company.*

possible, in the hope of preventing further ocular changes and preventing further growth of the thyroid, desiccated thyroid up to tolerance, or sodium l-thyroxine, 0.1 to 0.3 mg. per day may be added.

The best guides as to the progress of a patient who is taking propylthiouracil are his weight, pulse rate, and basal metabolic rate. The use of the uptake of  $I^{131}$  test is of little value, inasmuch as pituitary hyperactivity and thyroid hyperplasia are being stimulated by the therapy. The protein-bound iodine level is of more value, but in some patients, as previously stated, it may be normal and hyperthyroidism still will exist because of a rapid turnover rate. We have noted that when during therapy with propylthiouracil the thyroid becomes soft and tends to shrink, the patient is apt to be experiencing a lessening of the fundamental force of the disease, and probably is entering a spontaneous remission. It is a good prognostic sign. Cassidy and VanderLaan<sup>12</sup> state that the  $T_3$  suppression test is useful in prognosis. They found that in those whose  $I^{131}$  uptake values were less than 35 percent, l-triiodothyronine suppression had a much lower incidence of recurrence than in those whose  $I^{131}$  uptake value exceeded that amount.

An adequate dose of propylthiouracil is effective almost immediately, preventing the iodination of basic thyroid protein and, since the decay curve of l-thyroxine is approximately three weeks, usually an adequate dose will allow the basal metabolic rate to decrease to normal or nearly normal in this length of time. It is our practice, when propylthiouracil is used, to continue the treatment for one year or longer and then to withdraw it completely, continuing desiccated thyroid, and if a recurrence of hyperthyroidism is evident, we usually do not treat again with propylthiouracil but prescribe  $I^{131}$ . In this event the administration of the drug needs to be stopped for three or four days before  $I^{131}$  is given.

*Radioiodine therapy.* The total effective dose of  $I^{131}$  in most instances is in the range of 4 to 8 mc. Doses as high as from 12 to 16 mc. are not often needed. Smaller doses have the disadvantage of taking considerably longer to control hyperthyroidism, will necessitate more repeated doses, although they may cause less hypothyroidism than do larger doses. Myxedema however, may occur after a dose as small as 2.5 mc.

In the last two years we have increasingly favored the treatment with  $I^{131}$  for hyperthyroidism in children. This is done largely in consideration of the fact that in the past the surgical results of Graves' disease in children have not been good.<sup>13</sup> Although, with good preparation, the mortality rate itself no longer is high, yet in the very best of hands there is a high recurrence rate, and permanent tetany occurs in from 1 to 5 percent. The fear of possible cancer after many years has deterred most physicians from prescribing  $I^{131}$  for children. Now, after the treatment of a total of perhaps 100,000 patients during 24 consecutive years, there is no evidence that  $I^{131}$  therapy will cause carcinoma. It appears now that we can feel secure with this evidence. Up to the present it appears that the prevalence of leukemia in



patients treated with  $I^{131}$  does not exceed that in the general population. No interference with fertility or appearance of genetic abnormalities has been reported.

$I^{131}$  in any dose we consider contraindicated in pregnancy. Theoretically,  $I^{131}$  could be prescribed harmlessly in the early weeks of pregnancy, but it is not good in principle. It is known that the fetal thyroid does not take up radioiodine before the fourteenth week,<sup>14</sup> nevertheless, we never administer  $I^{131}$  knowingly during pregnancy. In pregnancy, my treatment of choice is propylthiouracil. Methimazole is being used increasingly, as it is presumed by some physicians to be slightly less toxic, though there is some doubt as to the validity of this claim. To control the hyperthyroidism, 100 to 400 mg. per day may be needed, and the dose then should be reduced to the minimum required. The infant frequently has some goiter at birth, but this disappears promptly. The infant should not be breast fed if the mother continues to receive antithyroid drugs.

Many methods have been used to calculate the proper dosage of  $I^{131}$  in Graves' disease. No method is perfect, and the extremely painstaking methods seem no better than those based largely on empiric rules. All methods have the disadvantage of one's lack of knowledge of the exact size of the thyroid. The method that we use is based on an estimate of the thyroid size by palpation and  $I^{131}$  uptake. From these figures we calculate the amount of radioiodine that will deliver 100  $\mu$ g. of  $I^{131}$  per gram of thyroid. With this method about 75 percent of the patients are cured by single doses, 15 percent need two doses, and the remaining 10 percent need three or, rarely, more than three doses. If the patient is severely ill, he is given large doses of  $I^{131}$  and is carefully instructed to follow a high-caloric diet. Though it was imperative formerly it is seldom necessary nowadays to prescribe severe restrictions in activity. Phenobarbital in doses of a  $\frac{1}{2}$  gr. or more four times a day is commonly prescribed. A supplement of iodine alone or with propylthiouracil may be given for a time as designated above. Iodine is usually given as potassium iodide tablets, 5 gr. three times daily, or Lugol's solution 10 drops twice daily. Usually administration of either form is withdrawn one month before estimation of progress and retesting is planned. Antithyroid drugs can be continued to within three days of retesting if desired, but this has the disadvantage of masking improvement due to the  $I^{131}$ .

The symptoms usually diminish in three weeks; the patient may feel quite comfortable in four or five weeks, and almost well in two months. Usually we do not see the patient until two months after treatment was started, when it is time to calculate the basal metabolic rate and the blood cholesterol value. Commonly a 24-hour uptake of  $I^{131}$  is measured again, not so much to estimate the hyperthyroidism (for which it is a poor test under these circumstances) but in the event that more treatment is needed, when it must be used as a guide to the dosage. If the basal metabolic rate is less than +15 percent no further treatment is given and the patient is seen again after one month or two months. In general, if the patient shows



considerable improvement, but active hyperthyroidism is present, the same dosage is given as was given before. If the patient has not improved, a dose calculated to give a retained amount of  $I^{131}$  of 25 percent or more than the original dose is given. The repeated dosage may have to be considerably greater than the original, since the thyroidal uptake is likely to have decreased considerably, and because the original estimated dosage based on uptake has been proved by the progress to have been insufficient.

The only complication of  $I^{131}$  therapy which occurs is hypothyroidism, which is permanent in approximately 10 to 15 percent of patients. In only one reported instance,<sup>15</sup> temporary parathyroid tetany occurred.

It has been suspected that  $I^{131}$  in large doses has precipitated a thyroid crisis, but this is doubtful. I believed for several years that I had seen this occur. The patient in question, after repeated doses of  $I^{131}$  had failed, was given 25 mc. of  $I^{131}$ . Within about one week she was in thyroid crisis. In retrospect, we find that propylthiouracil, which was given until a few days before the last dose of  $I^{131}$ , was not restarted after the  $I^{131}$ . The hyperthyroidism we now believe went into spontaneous exacerbation before the  $I^{131}$  became effective. From one of my students I heard of a patient thought to have died from thyroid crisis precipitated by  $I^{131}$  therapy. On close investigation it was found that at autopsy there was evidence of extensive pneumonia present, which had not been diagnosed before death. Lamberg<sup>16</sup> reported on two patients who died after  $I^{131}$  therapy, in whom he believed the radioiodine was a factor in precipitating the deaths. His patient (no. 7) died one week after 14 mc. of  $I^{131}$ . The "patient expired showing a picture of cardiac failure." Patient no. 17 "expired quietly" in cardiac failure five weeks after 40 mc. of  $I^{131}$ . Neither patient had what we call "thyroid crisis."

### Exophthalmos

In the treatment of exophthalmos we try to produce pituitary suppression clinically. This is done by feeding thyroid hormone in the hope that the suppression, which may be measurable in the thyroid by uptake, will be paralleled by some improvement in the exophthalmos. Such suppression is commonly difficult to produce and the relationship is not proved. If this fails, large doses of prednisone, as high as 200 mg. daily, have been used, and sometimes with prompt and striking reduction in ocular signs, especially the infiltrative phenomena. In some cases, if after two weeks of prednisone therapy there is little or no improvement, the addition of adrenocorticotropin (ACTH) in a dosage of 40 units intravenously daily may be followed by further improvement rapidly enough to make it appear that the treatment itself is actually responsible. If the ocular signs are advancing relentlessly and loss of the eyes is threatened, we have sometimes prescribed section of the pituitary stalk, and the placement of a diaphragm above the sella turcica. Such a procedure may fail to produce measurable hypopituitarism. For example, in four of nine women treated, the menstrual periods continued uninterruptedly. In some patients partial

hypophysectomy has been done by cautery or surgical ablation. We have not yet treated exophthalmos with yttrium<sup>90</sup> implantation, but it is anticipated. Molinatti, Camanni, and Pizzini's<sup>17</sup> experience in two patients is promising. If the progress of the disease is severe and extremely rapid, if various other measures have failed, and if pituitary surgery is considered inadvisable, orbital decompression is performed. In the past we have prescribed orbital decompression of the Naffziger<sup>18,19</sup> type only in patients in whom we thought there was a great likelihood of loss of the eyes. Recently, lateral decompression has been done; it is less debilitating, and, apparently if the decompression is wide enough, the results are usually excellent. This is a pterional approach similar to that described by Welti and Offret,<sup>20</sup> unlike the Krönlein procedure and less deforming. We have seen much better results recently with this type of decompression than we have from unroofing of the orbit by the transfrontal route. Not only is the proptosis improved but in some instances there has been a great improvement in the ocular muscle motion and vision, which was seldom seen following technics formerly used.

### Thyroiditis

The three types of thyroiditis which are of greatest interest clinically are: (1) subacute granulomatous thyroiditis, (2) fibrous invasive thyroiditis (Riedel's struma), and (3) struma lymphomatosa (Hashimoto's thyroiditis).

*Subacute granulomatous thyroiditis. Diagnosis.* This condition, which may follow symptoms of a mild upper respiratory tract infection, declares itself relatively acute with a solid, tender, and painful area in the thyroid, usually beginning in one lobe, and possibly spreading in the course of days or weeks to the opposite lobe. It is usually considered to be due to a virus, though this has not been proved. A mumps-like virus has been shown to be present in some cases,<sup>21</sup> but certainly the condition is not commonly associated with ordinary clinical mumps. The condition is sometimes mistaken for tracheitis or laryngitis. The tenderness immediately over the affected area may be exquisite, and referral of this pain to the lateral part of the neck upward to the jaw angles, ears, and sometimes to the back of the neck is fairly typical. Despite the acute or subacute clinical picture, microscopic evidence comprises cell disintegration and histologic features that characterize the lesion as granulomatous with focal collections of histiocytes and foreign-body giant cells. Excessive numbers of polymorphonuclears also may be present.

When the disease is sufficiently intense, so large a part of the thyroid may be destroyed as to cause a release of thyroxine into the blood, and probably thyroglobulin also, resulting in a considerable increase in the amount of protein-bound iodine, as high as 15  $\mu\text{g.}$  per 100 ml. The uptake of I<sup>131</sup> at this point is low. As the disease progresses the protein-bound iodine levels tend to decrease temporarily to low normal or subnormal levels, and in some patients, clinical hypothyroidism appears.<sup>22</sup> If surgery or radiation therapy has not been used, permanent myxedema is rare.<sup>23</sup>

*Treatment.* The treatment we have preferred is the use of prednisone, which is quickly effective in most patients. It is cheaper than cortisone and has less tendency to cause edema. A dose of 5.0 mg. four times a day usually will relieve the discomfort in the course of a few days. As soon as the symptoms are controlled, the dosage can be diminished and withdrawn, depending upon the symptoms. A peptic ulcer regimen is commonly advised during the use of large doses of prednisone, the strictness of which depends upon whether or not the patient has had a history suggestive of peptic ulcer. For the patient who has a family history or any history remotely suggestive of diabetes, blood sugar determinations should be made from one to two hours postprandially, or preferably after ingestion of 75 or 100 gm. of glucose. If the level is above 110 mg. per 100 ml., it is advisable that it be brought to normal by whatever means is necessary as long as the prednisone is continued.

*Fibrous invasive thyroiditis (Riedel's struma).* Fibrous invasive thyroiditis was described by Riedel<sup>24</sup> in 1896. It is considered still to be a rarity. Woolner, McConahey, and Beahrs<sup>25</sup> and others observed 20 cases among 42,000 thyroidec-tomies during a 36-year period. I can recollect having seen it only four times. In this disease, fibrous tissue destroys the architecture of the thyroid gland, extends invasively beyond the thyroid capsule, not at all like the closely encapsulated changes in struma lymphomatosa. The invasiveness of this dense fibrous tissue is such that it may involve the trachea severely, causing obstruction. It may so involve the blood supply of the thyroid and parathyroids as to cause tetany, and it may involve the surrounding musculature and even extend up the great vessels of the neck to the skull.

*Treatment.* If the disease is diagnosed when it is unilateral, subtotal thyroid resection may be attempted but is difficult to accomplish. If it is generalized and obstruction is occurring, then wedge resection of the isthmus and medial portion of both lobes, sufficient to free the trachea against subsequent obstruction, is usually the best treatment that can be offered.<sup>24-26</sup>

*Struma lymphomatosa (Hashimoto's thyroiditis).* In recent years, since it was discovered that struma lymphomatosa is so intimately connected with autoimmune mechanisms, it has also been called "autoimmune thyroiditis." This disease was first described by Hashimoto<sup>27</sup> in 1912, and the first cases to be described in this country were those reported by Graham and McCullagh<sup>28</sup> in 1931. The cause of the condition is not known. One theory is that an unknown factor damages the cells, allowing thyroglobulin to escape and thus causing production of autoimmune antibodies, which are secondary to the damaging agent. Others favor the idea that the disease is a result of autoimmunity, and there is experimental evidence to support this. Today it is commonly believed that Hashimoto's thyroiditis and primary myxedema without goiter are clinical variants of the same disease. In Hashimoto's thyroiditis, functional thyroid cell failure occurs which leads to excessive activity of the pituitary gland and compensatory goiter. In primary

hypothyroidism the thyroid cell destruction is so severe that the hyperpituitarism is unable to produce thyroid hyperplasia or hypertrophy.

There is some evidence that there is a genetic predisposition to this disease.<sup>29</sup> A high titer of thyroglobulin antibodies is common in relatives of those patients who have the disease, and it has been known to be present in identical twins.

Almost certainly, early in the disease, there is some degree of failure of thyroxine production. Initially this is asymptomatic. It can usually be demonstrated by the fact that the butanol-extractable iodine in the serum is abnormally low even though the total protein-bound iodine may not be low. Under these circumstances the plasma contains less than normal amounts of thyroid hormone and more than normal amounts of other iodinated compounds.

Evidence of thyroid cell failure can be demonstrated histologically in most patients by various degrees of pink-staining cytoplasm in the thyroid cells (the so-called "Askanazy change"). There are also the hypertrophy and hyperplasia of the acinar cells, caused it is believed by an increase in TSH. As the degree of thyroid cell failure increases, the characteristic symptoms and signs and laboratory evidence of the deficiency become more apparent. Finally, the amount of colloid stored in the follicles decreases in proportion to the increase in cell damage. As thyroid function decreases further, the ability of the thyroid cells to trap iodine diminishes. The radioiodine thyroidal uptake falls to low levels, and the uptake cannot be stimulated to a normal amount by injected TSH.

The thyroglobulin antibodies probably are formed by plasma cells in particular and, to a lesser extent, perhaps by the lymphocytes that are such a prominent feature of the lesion. Lymph nodes in the adjacent areas may also be affected, showing lymphocytic hyperplasia. The infiltration of lymphocytes and plasma cells as well as the prominent epithelial changes within the thyroid tends to obscure the mild degree of loosely arranged fibrotic tissue present. In some cases the fibrosis may become extremely dense and histiocytes appear.

An increase in frequency of carcinoma in patients with Hashimoto's thyroiditis has been reported.<sup>30</sup> Such reports can frequently not be evaluated well in clinical terms because they are based on microscopic examinations. Meier and associates<sup>31</sup> reported an incidence of less than 1 percent of Hashimoto's thyroiditis in 256 patients with cancer of the thyroid. In our own institution, carcinoma has been found with Hashimoto's thyroiditis in 7 of 209 patients with the latter disorder. Crile and Hazard<sup>32</sup> observed 119 patients with Hashimoto's thyroiditis, proved by needle biopsy, treated with desiccated thyroid, and followed more than a total of 1000 patient years, none of whom showed clinical development of papillary carcinoma. In one of our patients the goiter failed to reduce during desiccated thyroid feeding, and the patient subsequently was found to have reticulum-cell sarcoma. In short, I believe that the risk of cancer in struma lymphomatosa is not sufficient to warrant thyroidectomy.

*Diagnosis.* Symptoms of Hashimoto's thyroiditis are few, and ordinarily comprise the appearance of a painless goiter, usually without obstructive symptoms, and if signs of hypothyroidism are present they are almost always mild. The character of the goiter itself is the most important diagnostic criterion leading to suspicion of the disease. The thyroid is diffusely enlarged and feels solid and rubbery, sometimes slightly lobulated, or the isthmus may stand out rather prominently and be mistaken for a nodule. Sometimes one side of the goiter is larger than the other and is thought to be multinodular goiter. In Hashimoto's thyroiditis all of the outer margins of the gland are usually easily defined by palpation, but it is the fact that the thyroid is of the same degree of firmness throughout that is likely to arouse suspicion. It seldom shows a single nodule that is hard, but if it does, malignancy should be suspected. Such a nodule may become evident only after treatment has been continued over a period of one month or two months.

As to diagnostic procedures, the best diagnostic criterion is that of microscopic proof of the pathologic changes, and this is ordinarily determined on a specimen obtained by needle biopsy.<sup>33,34</sup> Another useful diagnostic test is the tanned red-cell thyroglobulin-antibody test.<sup>35</sup> The complement-fixation tests are less dependable. With the tanned red-cell hemagglutination test, titers above 1 to 2,500 may be considered high. Positive tests were found in 65 percent of Roitt and Doniach's<sup>36</sup> 106 patients, and in 83 percent of a series of 54 of our patients.<sup>37</sup> A TSH test response is useful also; the test has been performed on more than 60 of our patients for whom the diagnosis was proved by needle biopsy, and the test results were abnormal and consistent with the diagnosis of struma lymphomatosa.<sup>38</sup> The test is performed as follows: On the first day a six-hour I<sup>131</sup>-uptake test is done (usually between 9 a.m. and 3 p.m.) and a dose of 5 units of TSH is given at 5:00 p.m. The I<sup>131</sup>-uptake test is repeated the next morning, and a significant increase is considered to be 50 percent or more of the original uptake value, provided that the initial uptake is greater than 10 percent of the tracer dose. The test may be invalidated by previously administered iodine or by the prior long-continued use of large doses of desiccated thyroid.

*Treatment.* Hashimoto's thyroiditis is treated as a compensatory goiter,<sup>36</sup> that is, by the administration of amounts of thyroid hormone larger than the physiologic amount. We have for many years used USP desiccated thyroid.\* Three grains daily is preferable, but 2 gr. a day may be all that is well tolerated. Caution in using large doses should be observed in the elderly patients, as well as in those with heart disease. Recently we have used triiodothyronine, † because the protein-bound iodine level will then be suppressed and will often provide a more convenient measurement of the degree of pituitary thyroid inhibition than will thyroidal I<sup>131</sup> uptake. Seventy-five micrograms per day is usually well tolerated; 100 µg. daily will produce suppression with greater certainty.

\*Armour Pharmaceutical Company.

†Cytomel, Smith Kline & French Laboratories.

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