autoantibodies as a risk factor for development of hypothyroidism after radioactive iodine therapy for single thyroid 'hot' nodule. *Acta Endocr (Copenh)* 1986;113:500–507.
8. Ratcliffe G, Cooke S, Fogelman I, Maisey M. Radioiodine treatment of solitary functioning thyroid nodules. *Br J Radiol* 1986;59:385–387.
9. Corstens F, Smals A, Buys W, Kloppenborg P. Letter to the editor. *N Engl J Med* 1984;310:1393.
10. Skillern P, McCullagh E, Clamen M. Radioiodine in diagnosis and therapy of hyperthyroidism. *Arch Intern Med* 1962;110:888–897.
11. Blum M, Shenkman L, Hollander C. The autonomous nodule of the thyroid: correlation of patient age, nodule size, and functional status. *Am J Med Sci* 1975;169:43–50.
12. Burman K, Earl J, Johnson M, Wartofsky L. Clinical observations on the solitary autonomous thyroid nodule. *Arch Intern Med* 1974;134:915–919.
13. Hegedus L, Veiergang, D, Karstrup S, Hansen J. Compensated ^{131}I-therapy of solitary autonomous thyroid nodules: effect on thyroid size and early hypothyroidism. *Acta Endocr (Copenh)* 1986;113:226–232.
14. Eyre-Brook I, Talbot C. The treatment of autonomous functioning thyroid nodules. *Br J Surg* 1982;69:577–579.
15. Corstens F, Huysmans D, Kloppenborg P. Thallium-201 scintigraphy of the suppressed thyroid: an alternative for iodine-123 scanning after TSH stimulation. *J Nucl Med* 1988;29:1360–1363.
16. DeGroot LJ. Graves' disease diagnosis and treatment. Multinodular goiter. In: DeGroot LJ, Stanbury JB, eds. *The thyroid and its diseases*, 4th edition. New York: Wiley, 1975:314–367 and 637–665.

EDITORIAL
The Autonomously Functioning Thyroid Nodule

Plummer in 1913 first reported hyperthyroidism resulting from nodular goiter as distinct from the hyperthyroidism seen in toxic diffuse goiter (Graves' disease) (*1*). He noted that the former type of hyperthyroidism was milder and was not associated with exophthalmos. We now know that Graves' disease is an autoimmune disorder in which thyroid stimulating immunoglobulins are produced resulting in thyroid hyperplasia and increased hormone secretion. In toxic nodular goiter, hyperthyroidism results from nodules which function antonomously, that is independent of the normal pituitary thyroid-stimulating hormone (TSH) control.

Plummer did not differentiate between the two types of toxic nodular goiter, toxic multinodular goiter (TMNG) and toxic autonomously functioning thyroid nodules (AFTN). This difference is useful clinically. Patients with TMNG are more likely to be older and have cardiac complications. A large multinodular goiter with autonomous function is often present for years before the onset of hyperthyroidism (*2*). This presence of autonomous function contraindicates the use of thyroid hormone suppression in patients believed to have nontoxic multinodular goiter since the exogenous thyroid hormone is simply additive to that secreted by the nonsuppressible autonomous nodules.

AFTN can occur at any age (amongst teens as well as the elderly) and are discrete and usually solitary nodules. Hamburger, in an excellent review, called this Goetsch's disease, named after Emil Goetsch who remarkably worked out much of the pathophysiology in 1918 (*3*). There is not total agreement on the pathogenesis of AFTN, but most researchers agree with Miller that the autonomous function develops at a very early stage in the evolution of clinical AFTN (*4*). In patients with palpable AFTN, he demonstrated micronodules possessing autonomous function elsewhere in the gland utilizing microautoradiographic techniques.

Most AFTN are nontoxic and the evolution of toxicity is usually very gradual if it occurs at all. A group of seven authors reported on 312 patients with nontoxic AFTN who were followed 1–5 yr. Only 20 evolved into the toxic state, and in only 15 others was an increase in size reported (*5*). Autonomous nodules 2.5 cm or less rarely cause hyperthyroidism. In 62 toxic AFTN reported by Hamburger, all but 4 were 3.0 cm or greater in size (*6*). In a total of 349 patients with AFTN, he found toxic lesions in 56.5% of patients over 60 yr of age but only in 12.5% in patients under 60. Degeneration of AFTN is also common and is seen on thyroid imaging as a central area of reduced activity surrounded by the functioning tissue. This should not be mistaken for malignancy. Although cancer may occur elsewhere in the gland, or even incidentally as a nonfunctional mass within an AFTN, carcinoma in the autonomously functioning tissue itself is exceedingly rare. In most cases of carcinoma reported in "hot" nodules, the dianosis of autonomous function was not conclusively established. For all practical purposes, one does not need to be concerned about malignancy in the AFTN.

Received Aug. 16, 1990; accepted Aug. 16, 1990.
For reprints contact: Donald A. Meier, MD, Department of Nuclear Medicine, William Beaumont Hospital-Troy, 44201 Deguindre Rd., Troy, MI 48098-1198.

The diagnosis of AFTN is considered when concentration of the radionuclide tracer is greater or equal to that of the extranodular tissue. Since a cancer occasionally can appear hot with a technetium-99m-pertechnetate tracer and cold with radioiodine, it would seem prudent to confirm that the nodule is functional with radioiodine or possesses autonomous function as described below. If the patient is hyperthyroid, this is not necessary.

When autonomous nodules do not secrete excessive amounts of thyroid hormone, TSH will not be suppressed and there will be good visualization of the extranodular tissue on thyroid scans. As the secretory activity of the AFTN increases, TSH will be progressively suppressed so that extranodular activity on the scan will be proportionately less. With toxic AFTN, there is little or no visualization of extranodular tissue.

Not all hot nodules on a scan are AFTN since occasionally areas of function may represent compensatory hyperplasia secondary to disease elsewhere in the gland. This differentiation is important from the clinical point of view since areas of compensatory hyperplasia may respond to levothyroxine administration, but for AFTN, treatment with thyroid hormone is contraindicated. Areas of compensatory hyperplasia are TSH-dependent, and with the more widespread use of ultrasensitive TSH assays, simple measurement of the serum TSH may be diagnostic. In patients with areas of compensatory hyperplasia, the TSH should be elevated or high normal, whereas a suppressed TSH would indicate an AFTN. If ultrasensitive TSH assays are not available, a thyrotropin-releasing hormone (TRH) test could be performed. An exaggerated TSH response to TRH would suggest compensatory hyperplasia. Repeating the thyroid scan after suppression with thyroid hormone (0.15–0.2 mg levothyroxine daily for 3 wk) also distinguishes AFTN from compensatory hyperplasia. With AFTN, there would be preferential suppression of extranodular tissue as TSH is suppressed by the exogenous levothyroxine (T4). Areas of compensatory hyperplasia, in contrast, should suppress in proportion to extranodular tissue. In older patients and in patients with cardiac disease, suppression scans may be hazardous if the lesion is an AFTN because of the additive thyroid hormone and should not be performed.

Overtly toxic AFTN will have elevated levels of circulating free thyroxine and triiodothyronine (T3), as well as suppression of extranodular tissue on imaging. Less toxic AFTN may just show elevated T3 levels, since these lesions characteristically first secrete increased T3 hormone as they develop increasing function. The first laboratory evidence of more than a physiologic amount of thyroid hormone secretion by an autonomous nodule is suppression of the ultrasensitive TSH or blunting of the TSH response to TRH. This may occur when the serum T4 and T3 levels are still well within the normal range.

Treatment of toxic AFTN can be accomplished by surgery or radioactive iodine. Toxic autonomous nodules are relatively radioresistant and usually are greater than 3.0 cm in size. Therefore, higher doses of iodine-131 (^{131}I) need to be employed, i.e., at least 20 mCi. Since there is a significant amount of gamma radiation delivered to the extranodular tissue from the ^{131}I concentrated in the toxic nodule (*7*), surgery is usually considered to be the treatment of choice for younger individuals. The number of carcinomas following ^{131}I therapy of toxic AFTN is quite low, but reported series contain few patients under the age of 50 treated with radioactive iodine. Before the relatively stable natural history of nontoxic AFTN was appreciated, prophylactic treatment was often employed to prevent anticipated future toxicity. Since we now know AFTN can undergo degeneration and smaller nodules are relatively stable, routine treatment of nontoxic AFTN is no longer recommended. Follow-up at 6-mo intervals with ultrasensitive TSH measurement is adequate. Prophylactic treatment can be considered for older patients with nontoxic AFTN greater than 3.0 cm in diameter, especially if the ultrasensitive TSH is suppressed and the serum T3 level is in the upper normal range.

Since the extranodular tissue is usually suppressed in patients with toxic AFTN, the incidence of hypothyroidism following ^{131}I therapy should be low. Support for this view is provided by the article of Huysmans et al. in this issue of the *Journal* (*8*). Of 52 patients with toxic solitary AFTN treated with 20 mCi of ^{131}I, 46 patients were clinically and biochemically euthyroid after a mean follow-up period of 10 ± 4 yr. Of the six patients on replacement T4, one was not hypothyroid when treatment was started and two were treated with ^{131}I while still under the stimulatory effect of exogenous TSH. Other series reporting higher incidences of hypothyroidism following ^{131}I therapy include cases of nontoxic AFTN where extranodular tissue is not suppressed and concentrates the radioiodine.

The natural history of AFTN suggests that a small number of patients become hypothyroid no matter what form of therapy is chosen. Eyre-Brook et al. (*9*) report that toxic AFTN was adequately treated employing lobectomy and presurgi-

cal treatment with anti-thyroid drugs in 60 patients. Four became hypothyroid (one had previously been treated with ^{131}I). This emphasizes the observation that AFTN does not occur in an otherwise healthy gland. The associated autonomously functioning micronodules (*4*) may well undergo degeneration leaving behind a compromised thyroid with decreased reserve. In extreme instances, this may predispose the patient to become hypothyroid. Thus, the hypothyroid effects of ^{131}I therapy reported by Huysmans et al. (*8*) may be little more than that expected from the natural history of AFTN alone in a thyroid where ablation of a toxic nodule has occurred.

We occasionally have observed that on scans of patients with toxic solitary AFTN there are varying degrees of extranodular activity. Huysmans et al. report total suppression of extranodular tissue in 48 of their 52 patients with single toxic AFTN, but 4 had "near-total suppression." We agree with Miller that this extranodular activity represents other areas of autonomous function in the form of micronodules of varying size accompanying the dominant toxic nodule (*4,10*). This occurrence of extranodular tissue function has been recognized more frequently in recent years as the larger doses of ^{123}I and technetium-99m-pertechnetate have replaced ^{131}I as a thyroid scanning agent. These patients with toxic AFTN and nonsuppressed extranodular tissue are those most at risk for developing hypothyroidism following ^{131}I therapy. Should these patients be treated surgically? Huysmans et al. (*8*) state that when the pretreatment radionuclide image reveals uptake of iodine in extranodular parenchyma,^{131}I therapy has to be postponed. This would not deter us from recommending ^{131}I therapy in the older patient, since ensuing hypothyroidism is easily treated and may be expected in about the same small fraction of patients not treated with ^{131}I therapy.

Long-term treatment with antithyroid drugs does not have a place in the management of toxic AFTN in contrast to its use in autoimmune Graves' disease. In the natural history of Graves' disease, remission may occur and antithyroid drugs can be used in selected patients in anticipation of this remission. AFTN undergo degeneration, but the toxic lesions are larger and only very rarely undergo enough degeneration to eliminate the hyperthyroidism. Antithyroid drugs may be employed for patients with toxic AFTN on a short-term basis in preparation for surgery or before ^{131}I therapy in older patients and those with cardiac complications since ^{131}I may release stored thyroid hormone into the circulation and may make the metabolic abnormalities of hyperthyroidism transiently worse. This may be the reason Huysmans et al. employed antithyroid drugs in 12 of their patients.

Finally, one should realize that administration of iodine (usually in X-ray contrast media) can induce transient hyperthyroidism in patients with nontoxic AFTN (Jod-Basedow phenomenon). If necessary, these patients could be placed on beta blockers before their radiographic study.

Donald A. Meier
Howard J. Dworkin
William Beaumont Hospital
Troy, Michigan

REFERENCES

1. Plummer HS. The clinical and pathological relationship of simple and exophthalmic goiter. *Am J Med Sci* 1913;146:790.
2. Hamburger JI, Hamburger SW. Diagnosis and management of large toxic multinodular goiters. *J Nucl Med* 1985;26:888–892.
3. Hamburger JI. The autonomously functioning thyroid nodule: Goetsch's disease. *Endocrine Rev* 1987;8:439–447.
4. Miller JM, Horn RC, Block MA. The autonomous functioning thyroid nodule in the evaluation of nodular goiter. *J Clin Endocrinol Metab* 1967;27:1264.
5. McConahey M. The autonomously functioning thyroid nodule. In: Ingbar SH, Braverman LE, eds. *The thyroid*, 5th edition. 1986:1080.
6. Hamburger JI. Evoluton of toxicity in solitary nontoxic autonomously functioning thyroid nodules. *J Clin Endocrinol Metab* 1980;50:1089–1093.
7. Gorman CA, Robertson JS. Radiation dose in the selection of I-131 or surgical treatment for toxic thyroid adenoma. *Ann Intern Med* 1978;89:85.
8. Huysmans DA, Corstens FH, Kloppenborg PW. Long-term follow-up in toxic solitary autonomous thyroid nodules treated with radioactive iodine. *J Nucl Med* 1991;32:27–30.
9. Eyre-Brook IA, Talbot C. The treatment of autonomous functioning thyroid nodules. *Br J Surg* 1982;69:577–579.
10. Miller JM. Plummer's disease. *Med Clin North Am* 1975;59:1203–1216.