A Study of the Natural History of "Hot" Thyroid Nodules

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In the evaluation of thyroid nodules the three major clinical concerns are malignancy, hyperfunction, and cosmetic effect. It is now well accepted that the isolated "cold" nodule is the clinical setting in which thyroid cancer most often occurs (1–2). The clinical problem most often inferred from the presence of a "hot" nodule is hyperfunction. However, the clinical course, and natural history of this lesion are not as clearly defined as for many other thyroid conditions. We have evaluated our past experience with this disease in an attempt to define the implications of the discovery, in a patient, of a "hot" nodule. Data are presented in a manner distinct from the usual consideration of whether a "hot" nodule is suppressible or not.

MATERIAL AND METHODS

The case records of the Nuclear Medicine Section at Yale–New Haven Hospital for 1966 through 1971 were reviewed. The initial criterion for the selection of cases was the presence, as judged by two observers, of an area of increased uptake of radionuclide, clearly delineated from the remainder of the thyroid tissue. Nearly all scans were performed using sodium pertechnetate.

There were 133 cases selected. These were then reviewed and subdivided as follows.

Group I. Patients with a hot nodule on scan, in whom a history of prior thyroid or neck surgery could be elicited (37% of all cases).

Group II. Patients with a hot nodule on scan, with RAI uptake values that were never higher, in their clinical course, than outlined below in Group III (27% of all cases).

Group III. Patients with a hot nodule on scan, whose radioiodide uptake, at any time during the known course, exceeded the following criteria: 2 hr 10%, 6 hr 20%, and 24 hr 30%. We recognize that these criteria are somewhat more

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stringent than are used clinically. However, by using these levels we would tend to include more patients in the "hyperfunction" group, and if anything, overemphasize any possible progression of patients from the euthyroid to hyperthyroid categories (25% of all cases).

Group IV. Patients with the appearance of a hot nodule on scan, whose actual diagnosis fell into other categories (e.g., thyroiditis, hypothyroidism, etc.). These occurred in numbers too small to analyze statistically (11% of all cases).

Each of the first three groups was analyzed in terms of sex, mean age, age distribution, length and surface area of the nodule, and radioiodide uptake per unit of scan surface area. In addition, a subjective judgment was made as to whether the nodule was suppressing the remaining thyroid gland to the extent of 90% or more (by comparing the density of the nodule with nearby tissue). Uptake studies were performed after use of 5–10 μCi of 131I-Na, while most scans were performed after use of about 3 mCi of sodium pertechnetate.

RESULTS

Groups I, II, and III are compared in Table 1. The average length of follow-up was 14.1 months for group II (range 1–68) and 28.7 months for group III (range 1–72).

Sex. The female to male ratio in each of the three groups was greater than eight to one.

Age. If there had been a significant progression of patients from group II to group III during the course of the disease (that is, having an elevated radioiodide uptake), patients in group III would be expected to be older than those in group II. The mean ages of these groups was not statistically different. This same information (Groups II and III), plotted in terms of a probability distribution (Fig. 1) showed lines which were not significantly different, and they (as well as the curve for Group I) were approximately normally distributed.

Length. The length of the nodule, as it appeared on a rectilinear scan, without contrast enhancement, was measured. Groups II and III were statistically different (P < 0.005) and the data for group III was approximately normally distributed (Fig. 2). The data from groups I and II were also normally distributed.

Surface area. Mean surface areas of the hot nodules in the three groups (measured by planimeter) were compared. The mean surface area of hot nodules from group II was significantly less than group III.

Uptake. In those cases in which there was suppression of the remaining thyroid (as judged from the scan), an estimate of the uptake/cm² of scan surface area

TABLE 1
A Comparison of the Three Groups of Patients

| Sex distribution | Mean age (yr) | Mean length (cm) of nodule | Mean surface area (cm²) of nodule | Mean uptake per cm² |
|------------------|--------------|----------------------------|----------------------------------|-------------------|
| female/male      |              |                            |                                  |                   |
| GROUP I          | 41/5         | 49.7                       | 4.5                              | 11.7              |
| GROUP II         | 32/4         | 46.9                       | 3.8                              | 9.8               | 1.8%            |
| GROUP III        | 38/2         | 51.4                       | 4.5                              | 14.0              | 8.4%            |

* The mean age was not statistically different between the groups. The mean length of the nodule, and the surface area were statistically different between groups II and III (P < 0.005). The mean uptake/cm² was also different between groups II and III (P < 0.005).
**FIG. 1.** A probability plot of the ages of the patients in Groups II and III.

**FIG. 2.** The length of hot thyroid nodules in Group III, plotted on probability paper. The slight deviation of the upper end may be related to the small number of cases there (2 out of 35).

was made. (Surface area estimated as described above). The uptake/cm² in the patients in group III was significantly higher than in group II.

**Surgical findings.** Two patients were found to have hot nodules with a "cold" center. This finding was felt to represent central necrosis in an adenoma. This was confirmed in one case that went to surgery. Five patients in each of groups II and III underwent thyroid surgery. All had histologically benign lesions.

**DISCUSSION**

In 1960 Sheline and McCormack (3) studied 15 patients with functional thyroid nodules. Suppression with T3 was attempted in all cases, and none suppressed. They concluded that "such nodules elaborate hormone . . . and are autonomous." This initial finding was tempered by the report of Green and Farren (4). They attempted T3 suppression in 46 patients, and in 16 the hot nodule diminished
in size. The 1967 McCormack and Sheline (5) reported on a series of 53 patients in whom the diagnosis of "solitary hyperfunctioning nodule" was made on initial study. Only one patient developed hyperfunctioning from increased function within the nodule. Silverstein et al. (6) described the long-term follow-up in nine cases of hot nodules of the thyroid. They noted four distinct courses: persistent autonomy, persistent autonomy with reduced function, partial resumption of TSH dependence, and (in one case) degeneration of the nodule.

Our results are consistent with the latter three series, in that we found "hot nodules," as noted on scan, to be a heterogeneous group in terms of etiology as well as physiologic response. The single largest number of cases of "hot nodule" turned out to be due to prior surgery. Presumably these do not represent loss of the normal pituitary-thyroid axis function.

Of the patients in Groups II and III, we found that 52% had elevated radiiodide uptakes, by our admittedly stringent criteria. We do not have sufficient clinical data to support the diagnosis of hyperthyroidism in all these patients however. We feel that the functional status can not be inferred from the thyroid scan alone. While 57% of the patients in the elevated radiiodide-uptake group showed scan suppression of the surrounding and contralateral thyroid tissue, 63% of the patients with a hot nodule and normal radiiodide uptake showed the same finding. It would seem logical to assume that suppression of the surrounding thyroid tissue indicates autonomous function in relation to TSH. The above results do not support this contention. Further, the results of the limited number of T3-suppression tests performed are counter to this conclusion. As expected, of nine patients in the elevated radiiodide uptake group tested, none showed suppression of the nodule. In the normal radiiodide uptake group, however (again with the nodule the only functional tissue seen on scan), four or five patients tested showed suppression after T3 treatment. The division of patients into suppressible or nonsuppressible may be less significant than previously thought. Whether any of the patients had T3 toxicosis is unknown.

We found that the progression of patients from the normal radiiodide uptake group to that with elevated uptake was strikingly small. We are aware of only one patient in our series who showed progression from the euthyroid state, with normal radiiodide uptake, to the clinically hyperthyroid state, with an elevated, nonsuppressible uptake (Fig. 3).

Miller and Hamburger in 1965 (7) noted that no primary carcinoma of the thyroid had been reported presenting as an autonomous nodule, although "incidental" thyroid carcinoma had been found at operation coincidentally with autonomous nodules. In 1971 Meier and Hamburger (8) reported a case of carcinoma and an autonomous nodule in a patient who had previously had radiotherapy. They reported three other patients with radiation who developed autonomous nodules and they suggested an etiologic relationship. We are unaware of any patients in our series with a similar history. Further, there were no thyroid cancers in 10 patients in our series who underwent surgery.

From the above results we draw the conclusion that this is a relatively benign disease in both the physiologic as well as the histologic sense. The incidence of cancer and/or progression to the clinically hyperthyroid state is very low. Thus, we feel there is sufficient justification for the conservative management of this problem ("watchful waiting" unless there are symptoms), reserving surgery for those patients with clear evidence of progression of the disease.
Fig. 3. The patient is a 19-yr-old girl in whom a functioning thyroid nodule was first noted at age 13. At that time her maximum radioiodide uptake was 12%. By December 1969 the size of the nodule had increased, and the maximum uptake was 53%. A TSH stimulation on Jan. 2, 1970 shows the presence of functional tissue on the opposite side, and a repeat scan on July 23, 1971 shows further enlargement of the nodule. This nodule did not suppress with triiodothyronine therapy. Surgery revealed a microfollicular adenoma.

SUMMARY

As judged by an area of increased uptake on a thyroid scan, 133 cases were selected. Thirty-seven percent of these had prior surgery on the neck and another 11% were judged to be due to thyroiditis or other miscellaneous causes. The remaining cases were divided into two classes, depending on whether the thyroidal radioiodide uptake value was above or below rather stringent criteria. Evidence was presented that there was little movement from the group with "normal" radioiodide uptake values into the hyperthyroid range. On the basis of this finding, and the benign nature of the lesions found in 10 patients who did undergo thyroid surgery, it was concluded that the "hot" nodules are relatively benign and that conservative management is likely indicated.

REFERENCES
1. Bantels, E. C. Evaluation of the thyroid nodule. Surg. Clin. N. Amer. 42, 655 (1962).
2. Veith, F. J., Brooks, J. R., Grigsby, W. P., and Selenkow, H. A. The nodular thyroid gland and cancer. J. Amer. Med. Ass. 270, 431–435 (1964).
3. Sheline, G. E., and McCormack, K. R. Solitary hyperfunctioning thyroid nodules. J. Clin. Endocrinol. 20, 1401–1408 (1960).
4. Greene, R., and Farran, H. E. A. On single "hot" nodules of the thyroid gland. J. Endocrinol. 33, 537 (1965).
5. McCormack, K. R., and Sheline, G. E. Long term studies of autonomous thyroid nodules. J. Nucl. Med. 8, 701–708 (1967).
6. Silverstein, G. E., Bunke, G., and Cogan, R. The natural history of the autonomous hyperfunctioning thyroid nodules. Ann. Intern. Med. 67, 539 (1967).
7. Miller, J. A., and Hamburger, J. I. The thyroid scintiscan: I. The hot nodule. Radiology 84, 66–74 (1965).
8. Meier, D. A., and Hamburger, J. I. An autonomously functioning thyroid nodule, cancer, and prior radiation. Arch. Surg. 103, 759–761 (1971).