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Long-Term Studies of Solitary Autonomous Thyroid Nodules[1,2]

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Correlation of function and histology of the solitary hyperfunctioning nodule was established by Cope, Rawson, and McArthur (1) in 1947. The relative decrease or lack of function in tissue outside such a nodule also was well documented in their report. Their studies were based on radioactive assays of surgically removed tissues. With the development of collimated scintillation counters and automatic scanning equipment and the use of thyroid stimulating and suppressing agents, solitary hyperfunctioning[3] nodules are now readily demonstrated *in vivo*.

Opinions as to the significance of the solitary hyperfunctioning nodule vary. Dobyns, Skanse, and Maloof (2), Rawson (3), and Dobyns (4) have stated that hyperfunctioning nodules may be the potential cause of hyperthyroidism or the source of masked hyperthyroidism, even though symptoms are not obvious. Roualle (5) and Cope (6) noted that in dealing with a true toxic adenoma, removal of the nodule alone would suffice to control the hyperthyroidism when the uninvolved tissue is relatively inactive. Werner (7) stated that sole removal of the toxic adenoma is transiently effective, but that hyperthyroidism recurs soon thereafter. According to Miller, Horn, and Block (14) additional small hyperfunctioning adenomas are occasionally noted when the primary hyperfunctioning nodule is removed surgically.

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[2]Presented at the 13th Annual Meeting of the Society of Nuclear Medicine, Philadelphia, Pennsylvania, June 22-25, 1966.

[3]The term hyperfunction as used in this paper implies that on a gram for gram basis, the tissue of concern appeared to be functioning at a rate in excess of that in the extranodular tissue. It implies nothing with respect to the clinical state of the patient.

The relationship of thyroid carcinoma to the solitary hyperfunctioning nodule is also of concern. At the time of a previous study in 1960 (8), only two reports could be located of carcinoma in association with such nodules. Apparently both these carcinomas had been noted incidentally when the nodules were excised. Since that time, a number of reports (9-12) have appeared, each describing one or two instances of malignancy in association with solitary hyperfunctioning nodules. Nearly all of these were thought to be coincidental findings. One exception was the carcinoma described by Dische (13) in which the malignant tumor was the hyperfunctioning tissue. The general conclusion is that thyroid carcinoma may be associated with solitary hyperfunctioning nodules, but that this is very infrequent.

Numerous studies have demonstrated that the solitary hyperfunctioning nodule is not responsive to suppressive doses of desiccated thyroid or triiodothyronine given for periods of several days. Furthermore, the extranodular thyroid tissue that is partly suppressed is responsive to both stimulation by exogenous thyrotropic hormone and further suppression by thyroid hormones. Change in the function of the nodule itself has not been demonstrated, however. To our knowledge, no studies have been undertaken to determine whether prolonged administration of an exogenous thyroid substance will suppress such nodules.

Little is known of the natural history of these hyperfunctioning autonomous thyroid nodules. In the present study, a number of euthyroid patients with solitary hyperfunctioning nodules, not subjected to surgical procedure or radioiodine therapy, have been followed for periods of up to nine years. Of particular interest was whether the size or number of nodules would change spontaneously and whether those that initially did not produce hyperthyroidism would ultimately do so. Several of these patients were given exogenous thyroid hormones for long periods and the effects of such therapy were observed.

This study also includes a group of patients whose solitary hyperfunctioning nodules were removed surgically or treated with radioiodine. In this group we were particularly concerned with change of function and possible development of new nodules in the remaining extranodular thyroid tissue.

MATERIAL

All thyroid scintiscans performed in the Nuclear Medicine Section of the University of California Medical Center, San Francisco, from 1956 through 1963 were reviewed. Among these, were 68, in which the scan and the clinical information regarding the patient were consistent with the diagnosis of a solitary hyperfunctioning nodule. During the past year, as many of this group as were available were recalled and their thyroid status reinvestigated. Clinical evaluation, triiodothyronine *in vitro* red-cell incorporation tests, radioiodine uptake studies and scintiscans were included in these evaluations of nodularity and clinical thyroid status. Reports of studies performed in other centers on six patients unable to return here, are also used in this review.

Clinical data and repeated laboratory studies were obtained on 53 of the 68 patients. This number included the following patients: eight treated with

radioiodine for associated hyperthyroidism; 23 whose nodules were removed surgically; eight treated for prolonged periods with replacement doses of exogenous thyroid substance; and 14 without definitive therapy.

Thyrotoxicosis-Radioiodine Treatment

At the time of their initial studies, eight patients were considered hyperthyroid and were treated with radioiodine, with individual doses ranging from 3 to 40 mc. The first three patents were treated with multiple small doses, totalling 8 mc. to 25 mc., of ^{131}I to control the hyperthyroidism. Single large doses (20 to 40 mc.) were given the latter five patients with the intent of destroying the hyperactive foci.

The follow-up evaluations ranged over a period of two to eight years, with an average of 4.3 years. Control of the hyperthyroidism was achieved in each patient and marked decrease in size or clinical disappearance of the palpable nodule was noted in those treated with the larger single doses. In each case, the extranodular thyroid tissue showed a uniformly distributed increase in function after cessation of hyperfunction in the nodule (Fig. 1). There has been no recurrence of hyperthyroidism nor evidence of new hyperfunctioning foci.

Hyperfunctioning Nodule—Surgical Removal (Nodulectomy or Lobectomy)

For 23 of the 27 patients who had surgical removal of the hyperfunctioning nodule either by nodulectomy or lobectomy, follow-up evaluations were obtained two to nine and one-half years after operation. Contact with two patients could not be established. Two others have died, one from gastrointestinal hemorrhage and one from widespread metastatic carcinoma of the gallbladder.

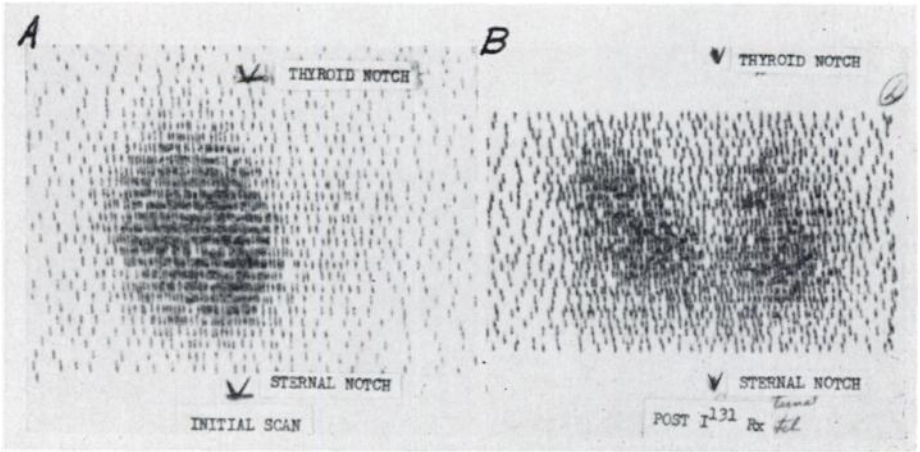

Fig. 1A. Scan showing solitary hyperfunctioning nodule prior to ^{131}I therapy for thyrotoxicosis.

Fig. 1B. Repeat scan done 1 year later showing uniform function in the entire gland.

No evidence of malignancy was seen in the thyroid tissue removed surgically in any of these 27 patients. Histologically, the nodules consisted of hyperplastic appearing follicles of various size with papillary infolding and large cuboidal to columnar cells. The follicles of the extranodular tissue appeared hypoplastic and were lined with thin flat cells. See description of typical histology in prior article (8).

At the time of surgical removal of the nodule, two of the patients were mildly hyperthyroid and the rest were euthyroid, according to clinical and laboratory data. One of the hyperthyroid patients had been followed clinically without definitive thyroid treatment for four years before operation, but neither the nodule nor the borderline clinical state had changed. Supplemental thyroid medication was begun in nine patients immediately after surgical ablation, as a routine method of management without establishing clinical need for supplemental thyroid substance. The remaining 14 have remained euthyroid without supplement.

At the follow-up examination, scintiscans obtained on 19 patients showed uniform function over the residual thyroid tissue and no evidence of further nodule formation (Fig. 2). The attending physicians of four other patients have noted no recurrent nodularity on recent and repeated palpations of the thyroid.

In one patient, hyperthyroidism developed in the surgical remnant four and one-half years after lobectomy. Preoperative scan information and histologi-

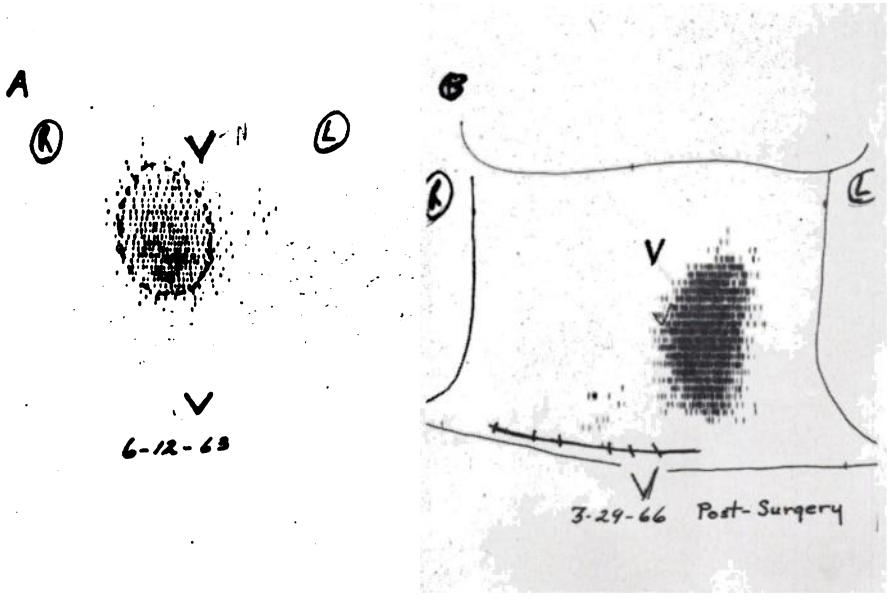

Fig. 2A. Initial scan showing the localization of the activity to the solitary nodule palpable in the right lobe.

Fig. 2B. Repeat scan following surgical total right lobectomy, with uniform function in tissue previously non-functional.

cal examination of the removed lobe demonstrated that initially this patient had a hyperfunctioning nodule with relatively little function in the extranodular thyroid tissue. At the time of the lobectomy the patient was euthyroid. Palpation and scintiscan have revealed no evidence of recurrent nodule formation in this patient. In the other 22 there has been no change in thyroid function during the period of follow-up.

Suppressive Doses of Thyroid Hormone Medication

Eight patients, all euthyroid at the time of their initial studies, were treated with exogenous thyroid hormones. One of these eight patients had been receiving exogenous thyroid medication for six years before entering this study. The particular thyroid hormone administered differed according to the clinician responsible for each patient; however, the doses were equivalent to one to four grains of desiccated thyroid. Treatment extended over periods of from two and one-half to four and one-half years after the initial studies. Repeated studies showed no change in the size or in the lack of suppressibility of the nodule in six of these patients. In two patients, however, the nodules became distinctly smaller and their hyperactivity ceased and function in the extranodular thyroid tissues is now uniformly distributed. These two nodules have not been removed surgically and there is no way to distinguish between the possibility that the changes observed were the result of spontaneous necrosis or were due to a suppressive effect of the medication.

No Definitive Therapeutic Management

Of the 29 patients in whom no definitive therapy was given for the hyperactive nodules, follow-up data have been obtained on 14. Seven patients are lost to follow-up and eight have died. Two of the 29 were hyperthyroid at the time of the initial examination but refused definitive therapy. One of these died of cerebral hemorrhage four years after the initial studies and the other could not be located. The follow-up period for the 14 restudied patients ranged from two and one-half to eight and one-half years. The average follow-up time was 4.8 years.

Neither the size of the nodule nor the hyperactive, autonomous nature has changed in 11 of these 14 patients. Four of the 11 have been followed for seven and one-half to eight and one-half years. In no instance has a second hyperactive nodule been demonstrated.

In two patients the size of the palpable nodule decreased and hyperactivity within the nodule ceased. In each patient uniform function in the extranodular tissues has appeared (Fig. 3) and both have remained euthyroid.

Thyroid function at the initial study in the fourteenth patient of this group was considered as high normal. The patient returned four years later with a three-month history of increased symptoms, consistent with hyperthyroidism. Repeated studies confirmed the hyperthyroidism. The nodule was removed by lobectomy and the patient became euthyroid. This is the only patient in whom euthyroidism changed to hyperthyroidism, the result of function within the autonomous nodule.

DISCUSSION

Nine of the 53 patients on whom follow-up data were obtained were considered overtly hyperthyroid and one patient questionably hyperthyroid at the time the initial studies revealed their hyperactive nodules. In none of these patients, after removal or destruction of the nodule, has the hyperthyroidism recurred. Furthermore, in no patient has a new hyperfunctioning nodule developed, regardless of whether the patient was, or was not treated. Hyperthyroidism associated with a diffusely enlarged surgical remnant did, however, develop in one patient whose hyperfunctioning nodule had been removed four and one-half years earlier. In another patient, hyperthyroidism developed four years after the first demonstration of a hyperactive nodule. This latter patient was considered euthyroid at the time of the initial studies and received no definite therapy before the overt hyperthyroidism developed. The hyperthyroidism was the result of increased function in the nodule.

The follow-up studies indicate that, occasionally, a patient with a solitary hyperfunctioning nodule will become hyperthyroid from changes in either the nodule or other portions of the gland. Such hyperthyroidism, however, occurred in only two of the 43 euthyroid patients of the present study.

A study of toxic nodular goiter by Miller, Horn, and Block (14) demonstrated the presence of more than one hyperactive nodule in some patients. Non-palpable micronodules which histologically and by autoradiography appeared more active than the remainder of the thyroid gland were also found by these authors incidental to surgical removal of the main hyperactive focus. There is a possibility that such microscopic hyperactive areas may develop into clinically evident hyperactive nodules at a later date. This possibility has not been substantiated by the present data. In follow-up periods of up to nine and one-half years (average 4.4 years), no new hyperactive nodule has been demonstrated in the 53 patients included in this study.

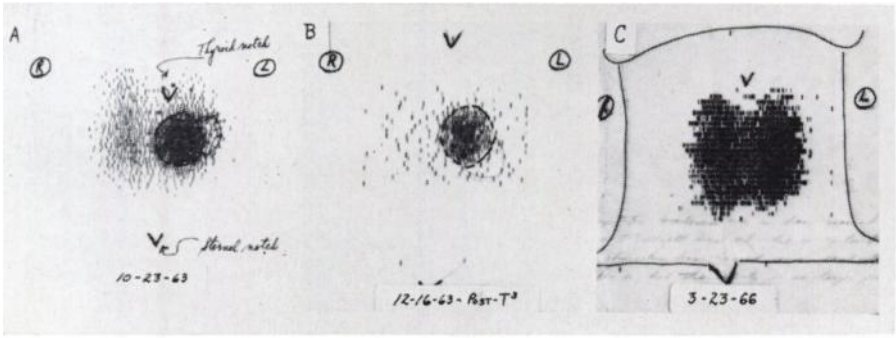

Fig. 3A. Initial scan in a euthyroid patient showing a solitary hyperactive focus and slight activity in the remaining thyroid tissue.

Fig. 3B. Repeat scan after one week on triiodothyronine. A suppressive effect is noted in the extra-nodular tissue.

Fig. 3C. Repeat scan showing uniform function throughout the thyroid. No definitive therapy was given in the interval between this study and the one demonstrated in 3b.

Miller and his associates (14) found cystic degeneration in some excised hyperactive nodules. With prolonged suppressive thyroid medication in two of our patients and no definitive therapy in two others, the size and function of their nodules decreased. Although cystic degeneration may have occurred in these four patients, none has been operated upon and this possibility can not be evaluated. No episode of tenderness or pain has occurred to suggest hemorrhagic degeneration.

The specimens obtained on 27 patients whose initial treatment was excision, gave no evidence of carcinoma on histologic examination. Neither was carcinoma noted in the one nodule excised because of subsequent hyperthyroidism. Furthermore, no clinically suspicious areas appeared in any of these glands during the observation period. The general impression that carcinoma is infrequent in thyroid glands which contain a solitary hyperactive nodule is supported by these findings.

SUMMARY

Clinical evaluation, laboratory studies, radioiodine uptake studies and scintiscans were repeated on 53 patients whose initial study had shown the presence of a solitary hyperfunctioning thyroid nodule. The clinical management varied. Some patients received therapeutic radioiodine and others underwent surgical removal of the nodule or received exogenous thyroid hormone. Another group received no definitive therapy.

Hyperthyroidism developed in one patient from increased function within the nodule and in another from an apparently diffuse change in the residuum after lobectomy. In two patients who received prolonged exogenous thyroid hormone and in two who received no therapy, the nodule became smaller and lost its hyperfunction. No new hyperfunctioning nodule was noted during the follow-up period of up to nine and one-half years. In those patients who were hyperthyroid, elimination of hyperfunction by surgical removal, or by radioiodine treatment of the nodule, has controlled the hyperthyroidism to the present time. No thyroid carcinoma was found.

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In December, 1966, the Board of Trustees voted to increase membership dues. This action was taken to meet rising operational costs and to provide funds for the expansion of educational programs.

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