The Diagnosis and Treatment of Carcinoma of the Thyroid*

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Before going into a discussion of the diagnosis and treatment of carcinoma of the thyroid, I would like to make a few observations on the means of detection.

Thyroid scanning, in my opinion, is useful only in the study of nodules. We see many patients who have had scans for diffuse thyroid enlargement, and I feel that in this instance, scans are useless. The basic reason for the scan is to discover which pieces of thyroid tissue have to be removed because of possible malignancy. I would like to emphasize, that the physician has to do the scan himself. He has to localize the nodule, properly mark it on the scan, and remain during the scan, as the patient may move his neck, thus moving the position of the nodule in reference to the marks. We have seen scans in the early days of isotope scanning where the technician, who was not taught to palpate the thyroid, marked the scan. This system is inadequate, as errors can occur.

Using the T-3 suppression test, the criteria for suppression is a fall in uptake below 20% in 24 hours after a week on T-3, 150μ daily. However, the normal uptake is often below 20%, and hyperthyroid patients may also have less than 20% uptake, so the test is losing some of its specificity. I think the criteria for the suppression test should be changed, or the interpretation of it, to indicate that there is *"no significant"* fall in uptake after T-3 for a week. It is very difficult to establish such criteria, because I do not know what normal figures to give. We recently saw a patient with a nodule who had 8% uptake in 24 hours prior to T-3. We went ahead with T-3 suppression, and he had 7% after T-3. We did not know what to do or how to interpret this. We treated the patient with radioactive iodine, thinking that the nodule was not suppressible, and the other lobe did reappear on later scanning. This patient had an autonomous nodule with an 8.0% uptake.

In my opinion, 3- and 5-hour uptakes are absolutely essential. I would not want an uptake run only at 24-hour intervals, because we do see patients who have taken iodides or, unknown to us, antithyroid drugs and who have normal 24-hour uptakes but who have blocked thyroid function and are not making thyroid hormone at the moment. Therefore, it is necessary to run 3- and 5-hour uptakes to identify this blocked type of function and, if diagnosis is not clear at that time, at a later 24-hour point.

In the hot nodule with low radioiodine uptake where the T-3 suppression test may not be of great value, one can give TSH and do a scan afterward to see if the other lobe reappears. If it does reappear, indications are that the nodule is an autonomous one which was suppressing TSH.

I now want to discuss the diagnosis and treatment of carcinoma of the thyroid. Carcinoma of the thyroid gland is both rare and common. It is a frequent diagnosis on pathological sections, but clinically it is a rare disease. Very few patients die from carcinoma of the thyroid. Each of us has seen so few thyroid carcinomas of clinical significance that it is difficult to gather a series sufficiently large to determine what treatment techniques are best. As some

* The following is an edited transcription of a lecture presented by Dr. Kirkland at the Postgraduate Course in Nuclear Medicine, February 27, 1975, in Williamsburg, Virginia.

evidence of the incidence, Dr. Fratkin showed that in one hundred cases of thyroid nodules 70% were cold. Of the 70% that were cold, he said 15% were carcinomatous. That is a high incidence of carcinoma of the thyroid. Recently, a student and I went around on the wards at the Medical College of Virginia and felt every patient's thyroid regardless of what the patient had been admitted for. Thirty-three percent of the women incidentally had palpable nodular thyroid disease. If we take these female patients with nodules—70% of them cold and 15% of them with carcinoma—3.48% of women in the Medical College of Virginia should have carcinoma of the thyroid. Obviously these figures are not true clinically. Even the pathologist has problems in diagnosing thyroid malignancy. Thyroid-stimulating hormone stimulation of the thyroid makes it so hypertrophic that sometimes the thyroid looks malignant although it doesn't behave that way.

In patients with carcinoma of the thyroid, the natural course of the disease is variable, so that a long-term follow-up is necessary to determine what happens to them. One cell type, such as papillary carcinoma of the thyroid, might change to follicular, or the metastases may show at the same time different pathological types. Any treatment I propose, therefore, would have to be very arbitrary.

I would like to mention something about the etiology of the carcinoma of the thyroid. Two Australians, Purves and Geishbach, in 1948, gave rats thiourea for two of their three-year life spans and found that 100% of the rats developed carcinoma of the thyroid. (This fact does not stop us from giving propylthiouracil to patients, and some clinics advocate this as the best treatment for hyperthyroidism). They stated in their article, "We think that the administration of thyroid extract to these rats would have prevented this." They gave thiourea to rats after hypophysectomies and none of these animals developed carcinoma of the thyroid. This suggests to me that the etiology for the carcinoma, or an etiological factor, was the TSH level which rose in the thiourea-treated rats and stimulated a blocked gland. That was the first finding that led me to think that carcinoma might be produced by long-term TSH stimulation of a blocked or damaged thyroid gland. There is also an increased incidence of carcinoma of the thyroid in patients who have congenital enzyme blocks. One type of congenital enzyme block is followed by nearly 100% incidence of carcinoma of the thyroid—another fact that makes me think that TSH stimulation might lead to carcinoma. There is a higher incidence of carcinoma of the thyroid in thyroiditis where the gland may be injured. The TSH may rise and the same circumstances occur. Irradiation of the neck in childhood is another etiologic factor. There are also cases of thyroid carcinoma which are TSH dependent. These tumors tend to grow more rapidly if the TSH levels are high. We should, therefore, keep the TSH low in patients who have carcinoma of the thyroid. This concept has been an important influence in my treatment of thyroid patients. Once hyperthyroidism is eliminated, I think anyone with thyroid disease should be on long-term suppressive thyroid hormones.

These factors led me to review the histories of patients with carcinoma of the thyroid at the Medical College of Virginia in order to see if I could find a thyroid-damaging factor. Fifty percent of the patients had had some thyroid destructive disease, such as thyroiditis or colloid goiter, or treatment for thyroid suppression, such as surgery. None of them had had radioiodine therapy, but I think the incidence of carcinoma of the thyroid might increase after radioiodine if we live long enough to observe this course.

How do we diagnose the carcinoma of the thyroid? Most cases are not diagnosed by symptoms, although there are some symptoms, such as hoarseness or a tracheal narrowing shown on AP and lateral x-rays. Hoarseness suggests that the recurrent laryngeal nerves might be invaded, and this might indicate the possibility of carcinoma, especially if it is accompanied by a mass in the thyroid area. Dysphagia is suspicious. X-ray studies of the esophagus showing real obstruction are helpful and do suggest that there is true disease present and not just an anxiety globus hystericus. We recently noted a bruit over the thyroid gland in the absence of hyperthyroidism. This indicated that there was high vascularity and suggested the possibility of

Thyroid	
Pathology found in "hot" nodules	
Nodular colloid goiter	70%
Hyperplastic goiter	7%
Adenoma	15%
Carcinoma	0%
Unclassified	8%

Fig. 1—Pathology in "hot" nodules at MCV.

Pathology found in cold nodules (184)	
Nodular colloid goiter	58%
Chronic thyroiditis	4%
Adenoma	17%
Carcinoma	13%
Unclassified	8%

Fig. 2—Pathology is 184 cold nodules at MCV.

malignancy. A distant metastasis might be a hint of carcinoma of the thyroid. If there are nodules, we want to do scans. If the scan shows a cold nodule, carcinoma is a prime possibility. Figure 1 shows the pathology we have seen in our "hot" nodules. Nodular colloid goiter was found in 70% of cases, hyperplastic goiter (we are not sure what the pathologist meant by this as these were supposedly nontoxic patients) in 15%, adenoma in 15%, but no carcinoma. Figure 2 shows the pathology in 184 cold nodules which were removed. Thirteen percent were carcinomas of the thyroid.

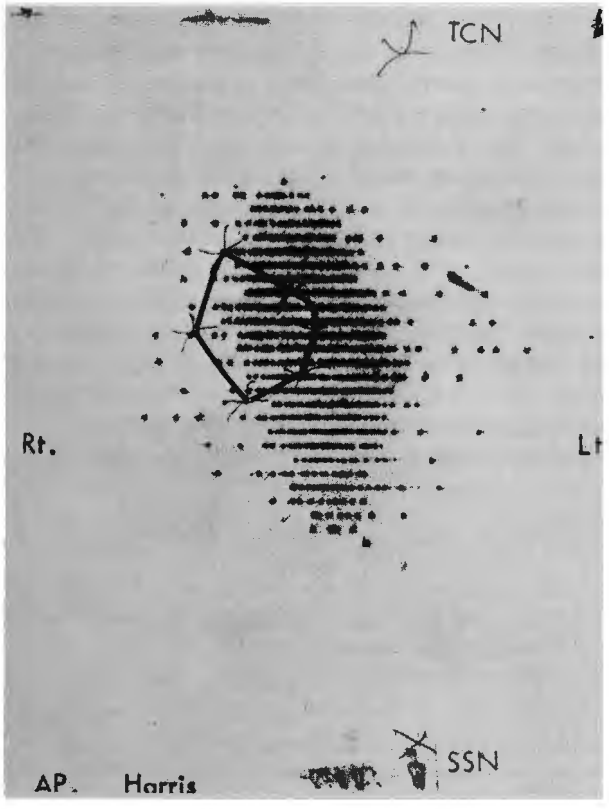

Fig. 3—AP scan of patient with suspect nodule.

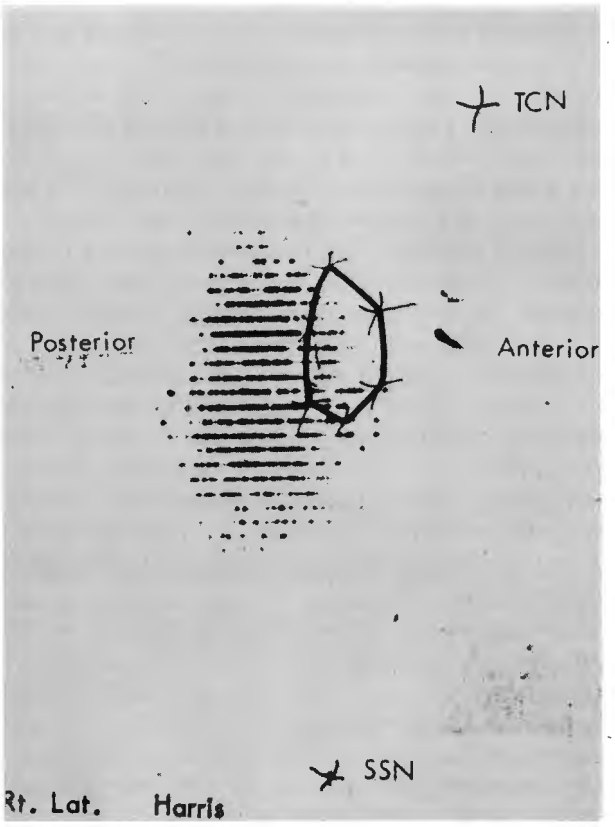

Fig. 4—Oblique scan of same patient, revealing cold nodule.

I want to emphasize the importance of lateral scans. Figure 3 is an AP scan of a patient who had had a nodule. One might think that this was a functional nodule and not malignant. But on the lateral or oblique scan (Fig. 4), a cold nodule is seen in front of the radioactivity. Figure 5 shows a nodule that might be interpreted as a hot nodule. There is suspicion that it might not be a hot nodule, however, for the center of the gland is thicker, and one would think it would have a higher radioactivity. On the lateral scan, it is confirmed as a cold nodule.

The treatment of carcinoma of the thyroid varies with the cell type, and Figure 6 shows the main types of the disease. The first approach to treatment of carcinoma of the thyroid is surgery. The extent of the surgery depends on the type of lesion. A biopsy with a frozen section will indicate what type of malignancy one is dealing with. The nodule should be removed along with any suspect tissue, and if it is carcinoma on a frozen section, a total thyroidectomy is indicated. The only exception would be that I would ask the surgeon not to take the parathyroid glands.

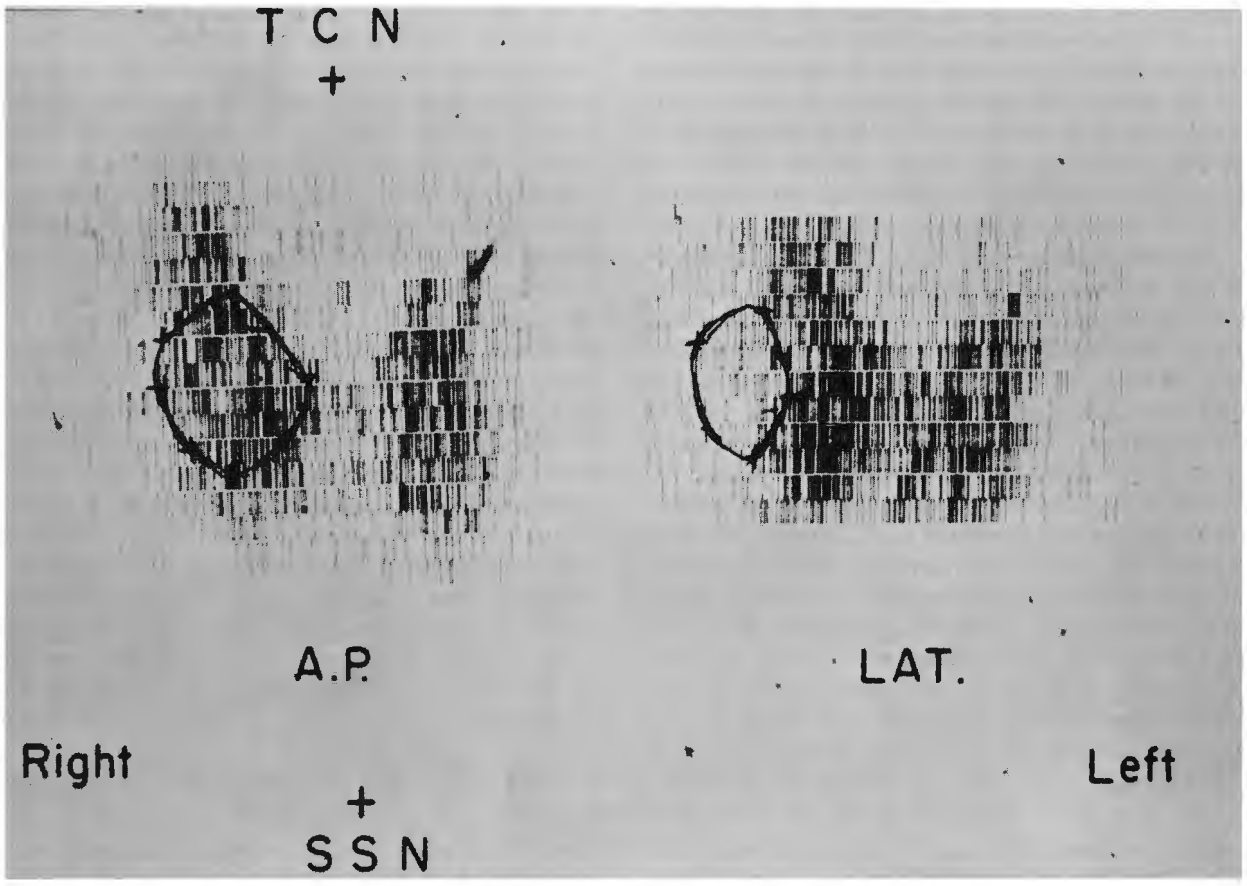

Fig. 5—*Left.* AP scan of possible cold nodule; *Right.* Confirmed on lateral scan.

As this might be difficult, he would perform a nearly total thyroidectomy. Myxedema as a result of surgery is of no concern because the patient will be placed on thyroid extract. All patients with carcinoma of the thyroid should be on thyroid extract for the rest of their lives in the hope that hormonal suppression of the tumor will be achieved, just as one might treat carcinoma of the breast with appropriate hormonal treatment. Radical neck dissection is not often my choice. The surgeon usually decides this. If he feels that the nodes are within the range of surgical resection, he should try to get them out, but in my opinion, severely disfiguring, radical neck dissection is of no great value. The prognosis for carcinoma of the thyroid is so good that, other than for anaplastic types, I would not urge extensive neck dissection. In a medullary carcinoma, there is one follow-up technique and that is to check on calcitonin levels, because this offers a marker for continuing disease. If the calcitonin levels were high before removal and afterwards fell to normal, it would be very reassuring that the malignancy had been completely removed. If calcitonin levels rose in the future, they would indicate that the carcinoma had recurred and that further treatment should be considered.

There is a difference of opinion regarding the surgical follow-up schedule. Some authors would wait a month and do a radioactive iodine uptake

Classification of Thyroid Neoplasms

A. Adenoma
B. Carcinoma
   1. Adenoma malignum
   2. Papillary
   3. Follicular
   4. Medullary
   5. Anaplastic

Fig. 6—Main types of thyroid disease.

study to see if there is any residual thyroid tissue in the neck. They would ablate it with radioactive iodine and put the patient on thyroid hormone while waiting to see whether the patient develops further disease. This seems to me unnecessary as the patient may have already been cured. I would put the patient on thyroid hormone after the initial thyroidectomy and wait. If disease appears, I would stop the thyroid replacement and do a ^{131}I scan. If there is uptake of ^{131}I in the residual thyroid area, a thyroid ablative dose of ^{131}I should be given. In one to two months, a tracer dose should be given to see whether there is any retention of the isotope after 48 hours. At the Medical College of Virginia, we determine 24- and 48-hour urinary excretions of ^{131}I at that stage, and if there is any significant retention (if the patient excretes less than 90% of the radioiodine in the urine in 48 hours), we scan the whole body searching for areas of retention and treat with large doses of radioiodine. If there were significant retention, we would try to stimulate maximal uptake of radioactive iodine prior to treatment by giving TSH intravenously or intramuscularly for three days and repeat the ^{131}I uptake. Should there be increasing retention, I would keep up the TSH for three more days until the maximal uptake was reached, because this may be the only opportunity to get an excellent uptake in the tumor. Therefore, I would continue TSH until I obtained maximum retention of the tracer dose, then give a large dose of radioactive iodine (150 millicuries of radioiodine), hoping to obtain the maximum uptake in the tumor. After radioiodine had had a chance to accumulate in the gland, I would put the patient on triiodothyronine (one of the few clinical uses for this hormone in treatment) in order to suppress TSH in the interim, while waiting for the effect of the dose. The patient should be kept on that dose for about six weeks. The dose should then be discontinued and the patient retested with radioactive iodine in eight weeks. As long as there is uptake of radioactive iodine or retention of the isotope with less than 90% excretion in 24 hours, I would continue to treat the patient with radioactive iodine at approximately two-month intervals until I had no further retention of the radioactive material. Of course, this has to be monitored by blood counts, primarily platelet counts. We have not seen significant platelet reduction until we have given 300 to 400 millicuries of radioiodine. Once I had achieved as much radioactive iodine treatment as possible, that is, there was no longer any retention of the isotope 48 hours after a tracer dose, I would put the patient on totally suppressive and replacement doses of levothyroxine or triiodothyronine. The triiodothyronine is used because it can be stopped more quickly, and its effect disappears more quickly. An additional method of treatment to consider, when radioactive treatment was no longer effective, would be x-ray therapy to any areas that were causing symptoms.

The major point I would like to make is that we should try to prevent thyroid carcinoma by administration of thyroid hormones to all patients with potentially high TSH and damaged-thyroid disease, using suppressive doses of levothyroxine. In my opinion, all patients who have thyroid disease should be treated with thyroid hormone indefinitely, once hyperthyroidism has been eliminated.