Endocrine Imaging in the Management of Goiter and Thyroid Nodules: Part I

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THYROID GLAND

The endocrine gland most commonly imaged by scintigraphy is the thyroid. The most common thyroid disease is enlargement of the thyroid gland (*1–3*). Approximately 85% of enlargements of the thyroid are colloid nodular goiter. The second most common cause of enlargement of the thyroid gland is Hashimoto's struma.

COLLOID NODULAR GOITER (ENDEMIC GOITER)

Prevalence

Secondary to Iodine Deficiency. Endemic goiter before 1920 was the physiologic adaptation of the patient to iodine deficiency (*4*). In 1924, the state of Michigan surveyed the prevalence of enlargement of the thyroid in school children. The prevalence of enlarged thyroids was 39% (*5*). The use of iodized salt was instituted and in 1928 a resurvey of school children in the same four counties showed that the incidence of enlarged thyroids had dropped to 9% (*6*). The principal source of increased iodine intake by humans, however, came from iodine in the milk of cows. Iodide-containing salt licks were instituted in practically every farm in the United States.

Whereas, 100 μg of iodine a day is adequate iodine intake (*6*), the average intake of iodine in the United States today is over 600 μg. The sources of increased iodine intake are too numerous to detail here, but they are not dependent on the use of iodized salt.

Secondary to Chemicals in the Environment with Antithyroid Action. In 1965, London and others published that the incidence of enlarged thyroids in school children in a county in Kentucky was 33% (*7*). Vought et al., in 1967 published that the incidence of endemic goiter in a county in Virginia was 29% (*8*). The iodine intake in both counties, however, was determined to be more than adequate.

Gaitan and others have published abundant evidence that the principal cause of endemic goiter or colloid nodular goiter in counties with adequate or more than adequate iodine intake is chemicals in the environment that have anti-thyroid actions as high as 27 times greater than propylthiouracil on a weight basis (*9–10*).

Inherited Biochemical Defects or Previous X-ray Therapy. It is of interest, however, that the environmental stress of iodine deficiency or chemicals in the environment causes goiter first in individuals with an inherited biochemical defect in their thyroid glands (*11*), or partial impairment of the thyroid function from previous x-ray therapy (*12*).

EVOLUTION AND DIAGNOSIS OF COLLOID NODULAR GOITER

In 1953, Selwyn Taylor published a landmark study on the evolution of colloid nodular goiter (*13*). He did thyroidectomies on 60 patients with simple and nodular goiters 48 hr after tracer doses of ^{131}I. He performed autoradiography on slices of the thyroid 2–5 mm thick to correlate function with morphology. He found five stages in the evolution of colloid nodular goiter.

Stage I

This is simple hypertrophy and hyperplasia and increased vascularity and increased uptake of radioiodine in physiologic response to increased thyroid-stimulating hormone (TSH) response to decreased serum and tissue thyroid hormone. Thyroid scintigraphy in the normal thyroid gland with ^{123}I shows a pencil-shaped right lobe somewhat longer than the left lobe, as shown in Figure 1, with little or no isthmus visible.

When the pituitary sends out increased amounts of TSH to stimulate the thyroid to work harder, the thyroid gland enlarges and the ^{123}I scan shows a "U-shaped" goiter due to enlargement of the isthmus. Figure 2 shows the U-shaped enlargement of the thyroid in a 43-yr-old woman. There was no palpable or visible goiter at the time of this scan. The scan showed a "U-shaped" simple goiter with a radioiodine uptake of 28%, a T4 subnormal at 3.2, and a TSH elevated at 17.4.

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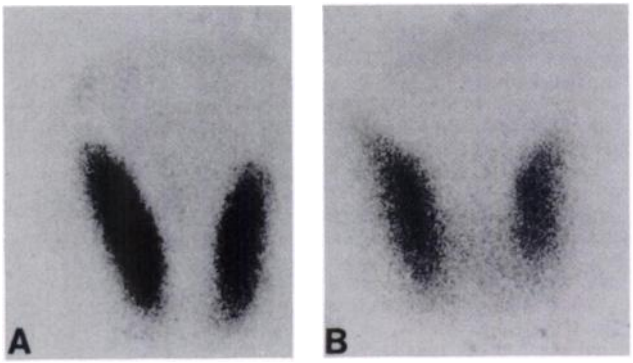

FIGURE 1. Normal thyroid gland scintigram. Little or no evidence of isthmus (^{123}I, 300 μci, at 24 hr after tracer).

Stage II

In the evolution of colloid nodular goiter, Stage II is represented by increased radioiodine uptake in an area of the thyroid that is "working harder" than other areas of the thyroid, at least in concentrating radioiodine. This has been referred to in the literature as a "radioactive hot nodule" or "hot nodule." These hot nodules can also be found by scintigraphy, when no goiter is palpable.

Increased Trapping in Hot Nodule. These "hot nodules" may have three stages of development in function. At first, the trapping of iodine, production of thyroid hormone, and growth of these radioactive hot nodules can be suppressed by the administration of thyroid hormone. Since the goiter and the hot nodule were caused by increased TSH activity, the first goal of thyroid hormone therapy is to decrease the TSH to subnormal levels, usually to 0.1 or less. The second goal is to concentrate on keeping the T4 and T3 within normal limits. Evidence has developed during the past 4–5 yr that elevation of the serum T4 and T3 above the normal range, in the suppression of goiters, may lead to an increased incidence of osteoporosis.

Autonomous Production of Thyroid Hormone. Later, and especially without treatment, the hot nodule may become autonomous and non-responsive to the administration of thyroid hormone in trapping iodine and the production of thyroid hormone. When this happens, the administration of thyroid hormone for therapy results in a disproportionate elevation of the serum T4 and symptoms of thyrotoxicosis.

Excessive Production of Thyroid Hormone Causing Plummer's Disease. These hot nodules may autonomously produce amounts of thyroid hormone that suppress the TSH to below normal as evidence that the patient has too much thyroid hormone. New evidence indicates that many if not most patients with colloid nodular goiter of some duration and in older patients may already have subclinical Plummer's disease (*14*). Plummer showed that, whereas the most common type of thyrotoxicosis was in persons 20–40 yr of age who required a sub-total thyroidectomy of both lobes to free the patient of the thyrotoxicosis, some older patients with nodular goiters could be cured by removing a solitary nodule that was overactive in producing thyroid hormone. In an earlier study (*15*), Plummer noted that 60% of patients greater than 60 yr of age with colloid nodular goiter have overt Plummer's disease (*15*) and that the average duration of colloid nodular goiter before the diagnosis of hyperthyroidism is 17 yr (*15*).

Figure 3 is the thyroid of a 38-yr-old woman who at age 4 had radiation to her tonsils. In 1984, she was found to have a 2 × 1.5-cm palpable nodule in the right lobe. Her TSH was 1.9. Scintigraphy showed, as shown in Figure 3, the palpable nodule in the right lobe was a 2 × 1-cm hot nodule, but unexpectedly there was a 1-cm hot nodule in the lower part of the left lobe. There also was an easily visible isthmus. The fact that the nodule in the lower end of the right lobe is a hot nodule is good news, because I'm only aware of one case reported in the world's literature where cancer of the thyroid was a radioactive hot nodule (*16*). In most cases of thyroid cancer, the cancer concentrates radioiodine less than 1/40 the extent of normal thyroid tissue (*17*). The fact that there is a U-shaped enlargement of this thyroid with a nodule in each lobe is strong evidence for colloid nodular goiter where the incidence of thyroid cancer is probably less than 2%.

When a patient has Plummer's disease the administration of 29 mCi of radioactive iodine as an outpatient usually shrinks the nodule so that it is no longer visible or palpable and frees the patient of thyrotoxicosis. Figure 4 is a scintigraph of the thyroid in a 58-yr-old woman who on 10/18/82 had a 2 × 3-cm nodule on the left lobe and a 1-cm nodule on the right lobe. On 8/18/87, her T4 was within normal limits at 9.5, but her TSH was suppressed to 0.1. She was started on 0.125 mg of Synthroid. On 1/22/80, her weight decreased (with an increased appetite)

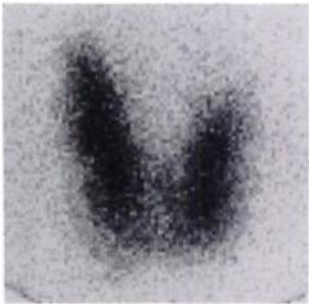

FIGURE 2. U-shaped enlargement of the thyroid, characteristic of Stage I colloid nodular goiter.

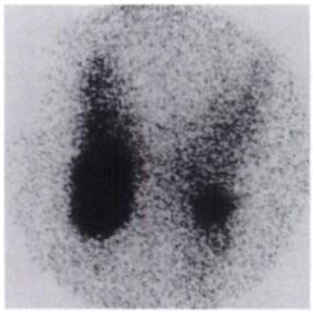

FIGURE 3. U-shaped enlargement plus radioactive "hot" nodule, characteristic of Stage II.

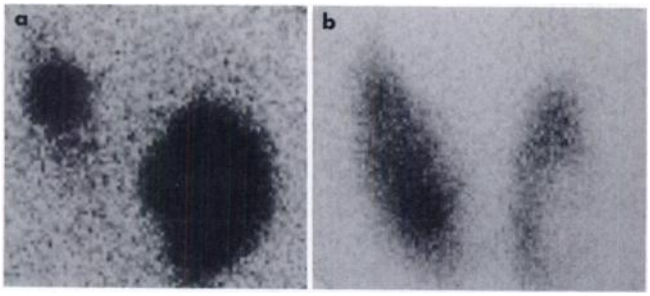

FIGURE 4. Stage II thyroid scintigram (A) before and (B) after treatment of a hot nodule with Plummer's disease.

and her pulse rose to 100. Her radioiodine uptake, which had been 21%, suppressed only to 16% on Synthroid. Normal suppression is 50% or more. Her T4 was now markedly elevated to 25 and her TSH was suppressed to less than 0.1. I therefore treated her with 29 mCi of radioactive iodine while she was on Synthroid. On 4/8/88, her T4 had normalized at 6.5 and her TSH had normalized at 4.7. The scan showed normalization of the right and left lobe except for a "cold" area in the normal left lobe. Figure 4A shows her scan at the time of the treatment and 4B after treatment. Once the T4 and TSH have been normalized, the patient is put on proper maintenance doses of Synthroid to prevent further development of the colloid nodular goiter.

Stage III: The Onset of Necrosis and Hemorrhage

In Stage III, the hard-working hot nodule commonly undergoes sudden necrosis and hemorrhage and becomes radioactively cold. A fine-needle aspiration is performed to prove that the radioactive cold nodule shows blood-tinged fluid, confirming the diagnosis of necrosis and hemorrhage. The surrounding tissue is also aspirated to rule in colloid nodule as the underlying substrate and to rule out thyroid cancer, which would require surgery. However, the fluid recurs in a majority of these patients. Most of these patients are referred for surgery when they have been on adequate doses of Synthroid and have had 3–5 aspirations with recurrence or growth. Figure 5 shows a U-shaped enlargement of the thyroid with at least four radioactive hot areas and at least three radioactive cool areas, typical of Stage III colloid nodular goiter with repeated areas that have undergone necrosis and hemorrhage.

Figure 6 is the scintigram of the thyroid in a 44-yr-old woman who in April 1987 developed the onset of wheezing. On 6/4/87, she had a sudden enlargement of the left lobe of the thyroid gland with "a stiff neck." On 6/9/87, she was admitted to the emergency room because of dyspnea. Figure 6 shows the large area of decreased radioactivity in the lower outer two-thirds of the left lobe. A chest roentgenogram showed marked tracheal deviation and compression to an airway of about 1 mm in diameter as the cause of her dyspnea. An emergency thyroidectomy was performed.

FIGURE 5. Stage III with several "hot" and "cold" nodules "in a U-shaped goiter."

Stage IV: Progression

Taylor describes Stage IV as a repetition of Stage III with development of numerous hot and cold nodules.

Stage V: Other Complications Occurring in the Stage IV Goiter

Complications in Stage V include failure to respond to thyroid hormone and repeated fine-needle aspiration (see above discussion) as well as the following.

Tracheal Compression and Deviation. Most of these patients should have a chest x-ray to check for tracheal deviation and compression. The patient's physician must look at these roentgenograms himself, since the radiologist usually reads them as "normal chest." The presence of significant compression is usually a good indication for the necessity of a thyroidectomy.

Thyroid Cancer. A fine-needle aspiration showing thyroid cancer is also an indication for surgery. If these complications have developed during the administration of thyroid hormone with the suppression of TSH, there is no indication for continuing treatment with thyroid hormone unless a thyroidectomy is done. There is no indication for radioactive iodine unless the patient has Plummer's disease. Figure 7 is the thyroid scintigram of a 63-yr-old woman whose mother and sisters had goiters. Her mother underwent a thyroidectomy. The patient had a goiter for 47 yr and her goiter shrank on thyroid hormone. She stopped her thyroid hormone 4 yr previously at the

FIGURE 6. Scintigram of Stage III goiter with necrosis and hemorrhage in the left lobe producing a large radioactively cold area with tracheal deviation and compression by chest roentgenogram requiring an emergency thyroidectomy at night to relieve the obstruction of the airway.

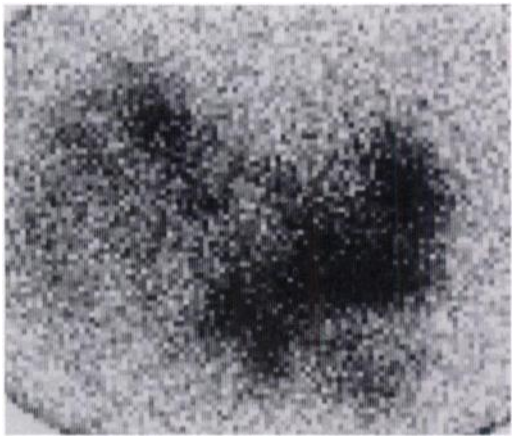

FIGURE 7. Stage V 284-g goiter resected surgically. There was papillary and follicular carcinoma in the right lobe and a sclerosing carcinoma of the isthmus and tracheal compression.

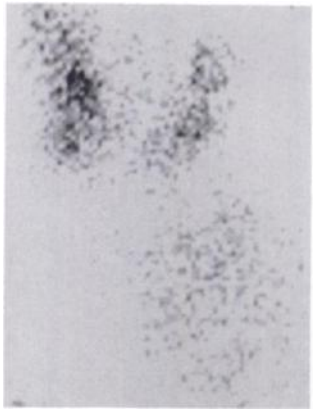

FIGURE 8. Substernal goiter 7 yr after a left lobectomy.

suggestion of her physician and her goiter enlarged. On 3/18/87, she had a 400–600-g goiter. The scan shows multiple cold nodules. On 2/20/87, a chest x-ray showed tracheal deviation and compression from the enlarged right lobe. On 6/25/87, a "near total" thyroidectomy removed 284 g of goiter and there was invasive papillary adenocarcinoma in the right lobe of the thyroid and sclerosing carcinoma of the isthmus. Figure 7 shows marked enlargement of the thyroid, U-shaped, with numerous hot and cold nodules. Most of the right lobe and isthmus are radioactively cold.

Substernal Goiter. Another complication with time is substernal goiter. Thompson and Allo published their 10-yr experience with substernal extension of colloid nodular goiter (*18*). The removal of substernal goiter accounted for 50 out of 872 thyroidectomies at the University of Michigan between 1972 and 1982. The mean age of the patients having these thyroidectomies for substernal goiter was 60 yr. The goiter was present for an average time of 10 yr. Twenty-two had airway compression. Eight were malignant. Four of five patients with benign disease with compression symptoms had superior vena cava syndrome. It is obvious that airway compression is more dangerous in the presence of substernal goiter.

Figure 8 is a scintigram of our latest patient with a substernal goiter who had merely had a lobectomy for colloid nodular goiter in the left lobe 7 yr previously and presented with this huge substernal goiter on the left. It should be noted that if the scintigram is stopped at the bottom of the lobe of the thyroid, a substernal goiter may be missed.

Many substernal goiters are detected first by chest roentgenogram or CAT scan and are referred to nuclear medicine for a radioactive scintigram because the experienced thyroid surgeon wants to be certain that the mass is a substernal goiter rather than mediastinal lymphadenopathy or a thoracic aortic aneurysm, etc.

Sequestered Nodular Goiter (versus Lateral Aberrant Thyroid Syndrome). We first described "sequestered nodular goiter" as an entity separate from "lateral aberrant thyroid" [in which patients have metastatic thyroid carcinoma to regional cervical nodes as the first symptom of thyroid cancer (*19*)]. Thyroid nodules can separate completely from the thyroid gland just as fibroid tumors of the uterus may separate completely from the uterus. This condition is rare, occurring in older patients who have colloid nodular goiter. The sequestered nodules are histologically similar to the nodules in the goiter and contain no evidence of lymph node tissue. Figure 9A is a scintigram of a patient with a U-shaped colloid nodular goiter with a radioactively hot nodule at the upper tip of the right lobe of the thyroid gland, freely movable in all directions, and about to separate from the thyroid gland.

Figure 9B shows a pathology specimen of an even further separated nodule in another patient.

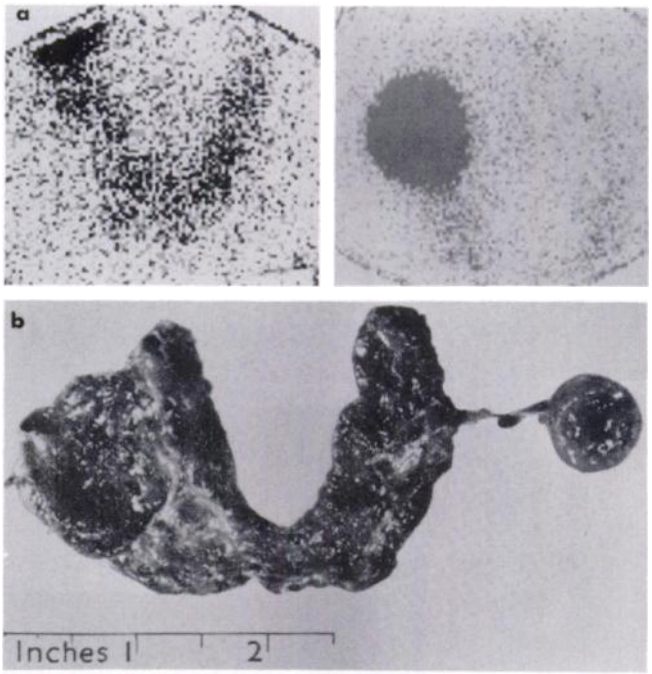

FIGURE 9. Scintigram showing a hot nodule sequestering off the tip of the right lobe of a colloid nodular goiter (A). (B) Pathology specimen of an even further separated sequestered nodule in another patient.

HASHIMOTO'S STRUMA

Struma Produced by Excess Iodine

With the advent of increased iodine intake, we showed that lymphocytic thyroiditis began to occur in 1924 with the use of iodized salt in the state of Michigan, and in patients prepared for surgery for Graves' disease with iodide (*20*). This incidence increased through 1952 in Michigan and has been reported at the Mayo clinic and elsewhere (*20*). Thus, the implementation of increased iodine intake resulted in the development of another goiter, Hashimoto's struma (*20*).

Scintigraphy

Normally, Hashimoto's struma is characterized scintigraphically by a relatively normal-appearing thyroid. Usually, there is an absence of an isthmus with ^{123}I scintigraphy in Hashimoto's struma goiters up to 50 or 55 g in size. Occasionally, however, the thyroid scintigrams may duplicate those seen in colloid nodular goiter. Figure 10A shows a U-shaped colloid nodular goiter and Figure 10B shows a hot nodule with apparent autonomous function with suppression of uptake in the left lobe and the rest of the right lobe. Both of these patients were later diagnosed as having Hashimoto's struma, had high anti-thyroid antibody titers and high serum TSH and shrank strikingly in 2 mo on Synthroid. It is the rule, rather than the exception, for patients with high serum TSH levels and high thyroid antibody titers to have the goiter disappear within 2 mo or more when thyroid hormones have been normalized.

THYROID CANCER

Thyroid cancer is an unusual anomaly in Stage III colloid nodular goiter; however it is common in a solitary cold nodule in a "normal thyroid gland." Figure 11 shows a cancerous cold nodule in the lower half of the left lobe in an otherwise normal thyroid. The chance of this nodule containing thyroid cancer in young people is 35%–40%.

Staging by Scintigraphy

Staging is dependent upon extent of surgical resection of the "normal" thyroid gland.

Lobectomy Versus Near Total Thyroidectomy. Lobectomy results in a biostatistically significant fall in the serum T4 and T3, but these values do not fall below normal. In response to this decrease in serum T4 and T3 in tissue, there is a biostatistically significant increase in the TSH, but never above the normal range. Compensatory hyperplasia and hypertrophy occur in the remaining lobe and the radioiodine uptake prevents visualization of residual uptake in the remnant left after the initial lobectomy and in metastases to regional nodes or lungs and bones.

FIGURE 11. Solitary cold nodule in the lower left lobe in an otherwise normal appearing thyroid gland. Thyroid carcinoma was found.

Lobectomy Plus Subtotal Lobectomy of the Opposite Lobe. A common operation for thyroid cancer is to do a "total" lobectomy on the lobe containing the nodule but to only remove four-fifths of the opposite lobe. When this procedure is followed, adequate staging is rarely obtained because there is about a 9%–11% uptake present, with most of the radioiodine going into the normal thyroid remnant.

Detection of metastases in lymph nodes or in lungs with ^{131}I versus CAT scan or MRI. We do not use CT scanning and MRI in patients who have had modified neck dissection because most of them show enlarged nodes by CT scanning and MRI. However, this does not prove that there are metastases in these nodes. Radioactive iodine uptake proves that the lymph nodes contain thyroid carcinoma metastases and can be treated with radioactive iodine. It must be remembered that after neck dissection, there is a tendency for the body to regenerate enlarged lymph nodes that are usually read as "benign lymphocytic hyperplasia." These enlarged lymph nodes may be as large as golf balls and there may be several in the region of a previous neck dissection.

Radioiodine Percent Uptake In Thyroid Remnant and Staging. About 3 out of every 1000 patients can be staged, partially at least, with the entire thyroid present. About 5% of patients with thyroid cancer can be staged fairly well with a residual uptake of 5%–9%. About 90% of patients can be adequately staged when the uptake is 1%–4%. The importance of the staging is shown by the excellent article by Schlumberger et al in 1986 on 283 patients with lung and bone metastases (*21*). They found that complete remissions were obtained after treatment with radioactive iodine in 64% of patients with a normal chest x-ray with diffuse radioactive iodine uptake in lungs as compared to 8% of 186 patients with a positive chest x-ray and positive lung scans.

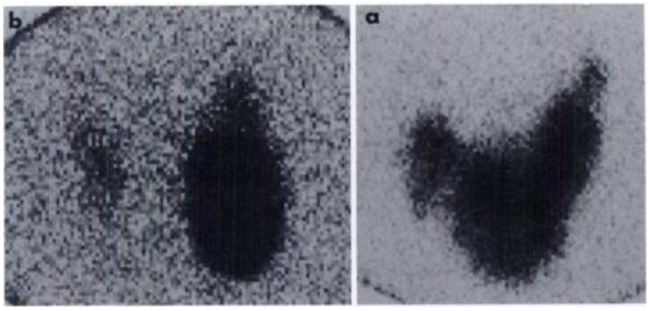

FIGURE 10. Scintigrams of two patients that appear to have colloid nodular goiter, Stage III, but actually have Hashimoto's struma (see text).

Human Serum Thyroglobulin (HTG) Plus Therapy Dose Scintigrams. Recently, Pacini et al. demonstrated that lung metastases from thyroid cancer could be imaged with ^{131}I in patients with elevated serum thyroglobulins after they had been given a treatment dose but not after a tracer dose (*22*). Most of his patients of this type also had a regression of lung metastases after a treatment dose. We are discouraged with the routine diagnostic use of HTGs because of the high frequency of increased anti-thyroid antibodies making these elevated HTGs non-reliable.

Large Lung Metastases Are Incurable. Figure 12B is a neck and lung scintigram in a patient who had a large goiter that had never been removed. The patient had received small doses of radioiodine for therapy without any previous radioiodine uptakes or scans. We achieved no uptake of tracer in lungs with ^{131}I before total thyroidectomy, but good uptake in lung metastases after a total thyroidectomy left her with a remnant showing an uptake of 2%. Her chest roentgenogram, however, showed numerous large metastases (Fig. 12A).

Unfortunately, when a patient has lung metastases of this size and volume, it doesn't really matter how much uptake the patient has because these patients all die of their thyroid cancer. This patient died within 4 yr despite strenuous treatment. Good results are obtained when the uptake is diffuse through micrometastases in lungs.

Of 750 patients treated with ^{131}I after surgery for thyroid cancer, only 6 have had recurrences after negative scans at 1 and 3 yr after treatment. These six had such extensive and aggressive thyroid cancer that we were surprised to achieve an apparent total regression of their cancer. If they had not had a repeat total-body scan every 5 yr "permanently," we would not have detected their recurrences at 15–25 yr after the initial treatment. With detection of recurrent uptake in micrometastases, one 200-mCi repeat treatment dose resulted in another apparent total regression.

Importance of a Total-Body Scan for Thyroid Cancer Follow-up. Figure 13 is a total-body scan done on a patient with an insular variant of well-differentiated thyroid carcinoma. She had had a near total thyroidectomy elsewhere (after she had delayed recommended surgery for 8 yr!) and one treatment dose of 175 mCi of radioactive iodine. Within 1 yr, she returned with severe pain in her right sacroiliac joint. A 2-min total-body scan, shown in Figure 13, was performed 24 hr after a 2-mCi tracer dose of ^{131}I. This total-body scan shows uptake in her known lung metastases and mediastinal nodes seen by chest roentgenogram and in her right sacroiliac joint. It also detected, however, a metastasis in the right parietal area of the skull, and the right parietal area of the brain immediately underneath the skull metastasis, in two lumbar vertebrae, and in the mid-right femur. Contrast-enhanced CT scan of the brain confirmed the metastasis to the skull and also to the brain immediately under the skull metastasis. She had a 27% radioiodine uptake in her lungs with a positive chest roentgenogram.

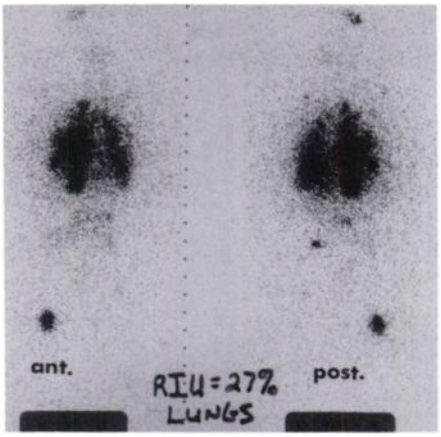

FIGURE 13. A 2-min total-body scintigram taken 24 hr post-tracer administration of 2 mCi ^{131}I on a whole-body scanner with two crystals (14 × 24), front and back, and two high-energy collimators. Numerous metastases were detected that were not suspected.

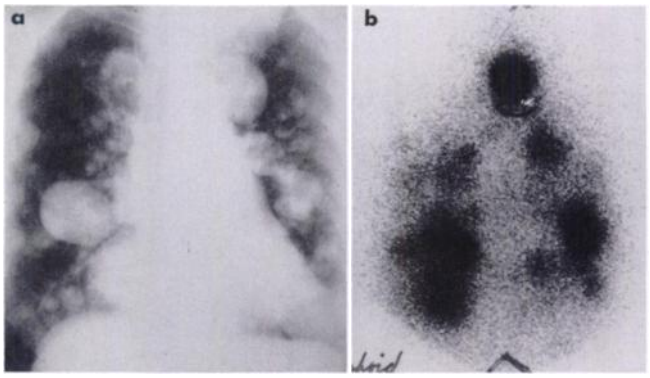

FIGURE 12. Scintigram of the lungs (b) in a woman with numerous large metastases in lungs after a "total" thyroidectomy with a residual 2% uptake in lungs. She was incurable.

THALLIUM FOR MEDULLARY THYROID CARCINOMA

Thallium will detect metastases that do not concentrate radioiodine. It also may be used while the patient is on thyroxine (*23*). The problem with thallium for papillary and follicular thyroid carcinoma is that it is nonspecific. We eliminated its routine use when it imaged a normal lymph node by histopathologic examination.

Thallium may be helpful, however, in managing medullary thyroid carcinoma. Figure 14 is a total-body scan of a 63-yr-old patient with chronic leukemia.

He had had a total thyroidectomy in July 1989 for medullary cancer with one positive node. His serum calcitonin was positive to a titer of 1:60,000 with a normal titer being less than 40. The thallium total-body scan showed numerous metastases throughout his skeleton and soft tissues.

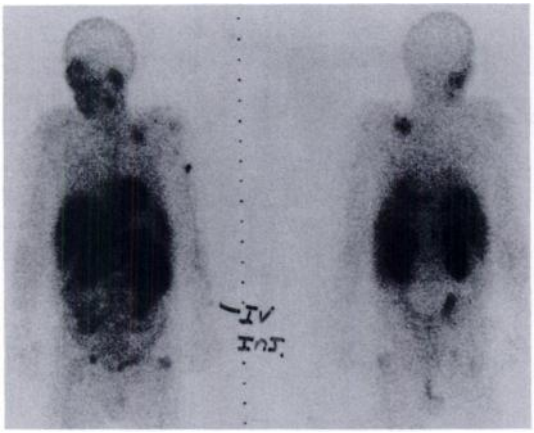

FIGURE 14. Total-body scan using the same total-body scanner (as in Figure 13) with a 6-mCi dose of ^{201}Tl in a man with a serum calcitonin of 60,000 (normal less than 40) from medullary thyroid carcinoma widely metastatic as shown in this scintigram.

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