Nuclear Medicine and the Thyroid Gland: A Retrospective Review

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The thyroid gland, iodine and nuclear medicine are interrelated through a complex history. The physiology and pathology of the thyroid gland were not understood until after the discovery of iodine 184 years ago. Nuclear medicine has grown up around the diagnosis and treatment of the thyroid gland. Like all sciences, the development of nuclear medicine has not proceeded in a straight line, but in several investigative directions at the same time. The development of nuclear medicine is the result of numerous individual and seemingly unrelated efforts which came together successfully. We have organized the history of nuclear medicine and the thyroid chronologically, starting with the discovery of iodine.

IODINE AND THE THYROID GLAND ARE RELATED

Iodine was discovered quite by accident in 1811 by a French chemist, Bernard Courtois, during the processing of seaweed to make gun powder. Violet-colored crystals formed from a gas given off by the reaction. This substance was subsequently named iodine by an English chemist, Humphry Davy, from the Greek iodes, meaning violet (*1*). Five years later, iodine was being used to treat endemic goiter in England (*2*). The reasoning was that if iodine was found in seaweed and seaweed was known to cure goiter, then iodine could be used to cure goiter as well.

Ubiquitous as iodine was, there were certain geographic regions where it was found to be in poor supply in the soil and groundwater. In these areas, endemic goiter was common in both humans and animals. The two best-known regions of endemic goiter were the Great Lakes region in North America and Switzerland in Europe. By the early 1900s it was recognized that disease, such as goiter, could be caused by the absence of something, such as iodine. This was a new concept. This led to early treatment with desiccated sheep thyroid gland to shrink the goiter (*3–5*). It was found, however, that if too much thyroid was given, the patient would develop hypermetabolic symptoms.

There was another category of patient, however, who had a goiter with symptoms which we now recognize as hyperthyroidism. These patients were often found in areas of iodine-rich soil and water. This group of patients was described by such thyroid luminaries as Robert Graves (*6*) and Karl A. von Basedow (*7*). The eye findings of Graves' disease were also described at this time in the mid to late 1800s (*8*).

Diiodotyrosine (T2) was discovered in 1911 (*9*) and tetraiodothyronine (thyroxin [T4]) in 1915 (*10*). About this time, public health experiments were being performed. The Akron Experiment involved dietary iodine enrichment in goitrous school children (*11*); goiters in World War I recruits were being correlated with the amount of iodine in their drinking water (*12*); and a study of the population of Rochester, New York showed a decrease in goiter following placement of iodine in the drinking water (*13*).

In the late 1920s a connection was noted between thyroid atrophy and the absence of a pituitary gland (*14*). This was the first hint of a thyroid-stimulating hormone (TSH), which would not be identified until much later. In the late 1910s and '20s, work on basal metabolism (*15,16*) led to widespread metabolic testing of suspected hypothyroid patients. This was performed by early morning office visits where patients' basal metabolic rate was measured by body temperature and other means. This became somewhat trendy and after a while was discontinued.

Following World War II, nuclear medicine as we know it came into being. Iodine and the thyroid led the way with reactor production of ^{131}I. Previously, during the 1930s, iodine isotopes had been generated in linear accelerators (*17–19*).

The 1950s saw advances in chemistry with the discovery of triiodothyronine (T3), which was found to be an active thyroid hormone (*20*). Thyroid suppression with T4 and the inability to suppress autonomous nodules was also described (*21*). Absence of thyroid hormone, causing congenital cretinism in one patient population (*22*) and myxedema coma in another (*23*),

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was defined. This again led to another medical trend which involved hyperpharmacy. Patients who were tired, achy and sluggish were treated with large trial doses of T3 for ill-defined metabolic insufficiency (*24*).

In 1957, Hashimoto's thyroiditis was recognized as an autoimmune disorder (*25*). This was to herald significant immunologic breakthroughs in the 1970s and '80s.

Iodine daily requirements were established in 1958. In the early 1960s, it was noted that iodine-supplemented white bread could interfere with radioiodine uptake and thyroid scanning. Of note, in 1974 the FDA compiled iodine dietary information in several foods. Most diet foods contained 1–50 ng/gm; seafood was noted to contain 300–3000 ng/gm; iodized table salt contained 76 ug/gm; and seaweed contained 1.2 mg of iodine per gram of kelp (*1*).

The 1960s saw further focus on biochemical pathways of the thyroid gland (*26*) and a thyrotropin releasing factor (TRF) of hypothalamic origin was discovered (*27*).

In the 1970s, biochemical work further revealed the relationship of T3 and reverse T3 (rT3) (*28*). Screening tests for congenital hypothyroidism were developed (*29,30*) and the first successful attempt to treat a hypothyroid fetus with intrauterine T4 was performed (*31*). Ultrasound technology was applied to thyroid imaging (*32*) and was found to be able to define a cyst versus a solid lesion, but was not able to tell a solid benign lesion from a malignant lesion. Ultrasound was also applied to evaluation of the orbit for Graves' ophthalmopathy (*33*).

The 1980s saw an explosion in biochemical evaluation of the thyroid with discovery and elaboration of TRH-like (*34*) and TSH-like (*35*) substances, as well as antibodies of various types which affect thyroid physiology. This included thyroid-stimulating antibodies (TSAb), thyroid-stimulating hormone inhibiting antibodies (TSHIAb), and thyroid-stimulating hormone enhancing antibodies (TSHEAb) (*36,37*).

On the clinical side of the 1980s, familial disorders such as familial dysalbuminemia and familial dysprealbuminemia were discovered (*38–40*). Amiodarone, a new cardiac anti-arrhythmic agent, was introduced. It has an extraordinarily high iodine content and, as expected, cases of thyroid dysfunction were reported (*41*). Osteoporosis was also implicated in patients being treated with T4. This became yet another variable in the management of thyroid patients (*42–44*).

The 1990s have seen further fine-tuning in the management of thyroid patients, including avoidance of osteopenia and cardiac disease secondary to excessive T4 administration, the management of hyperthyroidism and thyroid cancer.

THYROID IMAGING AND THERAPY AGENTS

Stable iodine is ^{127}I. Iodine-123 and ^{124}I were discovered in 1949 and are cyclotron produced. Iodine-123 has a physical half-life (T½) of 13.3 hr and decays by electron capture. Its principle gamma emission is 159 keV. It also has other gamma peaks at 440 keV and 529 keV. It is suitable for both imaging and uptake calculations (Fig. 1–3). The total absorbed dose to the thyroid gland is approximately 1% that of ^{131}I. Usual

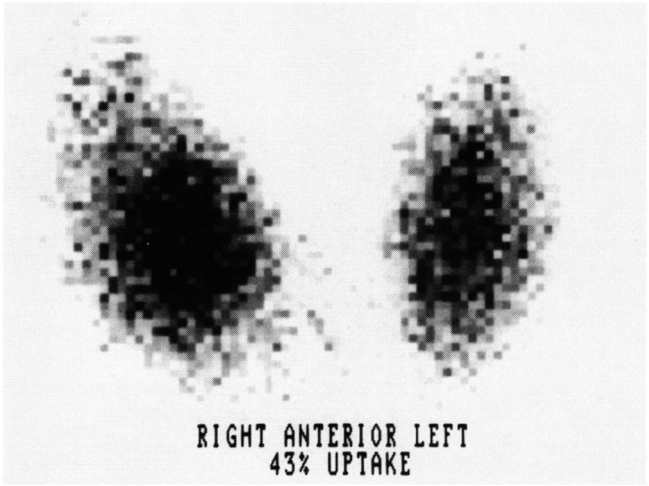

FIGURE 1. An ^{123}I scan of the thyroid shows uniform tracer activity and an elevated 4-hr uptake of 43% (normal range = 4–16%). The gland was enlarged to palpation. This is classic Graves' disease.

imaging doses range from 100–400 uCi (3.7–14.8 MBq). Its drawbacks include a relatively high cost and possible contamination with ^{124}I (T½ = 4.2 days and high energy peaks, which degrade the ^{123}I images). This is no longer a significant problem in clinical practice because of improved manufacturing techniques. Iodine-125 has a long T½ of 60 days and low energy peaks (27–32 Kev). Both of these facts make ^{125}I less suitable for imaging. It is, however, well suited for well counter work as was discovered in 1962. Iodine-128 which has a T½ of 25 min, is cyclotron produced and was discovered in 1934. Iodine-129 has a T½ of 1.7×10^7 yr and was discovered in 1946. Iodine-130 has a T½ of 12.36 hr and a principal gamma

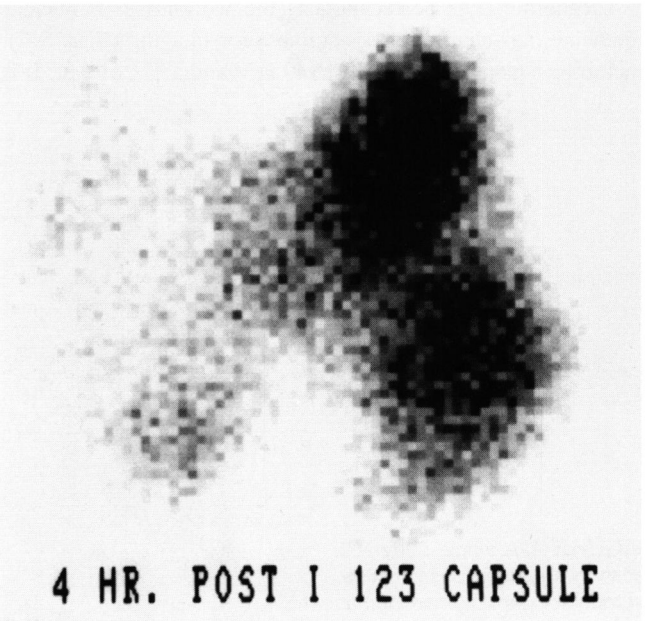

FIGURE 2. An ^{123}I scan with an elevated 4-hr uptake at 57% (normal range = 4–16%). The patchy uptake with areas of increased and decreased uptake (hot and cold nodules) and enlargement of the gland are consistent with a toxic multinodular goiter.

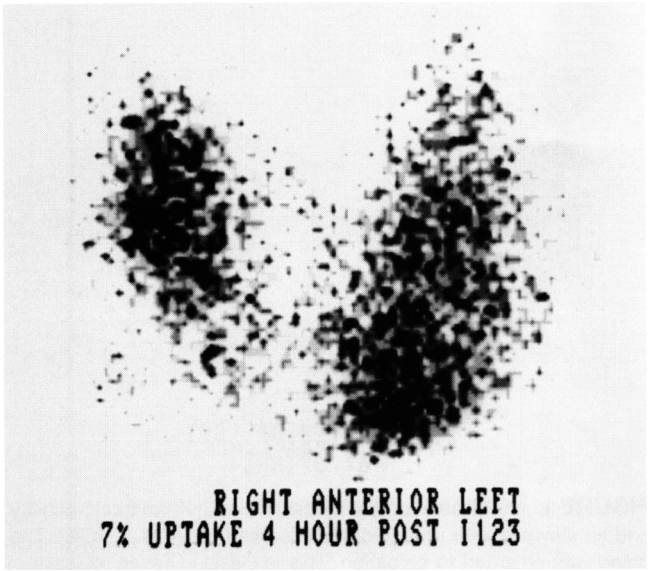

FIGURE 3. An ^{123}I scan shows patchy inhomogeneous tracer distribution and a 4-hr uptake of 7% (normal range = 4–16%). The gland is bosselated to palpation. The patient was antibody-positive for Hashimoto's thyroiditis.

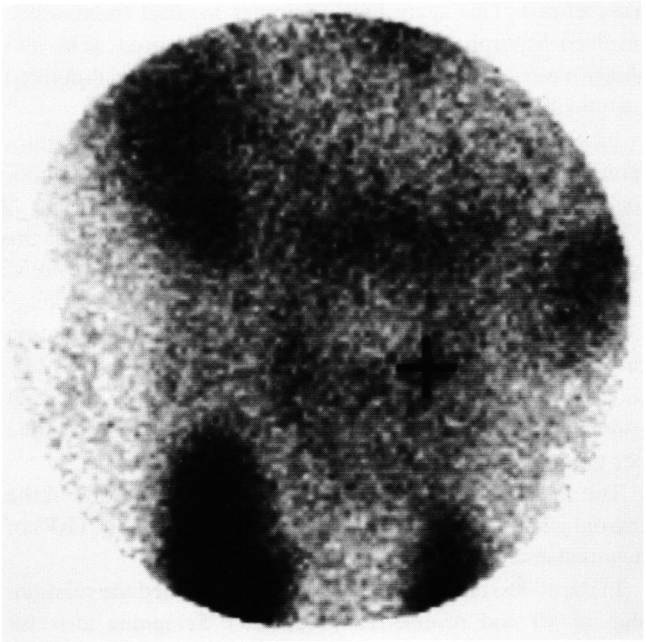

FIGURE 5. A young patient with a palpable midline neck mass. The ^{99m}Tc-pertechnetate scan of the anterior neck shows the cross marker overlying a ring of uptake between the salivary glands and the thyroid gland. This is a thyroglossal duct cyst. Thyroid tissue in the walls of the cyst take up the tracer.

emission of 536 keV, and beta emissions of 1.69 MeV and 2.763 MeV. It was discovered in 1934, and was initially used for therapy in 1941 with a dose of 0.25 mCi (9.25 MBq). Subsequent to ^{131}I development, ^{130}I was no longer used clinically. Iodine-131 is a byproduct of reactors and has a primary gamma of 364 keV and a T½ of 8.05 days. It also has a high maximum beta particle energy emission of 806 keV. While no longer used for primary imaging, it can be used for evaluation of ectopic thyroid tissue, including functioning metastatic disease (Fig. 4). It became widely available following World War II.

Technetium-99m-pertechnetate, the workhorse of nuclear medicine, has characteristics suitable for imaging (Figs. 5–7), including a gamma emission of 140 keV and a T½ of 6 hr. It is cheap and readily available. It is trapped by the thyroid gland, but not organified. Its radiation dose to the thyroid on a mCi to mCi basis is approximately 1/6000 that of ^{131}I. This is estimated at 0.13 rad/mCi (0.035 mGy/MBq) for ^{99m}Tc-sodium pertechnetate (*45*) compared to 800 rad/mCi (220 mGy/MBq) for ^{131}I as sodium iodide (*46*), assuming an uptake of 15%. Technetium, from the Greek tekhnetos meaning man-made, was discovered in 1937 by Perrier and Segre. It filled a vacancy in the periodic table at number 43. Initially, it was thought to be an exotic element.

Thallium-201 is a cyclotron product which decays by electron capture with a T½ of 73 hr. It is neither trapped nor organified

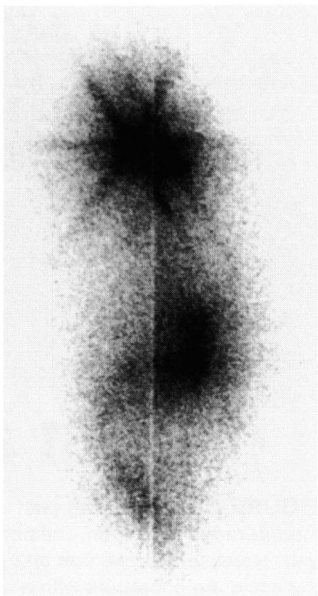

FIGURE 4. A whole-body ^{131}I scan in a patient, post-thyroidectomy for papillary carcinoma. There is uptake in the thyroid bed and in cervical lymph nodes. This scan was obtained prior to ^{131}I therapy while the patient was hypothyroid.

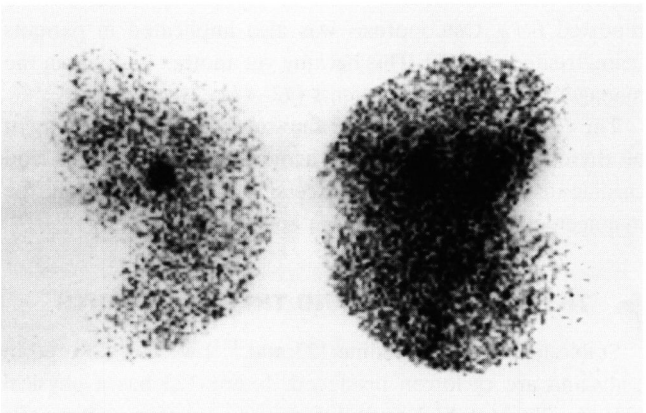

FIGURE 6. Anterior and lateral views of a ^{99m}Tc-pertechnetate of the neck in a newborn male infant with an elevated screening TSH. A focal area of increased tracer activity is seen at the base of the tongue. No activity is seen in the thyroid bed. This is an ectopic lingual thyroid gland.

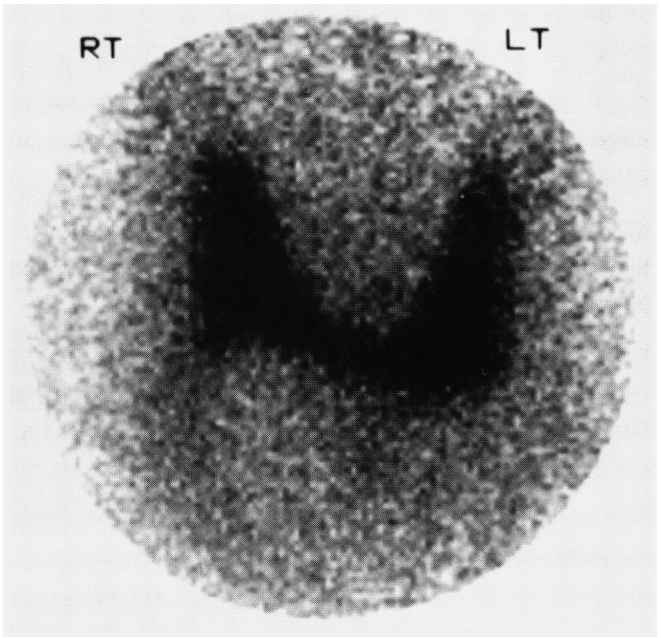

FIGURE 7. A^{99m}Tc-pertechnetate scan of the thyroid showing a cold nodule at the right lower pole. This nodule was painful to palpation. Needle biopsy showed Hodgkin's lymphoma. (Photo courtesy Donald Meier, MD.)

by the thyroid gland. Its uptake is possibly due to perfusion alone. It is limited to the evaluation of differentiated thyroid cancer and medullary and Hurthle cell tumors. Stable thallium was discovered by Crookes in 1861.

Technetium-99m-sestamibi can be used like ^{201}Tl, but it demonstrates better photon flux and a more favorable photon for imaging. Gallium-67 has little primary use in thyroid imaging, although it may be of value in thyroiditis (Fig. 8).

Fluorine-18-fluorodeoxyglucose, a positron emitter, currently requires a PET scanner for adequate thyroid imaging.

Technetium-99m pertechnetate, ^{123}I and ^{131}I are the main thyroid radioactive agents, with the former two most commonly used in diagnostic imaging and RAIU, (^{131}I can also be used), and the latter used in treatment.

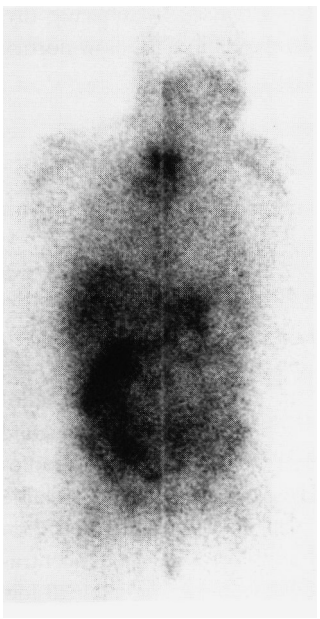

FIGURE 8. A whole-body ^{67}Ga scan shows diffuse uptake within the thyroid gland indicating thyroiditis which correlated with the patient's clinical and laboratory evaluation.

DEVELOPMENT OF THYROID DETECTORS AND IMAGING DEVICES

There have been three generations of thyroid uptake probes and cameras. Geiger-Müller (GM) tubes, rectilinear scanners and scintillation detectors and cameras (*47*).

The GM tube dates from 1928, when Geiger announced the development of a beta-avalanche tube which was modified with addition of various circuits and meters in the latter 1920s and the 1930s. For years, until Ben Cassen developed the rectilinear scanner, patients had their thyroid uptake measured with a GM tube pressed against their throats. No images were obtainable.

The rectilinear scanner was developed in 1949, but did not come into use for thyroids until the following year. Its advantage was that the thyroid was literally scanned back and forth and a life-sized image of the thyroid was produced. Anatomy could now be seen and thyroid nodule function could be evaluated. Its disadvantages were relatively poor detail, due to the size of the scan dots, and difficulty in obtaining oblique views because of interference by the patient's shoulders.

Scintillation technology actually goes back to William Crookes in 1903. However, the scintillation crystal was not invented until 1950. In 1952, Hal Anger developed the pin-hole camera and six years later introduced his gamma camera. The small size of the original Anger crystal and the pin-hole camera were both remarkably suited for thyroid imaging.

THE EVOLUTION OF TREATMENT OF THYROID CANCER

Up until the advent of radioiodine therapy, surgery was the only means of treating thyroid cancer. In the 1800s, thyroid surgery was considered very dangerous and was often fatal, even in the best hands (*48*). The mortality rate was up to 40% and was due to exsanguination or sepsis. This improved with advances in surgical techniques following the application of anesthesia in the 1840s and anti-sepsis in the 1860s leading to aseptic technique in the 1880s. Hemostasis was also improved in the 1870s. By the turn of the century, the mortality rate was decreased dramatically if hypothyroidism, nerve paralysis and tetany (from removal of the parathyroid glands) could be avoided (*49,50*). Pathologic correlation in the 1800s was also difficult due to the limited knowledge of thyroid tumors. Anaplastic tumors were referred to as sarcomatous degeneration; all other thyroid malignancies were called thyroid tumors.

We now know there are four basic types of thyroid cancer: papillary and follicular, which are often mixed; medullary (from C cells); and anaplastic. Papillary is the most common type. Most thyroid cancers are slow growing.

Joel Hamburger described thyroid nodules with what he calls clinical axioms (*51*): Many patients have thyroid nodules. Some thyroid nodules are malignant, but not many. Some patients die from thyroid cancer, but not many. Some patients with thyroid cancer are saved from death by surgical treatment,

but not many. Some patients with benign or malignant thyroid nodules experience important complications from surgical treatment, in some cases even death. Therefore, the excision of all thyroid nodules to prevent death from thyroid cancer is not only impractical, but may do more harm than good.

These axioms suggest the need for an alternative treatment. This is where radioiodine imaging and aspiration needle biopsy come in.

Radioiodine actually made its impact felt following World War II with the availability of ^{131}I for general medical use. In 1946, Seidlin announced the first cure of thyroid cancer with metastatic disease (*1*). There was some concern in the 1960s about the potential carcinogenic effects of radioiodine therapy. However, a large cooperative study following up on 36,000 cases of Graves' disease showed no evidence of carcinogenesis (*52*). In the 1970s, it was noted that thyroglobulin could be used as a marker for metastatic recurrence of thyroid cancer following thyroidectomy (*53*). Fine-needle aspiration cytology came into being in the 1970s as well (*54*). Initially, there was concern of seeding along the needle track; however, this turned out not to be a problem. Such a champion as Beierwaltes pioneered the use of radioiodine and showed its efficacy in large patient studies (*55*).

Some controversies regarding the management of thyroid cancer patients remain. One controversy revolves around the type of thyroidectomy performed (*56*): total, near total or partial. Post-surgical ablation of thyroid remnants with ^{131}I remains controversial. Reasons for post-surgical thyroid remnant ablation include treatment of residual microscopic foci of cancer and removal of residual thyroid tissue as a source of thyroglobulin and TSH-inhibiting thyroid hormone (*57–62*). Another controversy is that of high- versus low-dose ^{131}I ablation therapy. Some groups contend that low-dose treatment (29.9 mCi [1106 MBq]) allows adequate ablation for patients with thyroid bed functional tissue (*63,64*). This can be performed on an outpatient basis. Other groups contend that high-dose treatment is best (100 mCi [3700 MBq]), as this avoids potential later occurrence of metastatic disease or transformation into an anaplastic thyroid carcinoma (*65*). Successful ablation of thyroid remnants with a single dose of ^{131}I averages 53% (104/195) of patients after a single administration of up to 30 mCi (1,110 MBq) as compared with 86% (248/287) of patients after a single administration of 100 mCi (3,700 MBq) (*66*). A middle ground is sought by others with two sequential doses, totaling nearly 60 mCi (2,220 MBq). This is performed on an outpatient basis in the low-risk population (small tumor, no metastatic disease, young age) (*67*).

MANAGEMENT OF HYPERTHYROIDISM

Thyrotoxicosis is any disease or set of signs and symptoms that results from excessive thyroid hormone in the blood. Hyperthyroidism is caused by stimulation of the thyroid gland resulting in overproduction and excess release of thyroid hormone into the circulation. Overproduction could be the result of a toxic adenoma, Graves' disease, thyroiditis or, rarely, a TSH-producing tumor. Thyrotoxicosis can result from thyroiditis not because of overproduction, but because of excessive leakage of thyroid hormone from the thyroid gland. Thyrotoxicosis might be due to ingestion of thyroid hormone (factitious hyperthyroidism). As was noted previously with thyroid cancer, surgery and antithyroid drugs were the mainstay for Graves' disease until the advent of ^{131}I therapy.

Radioiodine was first used in the treatment of hyperthyroidism in the 1940s (*1*). Subsequently, retrospective reviews of thousands of ^{131}I thyroid therapy patients were performed and have not shown an increase in cancer incidence (*68*).

One of the undesirable side effects of radioiodine therapy for hyperthyroidism is the induction of hypothyroidism. Some authors think that hypothyroidism is the ultimate end-point of Graves' disease, an autoimmune disorder. Many authors suggest that efforts should be made to preserve thyroid function for as long as possible. Along these same lines there are two schools of thought. The first school says that patients are likely to become hypothyroid subsequent to radioiodine therapy and that strict calculation of dose is not practical. Therefore, why not give a dose large enough to induce hypothyroidism within a short time interval, such as 6–12 mo? This reduces morbidity and costs. Others calculate the dose of radioiodine based on the estimated gram weight of the thyroid gland (usually obtained by palpation), the percent uptake of radioiodine at 24 hr, and assume a dose per gram of thyroid tissue at 100 uCi (3.7 MBq). Even at this level, hypothyroidism is expected even if delayed. These topics have been extensively reviewed by Shapiro (*69*).

Other treatments for hyperthyroidism include antithyroid agents. These include methimazole (MTZ or MMI) and propylthiouracil (PTU). The former was introduced in 1942, the latter in 1945. These anti-thyroid drugs are often used as an initial treatment prior to radioiodine therapy or in conjunction with radioiodine therapy as a means to control the patient's symptoms prior to radioiodine treatment. Beta blockers are also useful for controlling cardiac symptoms. A radioactive iodine uptake test is required prior to treatment for hyperthyroidism (*70*) in order to distinguish Graves' disease from subacute thyroiditis or fictitious thyrotoxicosis. In subacute thyroiditis or fictitious thyrotoxicosis, the uptake is below normal and radioiodine is not indicated.

THYROID LABORATORY EVALUATION

Thyroid function tests (TFTs) are of two basic types: in vivo and in vitro. The in vitro tests will be discussed first.

Thyroid-stimulating hormone (TSH) measurement has undergone three generations of sensitivity evolution. The first generation of analysis appeared in 1965 (*71*) and was able to identify those who had an elevated TSH in primary hypothyroidism. It eliminated the need for a TSH-stimulation radiotracer test to diagnose primary hypothyroidism. The second generation assay occurred in the 1970s (*72–74*) and was radioimmunoassay (RIA). Most euthyroid patients had a detectable TSH. This was a more sensitive test than the first generation assay. Hyperthyroidism showed suppressed TSH concentrations, but the test was not very sensitive or reproducible at low

levels. The third generation TSH assay was developed in the 1980s (*75,76*) and is sometimes called a sensitive, ultrasensitive or super sensitive TSH assay. This is an immunometric test using mono- or polyclonal sandwich assays and has a normal range of about 0.5–5 μIU/ml. It is greater than 10 times more sensitive than the previous TSH RIA. It can detect extremely low TSH levels (<0.1 μIU/ml). It is, therefore, useful in the identification of hyperthyroid states as well as to assess TSH suppression in the course of exogenous thyroid treatment.

The serum total T4 may be performed by an RIA method. The assay can measure both bound and free T4. The free portion of serum T4 is about 0.04% of the total and is biologically active. This total T4 test is multiplied by the T3 resin uptake test to determine the free thyroxin index (FTI). The FTI is an approximate surrogate for the free T4, but is less expensive and easier to perform.

The T3 resin uptake (T3RU or TBGs) serves as a measure of the saturation of all binding sites for thyroid hormone in the serum. These sites are found on circulating thyroid-binding globulin (TBG), albumin and thyroid-binding pre-albumin. This is not a measure of circulating T3 and should not be confused with the total T3 immunoassay.

These four tests (TSH, serum total T4, T3RU and free thyroxin index) constitute the main in vitro studies. Other useful in vitro assays include antibody studies such as thyroperoxidase (antimicrosomal) antibody and antithyroglobulin antibody. These are commonly elevated in Hashimoto's thyroiditis, although thyroperoxidase antibody elevations can be seen in Graves' disease as well. Another antibody study not routinely performed is thyroid-stimulating antibody (TSAb). While not routinely indicated, it can be useful when the diagnosis of Graves' disease is not clearly established.

Other in vitro thyroid tests include: the serum thyroglobulin, which can be used as a tumor marker; serum calcitonin, which is elevated in medullary thyroid cancer; rT3, which can be elevated in illnesses impairing deiodination of T4; and serum total T3 by immunoassay.

In vivo thyroid function tests include the radioactive iodine uptake (RAIU) test, thyrotropin-releasing hormone (TRH) test and the T3 (Cytomel) suppression test.

The RAIU is usually obtained after oral ingestion of either ^{123}I or ^{131}I radioiodine. Uptake can be measured at 4 hr and/or 24 hr. Following intravenous administration of ^{99m}Tc-pertechnetate, a visual comparison of the intensity of thyroid uptake to the intensity of salivary gland uptake is noted using gamma camera images at 20 min postinjection. A normal ^{99m}Tc scan of the thyroid shows activity in the thyroid approximately equal to that in the salivary glands. This gives a useful estimate of thyroid trapping for diagnosing Graves' disease, but does not measure organification.

The TRH test is performed following intravenous infusion of synthetic TRH and the TSH response is measured. In normal patients, the TSH concentration increases. In hyperthyroid patients, the TSH response is flat due to the enhanced negative feedback effect on TSH secretion. The TRH test is most useful in evaluating TSH suppression such as in mild or subclinical hyperthyroidism, especially where T4 and T3 serum levels are equivocal. The ultrasensitive TSH test has largely replaced the TRH test.

The T3 suppression test may be used in the evaluation of autonomous thyroid function (e.g., Graves' disease or hyperfunctioning thyroid adenoma). The test is performed by obtaining a baseline RAIU and then giving 75–150 μg oral T3 (Cytomel) daily for seven days, followed by a repeat RAIU test. A normal result (euthyroid patient) shows a decrease of RAIU by at least 50% of the baseline RAIU value. Autonomous function is indicated by a lack of suppression. This test is rarely used today because of the availability of TSH and imaging tests.

THE STATE-OF-THE-ART IN THYROID MANAGEMENT

The state-of-the-art in thyroid management involves a careful history and physical examination, and correlation with appropriate serum tests, the RAIU, thyroid scan and fine-needle aspirate, as indicated. Darlene Fink-Bennett has written an excellent review article on nuclear thyroidology in which she correlated the thyroid scan, the technetium-trapping estimate and physical examination with laboratory values to make an imaging diagnosis of thyroid pathology in 20 min (*77*). A similar evaluation could be performed using ^{123}I and a 4-hr or 24-hr uptake.

Since approximately 15–20% of cold nodules seen on the thyroid image will ultimately be cancerous, cold nodules should be biopsied using the fine-needle aspirate (FNA) technique. There are two schools of thought regarding scanning and FNA. The first is to scan all nodules and perform an FNA on all cold nodules and possibly on the few hot nodules seen. The other would perform FNA on all palpable nodules and scan those which have FNA results that are suspicious for malignancy. A repeat FNA can always be obtained if the first was equivocal. Several algorithms have been designed (*78*).

Medullary cancers can sometimes be investigated with ^{99m}Tc-DMSA, ^{131}I-MIBG (*62*), or ^{111}In-somatostatin analogue (*47*). Undifferentiated carcinoma can sometimes be imaged with ^{201}Tl, ^{99m}Tc-sestamibi or ^{18}F-FDG.

Indium-111-octreotide is a new agent designed for evaluation of somatostatin receptor positive tumors. Medullary thyroid cancer or paraganglioma usually fit in this group. The majority of these patients are visualized with this new peptide (*79*).

Serum thyroglobulin is a useful tumor marker in the setting of thyroid cancers where total thyroidectomy has been performed; even those which do not concentrate ^{131}I. Whole-body dosimetry studies are being used at some institutions to allow maximum, but safe, ^{131}I dosing (*66*).

The management of hyperthyroid patients depends on their clinical presentation and on the cause of their thyrotoxicosis. Imaging is helpful to differentiate diffuse toxic goiter (Graves' disease) versus toxic multinodular goiter versus hyperfunctioning adenoma.

FUTURE DIRECTIONS IN NUCLEAR THYROIDOLOGY

When you consider how far we have come in the evaluation of the thyroid since the discovery of iodine in 1811 and the discovery of natural radioactivity by Becquerel in 1896, it is difficult to have any real idea where nuclear thyroidology may go in the future. However, an educated guess might conclude that antibody techniques may be developed for both diagnosis and treatment of various thyroid diseases. Perhaps immune therapy will be developed in the management of hyperthyroidism. The antibody which would be tailored to the hyperfunctioning portion of the gland (diffuse versus nodule) could be tailored to throttle back the hyperfunctioning portion and allow the gland to maintain a euthyroid state.

Antibody diagnosis and treatment of thyroid tumors could be obtained, even in those thyroid tumors which do not concentrate ^{131}I. The tumor could be sampled and antibodies derived which would then seek out tumor cells. The antibody could be labeled to a radionuclide whose beta emission could be useful in destroying tumor cells, even though the tumor cell itself need not be iodine avid.

New developments in PET or SPECT could be coupled to new antibody techniques or could be used on their own, especially if whole-body imaging techniques can be improved.

CONCLUSION

Nuclear thyroidology is one of the most complex fields in nuclear medicine. There are many diseases, manifestations, laboratory values and diagnostic approaches. The art of medicine is practiced properly when an elicited history and physical examination are combined with biochemical and nuclear testing.

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