ASSESSMENT OF THYROID FUNCTION AND ANATOMY WITH TECHNETIUM-99m AS PERTECHNETATE

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A number of elements other than iodine are selectively concentrated by the thyroid gland (*1–7*). Among these are elements in the periodic group VIIa (manganese, technetium and rhenium) which are taken up by the thyroid gland but, in contradistinction to iodine, are not organically bound.

Technetium is not a naturally occuring element and exists only in radioactive form. One of the isotopes of technetium is ^{99m}Tc which is available as the daughter product of ^{99}Mo in a generator system (*8*). Its physical characteristics make it particularly suitable for scintillation scanning; it has a short half-life of 6 hr, virtually no beta emission and a moderately low-energy gamma emission (140 kev) that can be efficiently collimated. The possibility of administering millicurie quantities of activity without delivering a high radiation dose to the patient allows studies to be performed rapidly and accurately. Because of these characteristics, the isotope has been widely used as a scanning agent (*9–11*).

Because the uptake of technetium in the thyroid reflects the state of the trapping function of the gland, its use in studying thyroid physiology has been suggested (*12,13*). It is the purpose of this study to evaluate the thyroidal uptake of ^{99m}Tc-pertechnetate in relation to the clinical state and to make an intercomparison with other tests of thyroid function. Several parameters of technetium uptake have been measured and correlated with each other as well as with the results of ^{131}I uptake and serum protein-bound iodine.

METHOD

The patients included referrals from the Industrial Medicine Clinic at the Medical Research Center, Brookhaven, patients hospitalized at the Medical Research Center primarily for other reasons than disturbances of the thyroid and referrals from several outside physicians who questioned abnormal thyroid function or the presence of palpable nodules.

The patient was placed supine, and a suitably collimated 2 x 2-in. NaI(Tl) crystal scintillation detector was placed over the neck 25 cm from the skin surface. The detector signal was fed through a discriminator and ratemeter to a strip-chart paper recorder. The radioactivity in the neck was continuously recorded after the intravenous administration of 2.0–2.6 mc ^{99m}Tc-pertechnetate. This amount of activity, which is suitable for scintillation scanning, produced counting rates too high for a flat-field collimator. Therefore 2.5 cm of Lucite were inserted over the end of the detector collimator which reduced the sensitivity by 30% and eliminated errors due to the resolving-time capability of the detector. The settings were: 300,000 counts/min scale, 1-sec time constant and 12-in./hr paper speed.

After the initial peak caused by the bolus of activity passing through the neck and great vessels, the counting rate dropped rapidly to a minimum value within 1 min after injection. There was then a gradual rise in counting rate over the next 15–20 min to a maximum value. The counting rate then remained fairly constant with only a slow diminution (Fig. 1). A "trapping index" was determined by dividing the minimum counting rate into the maximum. An "accumulation gradient" was determined by measuring the average slope of the curve from the minimum to the half-maximum value. A modification was introduced after the study had been started which reduced the size of the initial "spike" of activity so that the recording needle would not go off scale. A $\frac{1}{16}$-in. lead sheet was placed over the neck and upper chest with an opening 4-in. in diameter over the thyroid area. This sheet reduced extraneous counts from activity in the heart and great vessels.

After recording over the neck, a recording was made over the thigh for 1 min. When this value was subtracted from the maximum and minimum values,

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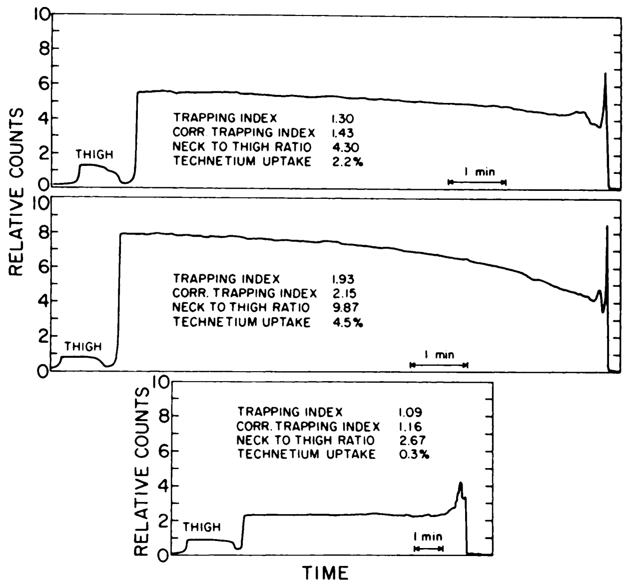

FIG. 1. Immediate uptake of ^{99m}Tc-pertechnetate in thyroid after intravenous injection. Trace proceeds in time from right to left. Traces are on individuals with hyperthyroidism (middle), normal function (above) and hypothyroidism (below).

a "corrected trapping index" was determined. It had been determined previously that the activity level over the thigh did not change during this time interval. A neck-to-thigh ratio was also computed.

When these steps were completed (about 15–20 min), the patient was placed under a rectilinear scanner (Picker Magnascanner, 3 x 2-in. NaI(Tl) crystal), and the isotope distribution in the neck was determined. Focusing collimators with 1,045 holes, developed in the Brookhaven Hot Laboratory, are used for scanning (*14*). Depending on the counting rate, one of the two collimator thicknesses is used. The most often used is a 1.3-in. collimator with a resolution of 0.16 in. (4 mm) at the 50% isoresponse level and 3.5-in. focal depth. When the counting rate is low, as in hypothyroidism or after suppression by exogenous thyroid medication, a 1-in. collimator is used. Its resolution is 0.23 in. (6 mm), but the sensitivity is about 40% greater. Maximum counting rates over the thyroid ranged from 20,000 to 40,000 counts/min for euthyroid patients. Scanning speeds of 30–50 cm/min with indexing steps of 0.15 cm are the usual scanning parameters. These provide a maximum counting rate density of 3,750–5,625 per square centimeter. The duration of the scan was 5–15 min.

A standard was prepared in the following way. A quantity of ^{99m}Tc equivalent to that injected into the patient (0.3–0.7 ml) was diluted to 100 ml. Three milliliters of this standard were then added to 20 ml of water in a Lucite vial cylinder with an inner diameter of 2.3 cm and a length of 6.3 cm. The vial, made of 1.5-mm-thick Lucite, was inserted into a Lucite cylindrical neck phantom 12.7 cm in diameter and 12.7 cm high. The center of the vial was 2.2 cm from the anterior surface of the neck phantom (Fig. 2).

We performed a scan of the phantom immediately after completing the patient study using the same parameters. The uptake of ^{99m}Tc in the gland was then determined by counting dots on the teledeltos recording over the thyroid, subtracting background and comparing the results with the standard that contained 3% of the injected activity (Fig. 3). This method is similar to that of Andros *et al* (*12*), but we made no corrections for size and depth of the gland because these estimates have a high degree of error, and we felt that the phantom represented a good average. The determination of thyroidal uptake using the "dot" scan is more accurate than the usual method because of the rather low uptake of technetium in the thyroid and the high background level of radioactivity, including localization in salivary glands.

Nearly all patients had a PBI determination on the day of the ^{99m}Tc study. If it was not inconvenient for the patient, an oral dose of ^{131}I was administered after the scan was completed, and a 24-hr uptake in the thyroid was determined. The ^{99m}Tc did not interfere with this study because the activity level had decreased by a factor of 16 in 24 hr, about 30% had been excreted and the discriminator setting of the detector effectively eliminated the 140-kev photons. Special studies, such as a BEI or a T-3 resin uptake, were performed as indicated.

In 47 patients the following procedure was used: A sample of blood was drawn at the end of the scan,

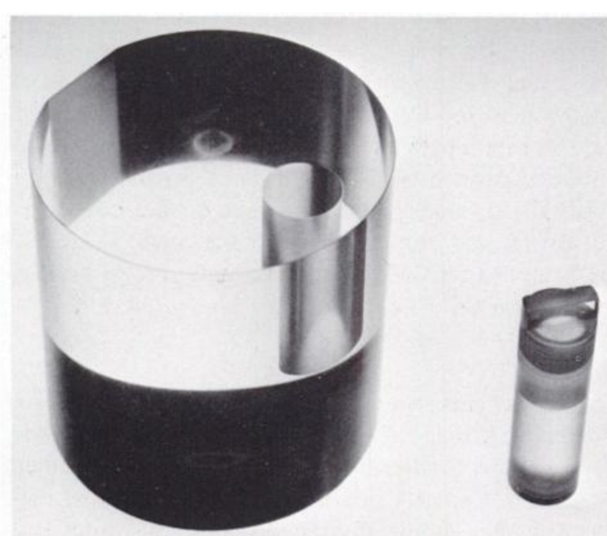

FIG. 2. Lucite neck phantom and vial representing thyroid are used for determining thyroid accumulation of ^{99m}Tc.

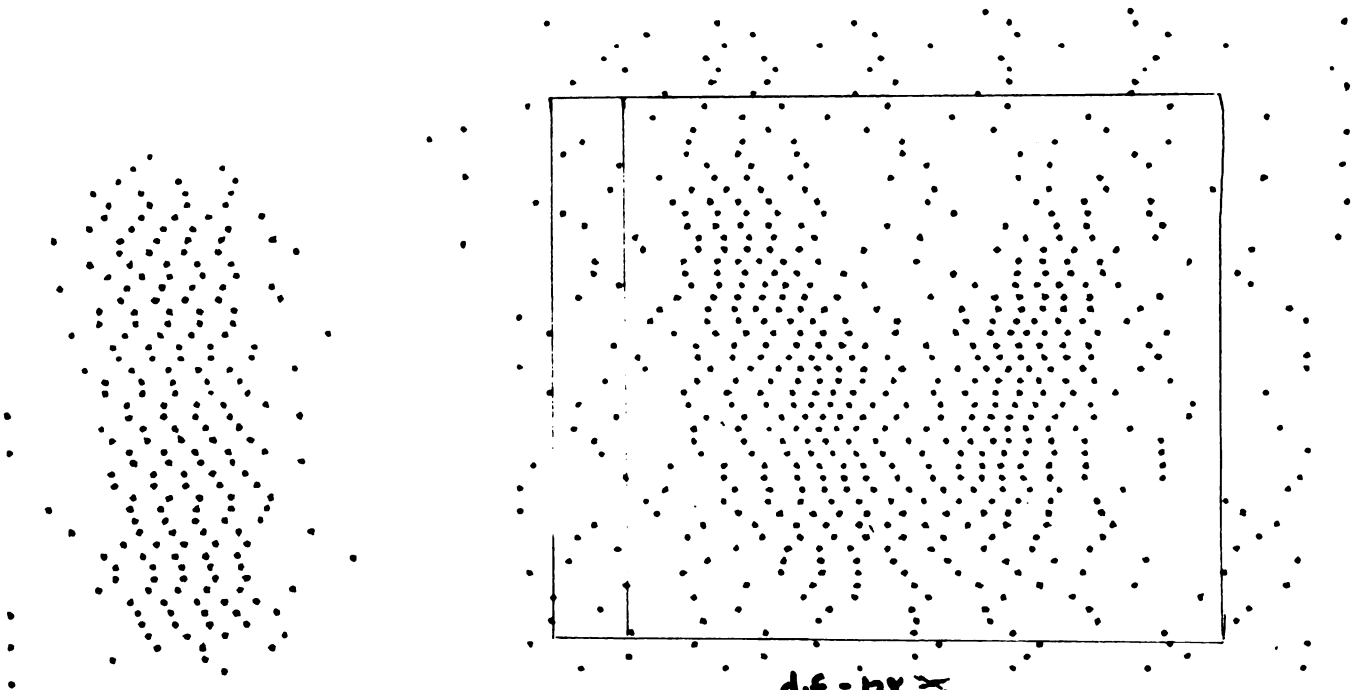

FIG. 3. Example of calculation of thyroidal concentration of ^{99m}Tc from teledeltos scans of neck and phantom. Background is measured in rectangular region and multiplied by 8 to compensate for difference in area. d.f. refers to dot scaling factor used in making scan.

and the ^{99m}Tc activity per milliliter of plasma was determined. The size of the thyroid was calculated from the scan using the method developed by Goodwin *et al* (*15*), and the ratio $[TcO_4^-]$ thyroid/$[TcO_4^-]$ plasma as well as the thyroidal technetium space were determined.

RESULTS

Technetium concentration in the thyroid. We performed a total of 208 studies on 193 patients. Technetium uptakes were determined in 143 patients who were not receiving suppressive medication. A number of other patients had to be excluded from the analysis of results because of previous x-ray studies with iodinated contrast media or because they were on dieting medication which included desiccated thyroid. In the comparison of technetium and iodine uptakes with PBI, patients who were on oral contraceptives or other hormone therapy for various reasons were also excluded. In most instances, the false elevation of protein-bound iodine in these patients was corroborated by a low T-3 resin-uptake determination.

The range of values encountered for technetium uptake is seen in Fig. 4. The limits of the normal range are from 0.5 to 4.0%. The average uptake, excluding the one very high value of 28.4%, is 2.2 ± 1.6%. Only four patients with definite hypothyroidism were studied, and they all had uptakes below 0.5%. In the diagnosis of the hyperthyroid state, two of 15 patients whose thyroids were definitely overactive had technetium uptakes below 4.0% for a diagnostic accuracy of 87%.

Four patients who were euthyroid had uptakes above 4% for a diagnostic accuracy of 97%. The over-all diagnostic accuracy is 96%. One of the patients with a diagnosis of thyroiditis responded well to thyroid 60 mg/day for 4 months and had marked suppression from 8.8% technetium uptake

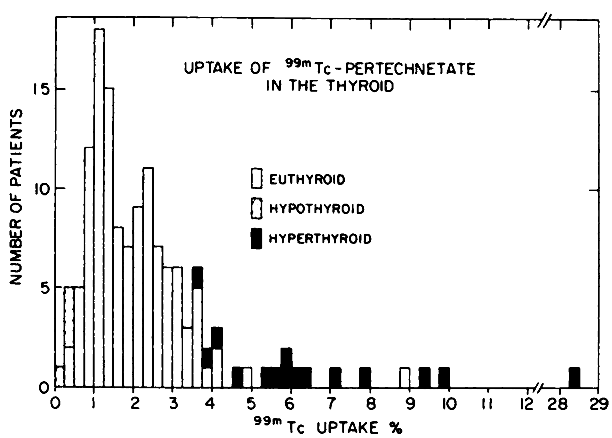

FIG. 4. Distribution of ^{99m}Tc uptake values in thyroid determined by method described in text.

TABLE 1. RESULTS OF TSH SUPPRESSION

Patient	^{99m}Tc uptake (%) Pre-suppression	Post-suppression	% change	24-hr ^{131}I uptake (%) Pre-suppression	Post-suppression	% change
J. V.*	4.97	0.68	−87	36.5	11.6	−68
T. F.*	3.71	1.52	−59	41.0	27.4	−33
R. deG†	8.80	2.66	−70	—	16.7	—
G. E.*	4.07	0.56	−86	35.5	12.1	−66
G. Em*	3.72	3.08	−18	38.8	40.2	+ 4

* L-triiodothyronine 25 μg three times a day for 8 days.
† Desiccated thyroid 60 mg/day for 4 months.

to 2.7%. Two other patients were well suppressed on 75 μg L-triiodothyronine per day for 8 days. The fourth patient, who showed an uptake of 4.05%, had a PBI of 4.6 μg% and a 24-hr ^{131}I uptake of 28.6% which were definitely normal.

The results of suppression tests are shown in Table 1. It is apparent that suppression of technetium uptake parallels the suppression of iodine uptake and in fact seems to be more pronounced in the former. One patient (T.F.) failed to suppress her radioiodine uptake below 20%, and her technetium uptake suppression was also less marked. Her PBI was 8.5 μg%, but she was on an oral contraceptive. Her T-3 resin uptake value of 21.6% (normal 22.6–31.6%) confirmed the impression that the PBI elevation was due to the hormonal intake. Her gland was large and firm. The scan (Fig. 5) showed a diffuse nodularity which may account for the incomplete suppression. This lack of suppression in non-toxic nodular goiter has been demonstrated previously (*16*). Another patient (G. Em), with a PBI of 8 μg%, and a previous history of hyperthyroidism, failed to demonstrate adequate suppression of both technetium and iodine uptake, and a diagnosis of recurrent hyperthyroidism was made. A further attempt at suppression with an increased dose of L-triiodothyronine was not made because of the symptomatology experienced on 75 μg/day of the medication.

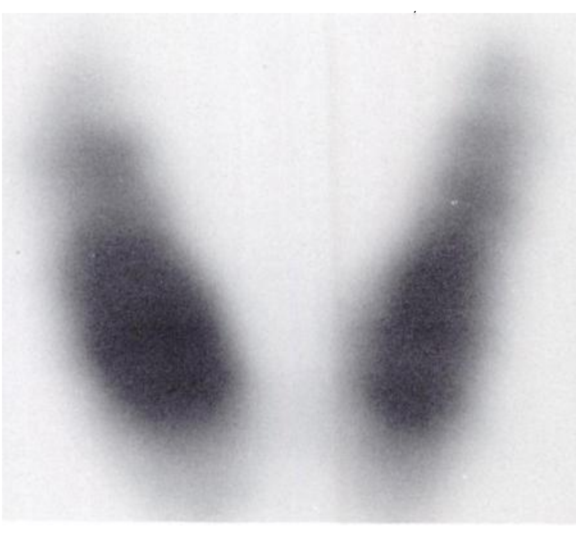

FIG. 5. Thyroid photoscan of patient T.F. with enlarged, diffusely nodular gland. Technetium uptake in patient was 3.71%.

We stimulated the thyroids of four patients by administering 10 units/day of TSH for 3 days. These patients were all abnormal since they had nodular glands with evidence of fibrosis after exposure to fallout radiation. The correlation of change in technetium uptake with the 2-hr ^{132}I uptake is rather good in three patients. In the fourth patient, the change in PBI seemed to follow the change in technetium uptake better than the iodine uptake. In one patient there was an increase in all three parameters of thyroid function from euthyroid to hyperthyroid levels. However, this was the only adult in the group, and she probably had less thyroidal damage compared to the others who were exposed during early childhood (*17*). The results are given in Table 2.

We calculated the relative concentration of technetium in thyroid and plasma as well as the thyroidal technetium space in 47 patients, eight of whom were hyperthyroid. The thyroid size was estimated from the scan using the formula of Goodwin *et al* (*15*). While this method is probably not accurate for any individual case, it gives a reasonable average for a group of cases.

The average thyroid-to-plasma ratio of technetium in the euthyroid individuals was 12.7 ± 7.2, with a range of 3.7–31.1. The thyroidal technetium space in these individuals averaged 241 ± 125 ml, with a range of 92–608 ml. There was a great deal of variability and some overlapping with the hyperthyroid individuals. The normal values are somewhat

TABLE 2. RESULTS OF TSH ADMINISTRATION (10 UNITS/DAY × 3)

Patient*	^{99m}Tc uptake (%) Pre-TSH	Post-TSH	% change	PBI (μg%) Pre-TSH	Post-TSH	% change	2-hr ^{131}I uptake (%) Pre-TSH	Post-TSH	% change	6-hr ^{131}I uptake (%) Pre-TSH	Post-TSH	% change
M. K.	1.15	1.34	+ 17	7.5	8.8	+17	7.2	15.7	+118	13.1	28.9	+121
J. K.	2.56	3.35	+ 31	6.2	7.7	+24	10.0	13.7	+ 37	22.0	29.1	+ 32
J. J.	3.64	4.59	+ 26	6.5	6.0	− 7	12.2	14.9	+ 22	17.9	25.7	+ 44
L. B.	1.70	6.78	+199	6.4	12.6	+97	11.6	29.7	+156	19.8	54.9	+177

* These patients were studied through the courtesy of Robert A. Conard.

lower than those of Berson and Yalow (*18*) which is rather surprising because of the low K_m for technetium determined by Wolff (*6*) and the higher concentration gradient in the thyroid *in vitro* in comparison with iodide.

The value for the hyperthyroid individuals are given in Table 3. They vary even more widely than in the euthyroid patients. For the most part they are well below the levels determined previously for iodide.

TABLE 3. CONCENTRATION OF Tc IN THYROID IN HYPERTHYROIDISM

Patient	^{99m}Tc uptake (%)	Estimated thyroid wt. (gm)	Thyroid / plasma $[TcO_4^-]$	Thyroidal Tc space (ml)
N. R.	3.9	21	29.1	609
C. B.	9.9	45	25.3	1,145
E. C.	7.1	18	44.4	808
H. B.	28.4	83	58.4	4,850
M. N.	5.8	25	32.8	830
J. L.	4.6	27	16.3	441
C. Ca	9.4	28	45.5	1,253
C. C.	6.3	28	32.6	909
G. Em	3.7	22	18.5	405

The greatest value of the ratemeter tracing is for determining the optimum time to scan. The correlation of technetium uptake with various parameters measured on the recording was determined by the product moment correlation (product of sample covariance/standard deviation times the standard deviation y). The correlation coefficients were as follows: trapping index (116 cases) 0.85, corrected trapping index (17 cases) 0.65, accumulation gradient (77 cases) 0.55, neck-to-thigh ratio (26 cases) 0.95. The neck-to-thigh ratio appears to be a clinically useful index.

Correlation with other thyroid function tests. Both the 24-hr ^{131}I uptake in the thyroid and the protein-bound iodine in the blood are measurements of the organic binding function of the thyroid. As one would expect, the correlation with technetium uptake is only fair. Figure 6 shows the relationship of ^{99m}Tc uptake to 24-hr ^{131}I uptake in 63 patients. The correlation coefficient is 0.70. The fit to the linear-regression curve would probably be much better if the one case with the extremely high technetium uptake of 28.4% were eliminated. There were two diagnostic errors in the ^{131}I-uptake determinations: one value is elevated in an euthyroid individual and one value is in the normal range in a hyperthyroid individual. The diagnostic accuracy of 98.5% is not significantly different from the accuracy with ^{99m}Tc ($P > 0.5$).

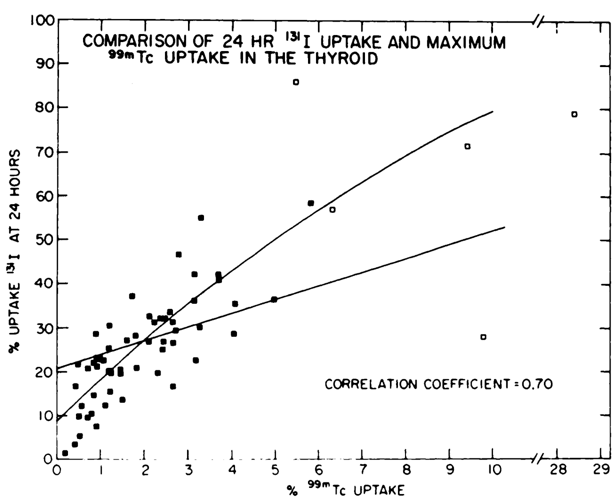

FIG. 6. Comparison of 24-hr ^{131}I uptake and maximum ^{99m}Tc uptake in the thyroid in 63 patients. Open squares indicate hyperthyroid patients in Figs. 6–8. Both linear and quadratic regression curves are shown.

The correlation of ^{99m}Tc uptake and serum PBI is also not very high (correl. coeff. = 0.61), but this is not much different from the correlation of ^{131}I uptake and PBI (correl. coeff. = 0.65) (Figs. 7,8). The PBI determination is subject to a number of inaccuracies aside from the difficulties in the chemical procedure. One patient with low normal technetium and iodine uptakes and a PBI of 3.4 μg% had a thyroxine-binding globulin deficiency. Two patients (excluded from the correlation) who had had radiographic contrast media for myelography and cholecystography had markedly elevated PBI values, while the T-3 resin uptake and the technetium uptake were normal. Apparently moderately elevated levels of iodide in the blood can interfere with the PBI determination without affecting the trapping function of the thyroid. The increasingly widespread use of progesterone-like hormones for contraception also reduces the accuracy of the PBI as a diagnostic test for hyperthyroidism, particularly in that age population where the condition is most common.

Scan quality. Early in this series we made scans with a conventional technique and found that a number of them were technically poor because of a high background. Since we started using a data-blending technique (*19*), this has no longer been a common problem. With data blending the outlines of the gland are more sharply demarcated, and we have obtained a much better appreciation of the anatomy. Of the 177 scans made with data blending, only six were poor, 20 were fair and 151 were excellent. Some of the poor and fair scans could probably have been improved by proper attention to technical details. When technetium scans are compared with ^{131}I scans, the technetium scans have always been superior.

It should be stressed that most of the advantage obtained with technetium is due to proper collimation. The 1,045-hole collimators used with our system provide a circle of resolution at the 50% isoresponse level of 4 mm for the 1.3-in. collimator and 6 mm for the 1.0-in. collimator, in comparison with the 8-mm resolution of the commercially available medium-energy collimator with 31 holes. In addition, the sensitivity is 3.5–5 times greater with the low-energy collimators. Some characteristic scans are shown in Fig. 9.

DISCUSSION

The 24-hr uptake in the thyroid after the oral administration of ^{131}I is probably the most common radioisotope examination of thyroid function. It is a simple and convenient examination to perform but, in the case of hyperactivity of the gland, tests performed earlier after isotope administration have been found to be more accurate (*20*). A number of early tests have been reported, including 1-hr uptakes after oral administration (*21–23*) and continuous or frequent recording over the neck after intravenous administration (*24–29*). These early tests have been used to estimate the "trapping" function of the thyroid separately from the "binding" function and production of thyroid hormone.

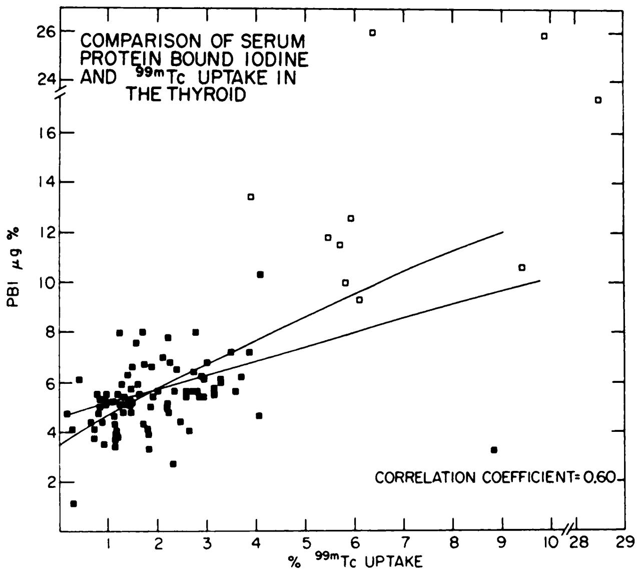

FIG. 7. Comparison of serum protein-bound iodine and ^{99m}Tc uptake in thyroid in 98 patients.

However, organic binding of iodide proceeds extremely rapidly. Administration of sodium iodide or thiocyanate fails to deplete the gland of accumulated ^{131}I at 1 hr after administration (*18,30,31*). The rate-limiting process in thyrotoxicosis has therefore been held to be the "trapping" rate, and a number of studies have been performed to separate this "trapping" function from organic binding of ^{131}I by prior administration of antithyroid drugs such as mercaptoimidazole, propylthiouracil or sodium iodide (*18,*

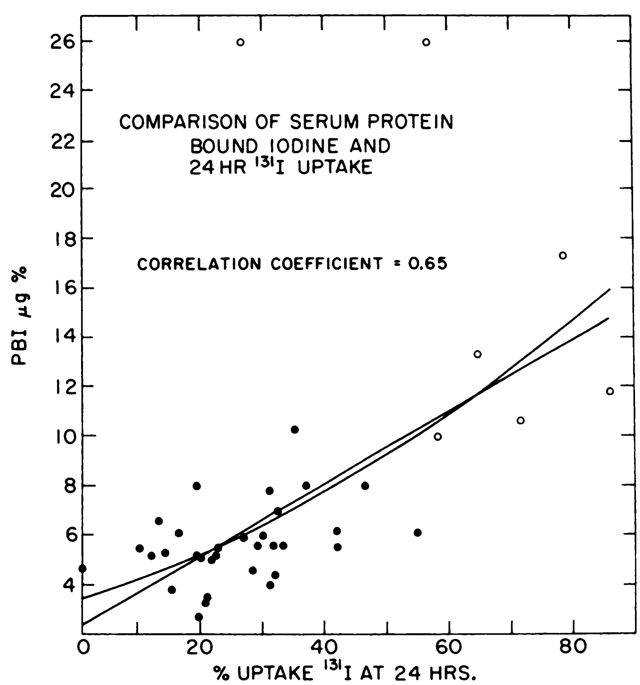

FIG. 8. Comparison of serum protein-bound iodine and 24-hr ^{131}I uptake in thyroid in 40 patients.

30–38). Separation of hyperthyroid from euthyroid individuals has been more accurate than with the 24-hr ^{131}I uptake.

The "trapping" mechanism is responsive to TSH stimulation. On the other hand, the thyroid also responds to a low serum organically bound iodide level by increasing its concentrating ability through an autonomous, internal regulatory mechanism (*30*). In hyperthyroidism the iodide trapping is increased and is nonsuppressible by exogenous thyroid hormone or triiodothyronine.

It is possible to study the "trapping" function of the thyroid with pertechnetate labeled with ^{99m}Tc without using premedication. Response to TSH administration and suppression has been demonstrated (*12*). A good correlation of ^{99m}Tc uptake with the 1-hr uptake of ^{131}I has been obtained although the uptake method differs from the present study and the range of values for ^{99m}Tc uptake is somewhat higher (*13*). The present study shows a moderate correlation of 24-hr ^{131}I thyroidal uptake with the maximum ^{99m}Tc uptake determined 20–30 min after intravenous injection. Although the correlation coefficient is less than that found with the ^{131}I 1-hr uptake, this is not unexpected because the two tests are measuring different aspects of thyroid function. However, there appears to be no significant difference in the diagnostic accuracy of the two tests.

There are several advantages to using ^{99m}Tc instead of ^{131}I. The radiation dose administered to the gland with the procedure outlined above is 0.2–0.6 rads (*39*) compared to about 10 rads with a 10-μc tracer dose of ^{131}I. The difference is even greater when 50-μc tracer doses of ^{131}I are administered for scanning. ^{99m}Tc also has advantages over ^{125}I. The radiation dose with 50 μc of ^{125}I is 18 rads, and the tissue absorption of the very-low-energy photons of ^{125}I is rather marked.

When pertechnetate studies are performed, the results are known immediately. The ratemeter tracing involves relatively simple equipment and no standardization. The study is completed in less than 20 min. When uptakes are made with a scan, the study can be completed in one patient visit.

Scans performed with ^{99m}Tc are superior to those performed with ^{131}I because of the high counting rates, greater statistical reliability and superior resolution. Even in patients who are hypothyroid or who have had marked suppression of thyroidal uptake by medication such as thyroid hormone or triiodothyronine, good scans can be obtained. The data-blending technique (*19*) is particularly useful with ^{99m}Tc scans because the relatively high background is blended to an even density. With the sharp resolution possible, stereoscopic scans can be obtained. The time involved is short because of the increased number of photons available, letting one move the detector rapidly.

Increased accuracy over the 24-hr thyroidal uptake of ^{131}I is to be expected with ^{99m}Tc in the diagnosis of hyperthyroidism, particularly in patients with a high turnover of ^{131}I where the amount in the gland at 24 hr may be in the normal range. However, factors that can result in spuriously high iodine up-

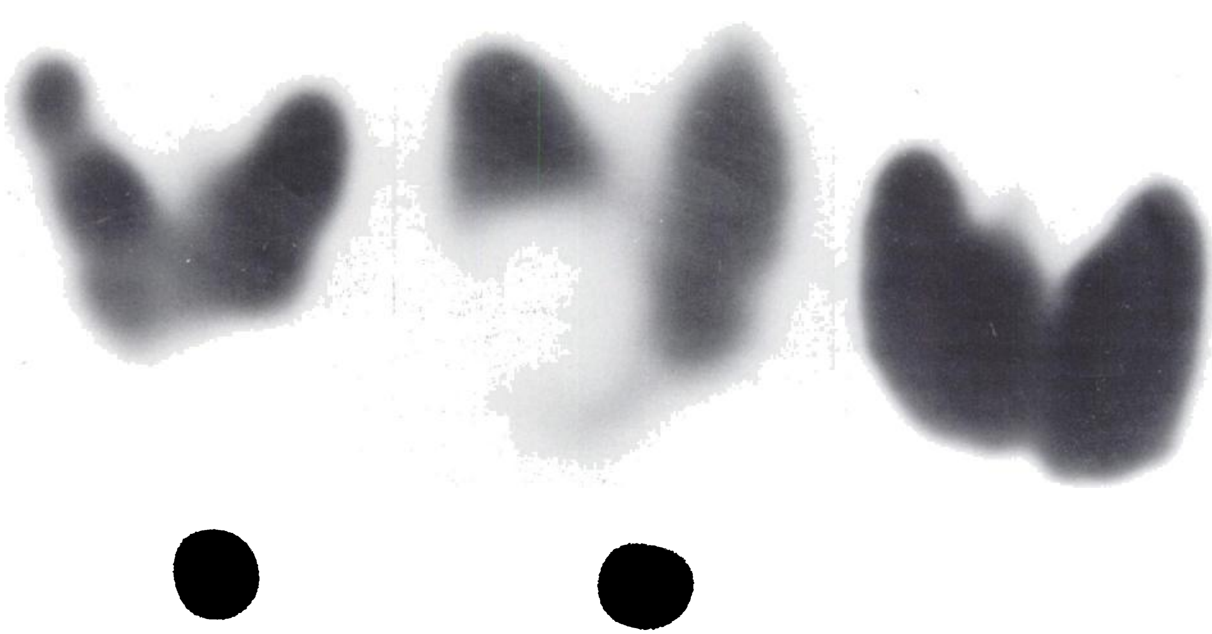

FIG. 9. At left, multiple hot nodules in thyroid that had undergone heavy exposure to fallout 12 years before. In middle, large cystic lesion of right lobe. At right, toxic diffused goiter with small pyramidal lobe faintly visualized. ^{99m}Tc uptake is 28%.

takes such as iodine deficiency goiter or in low uptakes such as suppression by exogenous thyroid also affect the technetium uptake. On the other hand, medications such as propylthiouracil which affect iodine binding do not affect technetium trapping. In the present series, the diagnostic accuracy of the ^{99m}Tc uptake is comparable to that of the 24-hr ^{131}I uptake.

Determining uptake with a scan is more expensive and more time consuming than merely counting over the neck. On the other hand, the information obtained is more extensive and often of definite assistance in determining therapy. In addition, in scanning with ^{99m}Tc, the time consumption is much less than with ^{131}I or ^{125}I.

The technetium study does not interfere with the iodine study if one wants to perform it as well because the 140-kev technetium gamma photon is easily discriminated against and in 24 hr physical decay alone reduces the amount present by a factor of 16. Thus both the "trapping" and "binding" functions of the thyroid can be examined separately. When technetium is used for thyroid scanning, it would be useful to perform function studies as well. In laboratories where the nuclide is used for scanning other organs such as brain and liver, consideration should be given to using it as a replacement for —or in addition to—^{131}I for studying thyroid function because it will be available in large quantities and therefore very economical to use.

SUMMARY

The "trapping" function of the thyroid can be studied with ^{99m}Tc-pertechnetate. The accuracy in diagnosing hyperthyroidism is comparable to that with the 24-hr ^{131}I uptake measurement. Suppression of TSH by exogenous thyroid medication and stimulation of the thyroid by TSH administration affect the ^{99m}Tc uptake in a similar way to the effect on ^{131}I uptake.

Superior thyroid scans can be obtained with ^{99m}Tc because of its favorable physical characteristics and because large amounts of activity can be administered safely. Therefore the use of ^{99m}Tc-pertechnetate is recommended both for physiological and anatomical studies of the thyroid.

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Space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

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