comments to make on management; this was discussed in detail by Jennett (1972). Nevertheless, although a relatively small percentage need neurosurgical intervention it may be life-saving for those who require it, and there is no certain way of identifying them beforehand. The policy of admitting large numbers of children as a precautionary measure has therefore to continue, and clearly head injury, although a relatively small burden on the neurosurgical services, must inevitably make heavy demands on paediatric beds. On grounds of both expediency and humanity there is need for continued effort to reduce the risks of injury in children.

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Technetium-99^m in the Diagnosis of Thyrotoxicosis

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Summary

The thyroid uptake at 20 minutes of intravenously administered Technetium-99^m (^{99m}Tc) was measured in 117 patients with a standard scintillation counter. Patients were divided into three groups on the basis of clinical assessment, four-hour ¹³¹I uptake, triiodothyronine (T-3) resin uptake, and protein-bound iodine measurements.

In 31 patients with no evidence of thyroid disease the mean ^{99m}Tc uptake was $1.8\% \pm \text{S.D. } 1.1\%$. In 32 patients with thyroid enlargement who were euthyroid the mean uptake was $2.5\% \pm \text{S.D. } 2.2\%$. In 54 thyrotoxic patients the mean uptake was 17.7% with a range of 4.1 to 44%, all cases having an uptake above the upper limit of normal (4.0%). These results agree closely with reported uptake studies using scanning techniques. In seven patients the extrathyroidal neck activity was measured by using a scanner, and the mean was 6.3% of the extrathyroidal total body radioactivity comparing favourably with an assumed 6% used in our calculations.

We have shown that the measurement of the thyroid uptake of ^{99m}Tc with a scintillation counter is of value, and that it is not necessary to use scanning techniques in the diagnosis of thyrotoxicosis. Advantages of ^{99m}Tc are minimal radiation, reduction in patient and laboratory time, and low cost.

Introduction

Harper *et al.* (1962) first showed that Technetium-99^m (^{99m}Tc) was concentrated in the thyroid gland, and because of its short half-life of six hours its ready availability and desirable radiation characteristics suggested that it might be used for thyroid scanning.

Since then a number of workers have shown that excellent thyroid scans can be obtained with ^{99m}Tc (Andros *et al.*, 1965; Degrossi *et al.*, 1965; Kuba *et al.*, 1966; Atkins and Richards, 1968; Haas *et al.*, 1968; Umek and Czemberek, 1968; Crema *et al.*, 1969). Technetium is trapped by the thyroid, as is iodide, but soon after administration no significant organic binding takes place (Andros *et al.*, 1965; Shimmings *et al.*, 1968; Shimmings *et al.*, 1969). Burke *et al.* (1972) suggested that some binding of ^{99m}Tc may take place in thyrotoxic patients as there is less discharge of ^{99m}Tc from these as opposed to euthyroid subjects after perchlorate. Twenty minutes after intravenous injection, however, there is a very good correlation between the thyroid uptakes of ¹³¹I and ^{99m}Tc (McGill *et al.*, 1971).

Early uptake studies of ¹³¹I have been shown to be helpful in the diagnosis of thyrotoxicosis (Goolden, 1960) but they have not become generally used, partly perhaps because of the necessity to administer the isotope intravenously. Because of its short half-life and reduced radiation to the patient ^{99m}Tc has obvious advantages over ¹³¹I, and, furthermore, unlike ¹³¹I, which emits high energy gamma rays, ^{99m}Tc can also be used for scanning.

A number of reports have appeared showing that early uptake studies of ^{99m}Tc by the thyroid would differentiate thyrotoxic from euthyroid patients (Kuba *et al.*, 1967; Atkins and Richards, 1968; de Garreta *et al.*, 1968; Höschl and Gimlette, 1971; McGill *et al.*, 1971), but Goolden *et al.* (1971) were the first to advocate its routine use as a test of thyroid function. One of the main difficulties of early thyroid uptake studies is that extrathyroidal neck radioactivity (E.N.R.) makes a significant contribution to the neck uptake, and most of the previous workers have used scanning techniques in order to make a correction for this. Goolden *et al.* (1971) used a dual-head scanner, although they have shown since (Williams *et al.*, 1972) that similar results can be achieved with a single detector scanner. Because of the disadvantages of scanning McGill *et al.* (1971) did not recommend the uptake of ^{99m}Tc for routine clinical use.

We have devised a method for measuring the uptake of ^{99m}Tc with a standard scintillation detector that gives satisfactory results.

Methods

30 μ Ci of ^{99m}Tc was injected intravenously and activity was counted 20 minutes later by using a directional (Ekco) scintilla-

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tion counter with a 1 in. (2.5 cm) NaI crystal and a standard collimator (International Atomic Energy Agency, 1962) at 30 cm from the patient, usually over 200 seconds without and then with a lead shield (4 by 4 by $\frac{1}{2}$ in—10.2 by 10.2 by 1.3 cm) over the thyroid to obtain the neck uptake. This was expressed as a percentage of the administered dose by counting a similar dose in a standard (International Atomic Energy Agency, 1962) phantom. In order to obtain the thyroid uptake we used the assumption of Hilditch *et al.* (1967) that the E.N.R. at 20 minutes is 6% of the extrathyroidal total body radioactivity (E.T.A.). Alexander *et al.* (1969) showed that a simple correction could be made with this assumption:

neck uptake at 20 min =

thyroid uptake at 20 min + $\frac{6}{100}$ (100—thyroid uptake at 20 min)

therefore, thyroid uptake at 20 min = $\frac{\text{Neck uptake at 20 min} - 6}{0.94}$

All patients were assessed clinically, with an oral four-hour ^{131}I uptake performed immediately after the $^{99\text{m}}\text{Tc}$ uptake, a T-3 resin uptake, and a protein-bound iodine measurement, and on the basis of these results put into three groups.

Results

The 20-minute intravenous $^{99\text{m}}\text{Tc}$ uptake by the thyroid was studied in 117 patients, of which 31 were thought to be euthyroid by the above criteria and had no evidence of thyroid disease (group 1). These we regarded as our normals. The mean $^{99\text{m}}\text{Tc}$ uptake in this group was $1.8\% \pm \text{S.D. } 1.1\%$, making the upper limit of normal (mean + 2 S.D.) 4.0%.

Group 2 consisted of 32 patients who were also regarded as euthyroid by the above criteria but had thyroid enlargement. The mean $^{99\text{m}}\text{Tc}$ uptake in this group was $2.5\% \pm \text{S.D. } 2.2\%$.

In Group 3 there were 54 patients who were thought to be thyrotoxic, in whom the mean $^{99\text{m}}\text{Tc}$ uptake was 17.7% with a range of 4.1 to 44%.

One patient (Case 1) in group 1 had a raised $^{99\text{m}}\text{Tc}$ uptake (Fig. 1). She remained euthyroid clinically one year later and ^{131}I uptake, T-3, resin uptake, and protein-bound iodine were again all normal. On this occasion the $^{99\text{m}}\text{Tc}$ uptake was repeated after T-3 40 μg three times daily for seven days, and suppression occurred (Table I).

In Group 2 four patients had raised $^{99\text{m}}\text{Tc}$ uptakes (Fig. 1). One of these had Hashimoto's disease, diagnosed histologically

FIG. 1— $^{99\text{m}}\text{Tc}$ uptakes of the three groups of patients.

TABLE I—Thyroid Uptake Tests in Euthyroid Patient (Case 1) in, 1971 and a Year Later Before and After T-3 40 μg three times daily for Seven Days (T-3 Suppression Test)

	$^{99\text{m}}\text{Tc}$ Uptake (%)		^{131}I Uptake (%)	
	Before	After	Before	After
1971... ..	4.7	—	33.0	—
1972... ..	5.1	0.5	18.2	—

TABLE II—Thyroid Uptake Tests in Three Patients with Euthyroid Goitre Before and After T-3 Suppression Test

Case No.	$^{99\text{m}}\text{Tc}$ Uptake (%)		^{131}I Uptake (%)	
	Before	After	Before	After
2	10.0	0.6	30.0	10.0
3	4.8	0.5	25.3	9.9
4	6.7	—	46.7	12.4

TABLE III—Thyroid Uptake Tests in Two Patients with Thyrotoxicosis Before and After T-3 Suppression Test

Case No.	$^{99\text{m}}\text{Tc}$ Uptake (%)		^{131}I Uptake (%)	
	Before	After	Before	After
5	4.1	5.9	36.9	44.0
6	4.9	14.1	22.4	53.1

In Case 6 there was an interval of six weeks before the suppression test, during which the patient became more overtly thyrotoxic.

after surgery, and the other three all suppressed with T-3 (Table II).

None of the thyrotoxic patients had normal $^{99\text{m}}\text{Tc}$ uptakes, but in the two with uptakes that were only just above normal T-3 suppression tests were carried out (Table III), and both failed to suppress.

In five patients out of the 117 the $^{99\text{m}}\text{Tc}$ uptake did not agree with the other criteria, giving a diagnostic accuracy of over 95%.

The relation between the $^{99\text{m}}\text{Tc}$ and the four-hour ^{131}I uptakes in the 117 patients in Groups 1, 2, and 3 is shown in Fig. 2, as well as four euthyroid patients who had previously had thyroidectomies and one patient with myxoedema all of whom had low normal $^{99\text{m}}\text{Tc}$ uptakes. There is a linear relation, with a correlation coefficient of 0.835, $P < 0.001$.

FIG. 2—Relation between 20-minute intravenous $^{99\text{m}}\text{Tc}$ and four-hour ^{131}I oral uptakes.

A linear relation was also found between the $^{99\text{m}}\text{Tc}$ uptake and the protein-bound iodine, the T-3 resin uptake, and the free thyroxine index (Table IV). The correlation coefficients were all significant at the 0.1% level.

Thyroid scans were performed in seven patients to check the assumption on which the correction for E.N.R. was based—namely, that the E.N.R. was 6% of the E.T.A. These patients

TABLE IV—Relation Between 20-minute Intravenous ^{99m}Tc Uptake and Other Thyroid Function Tests

	Correlation Coefficient	P
^{99m} Tc and four-hour ¹³¹ I uptake	0.83	<0.001
^{99m} Tc and protein bound iodine	0.91	<0.001
^{99m} Tc and T-3 resin uptake	0.92	<0.001
^{99m} Tc and free thyroxine index	0.82	<0.001

were given 500 μ Ci ^{99m}Tc intravenously and a scan was performed with a Picker Magnascanner 500 immediately after the neck uptake had been done in the way previously described, and 25 minutes after the injection. The E.N.R. was assessed by a method of dot counting similar to that of Andros *et al.* (1965). A square 4 by 4 in (10.2 by 10.2 cm), corresponding to the lead shield, was drawn around the thyroid area of the scan and the number of dots within this area was related to the previously measured neck uptake. A rectangle 2 by 4 in (5.1 by 10.2 cm) (half the area of the square) was drawn immediately below the square, and twice the number of dots in this rectangle, after allowing for room background, was taken to represent the E.N.R.

The mean E.N.R. in the seven patients was 6.3% of the E.T.A. with a range of 4.5 to 8.6% (Table V). If in these patients the measured instead of the assumed E.N.R. was used the mean difference in thyroid uptake was less than 1% (Table VI).

TABLE V—Measurement of Extrathyroidal Neck Radioactivity in Seven Patients using Scanning Technique

Case No.	N.U. (%)	E.N.R. (%)	T.U. (%)	E.T.A. (%)	E.N.R. $\times 100$ E.T.A. (%)
7	7.87	6.2	1.7	98.3	6.3
8	18.70	4.5	14.2	85.8	5.2
9	32.80	5.2	27.6	72.4	7.2
10	11.90	4.2	5.7	94.3	4.5
11	17.60	6.2	11.4	88.6	7.0
12	34.80	3.6	31.2	68.8	5.2
13	12.30	8.2	4.1	95.9	8.6
Mean		5.4			6.3

N.U. = Neck uptake. E.N.R. = Extrathyroidal neck radioactivity. T.U. = Thyroid uptake (N.U. - E.N.R.). E.T.A. = Extrathyroidal total body activity (100 - T.U.).

TABLE VI—Comparison of Thyroid Uptake in Seven Patients using Measured E.N.R. and Assumed E.N.R. 6% of E.T.A.

Case No.	Thyroid Uptake (%)		
	With Measured E.N.R.	With Assumed E.N.R.	Difference
7	1.7	2.0	0.3
8	14.2	13.5	0.7
9	27.6	28.7	1.1
10	5.7	6.3	0.6
11	11.4	12.4	1.0
12	31.2	30.6	0.6
13	4.1	6.7	2.5
Mean			0.97

N.U. = Neck uptake. E.N.R. = Extrathyroidal neck radioactivity. T.U. = Thyroid uptake (N.U. - E.N.R.). E.T.A. = Extrathyroidal total body activity (100 - T.U.).

Discussion

The difficulty of assessing the E.N.R. has been one of the main problems associated with the use of early thyroid uptake measurements.

The assumption we used that the E.N.R. was 6% of the total body E.T.A. was based on work using ¹³¹I (Hilditch *et al.*, 1967). Subsequently Shimmins *et al.* (1969) performed similar studies using ^{99m}Tc and found that the mean E.N.R. was 5.5% of the total body E.T.A., but added that the difference was not statistically significant. As we found the mean E.N.R. to be 6.3% of the total body E.T.A. in the seven patients we studied

with a scanning technique, and as the difference in the thyroid uptake with the measured as opposed to the assumed E.N.R. was less than 1%, we feel justified in using the assumption for routine clinical purposes.

The separation between the present normal and thyrotoxic patients is good, and is very similar to that obtained by Goolden *et al.* (1971). Furthermore the present uptake measurements also agree closely to published series all of which used scanning techniques (Table VII). The only significant series in which a scintillation detector was used is that of Kuba *et al.* (1967).

TABLE VII—Mean 20-minute ^{99m}Tc Uptake in Reported Series. Scanning Technique Was Used in All Except the Present Series

	Euthyroid (%)	Euthyroid Goitre (%)	Thyrotoxicosis (%)
Atkins and Richards, 1968	2.2	—	—
de Garreta <i>et al.</i> , 1968	1.62	2.81	11.7
Shimmins <i>et al.</i> , 1968	3.7	—	19.0
McGill <i>et al.</i> , 1971	0.9	2.87	16.7
Goolden <i>et al.</i> , 1971	1.6	—	—
Hauser <i>et al.</i> , 1971	—	1.69	—
Höschl and Gimlette, 1971	1.71	2.38	10.6
Present series	1.8	2.5	17.7

Measuring the uptake at 30 minutes they found the mean to be 2.46% in normals and 18.2% in thyrotoxic patients. Kuba *et al.* (1966) used potassium perchlorate to block uptake by the thyroid of ^{99m}Tc in order to measure E.N.R., which has the disadvantage of two separate uptake measurements on successive days. It is nevertheless interesting that they found the E.N.R. to be 5.5% of the administered dose at 15 minutes and 5.0% at 30 minutes, which agrees well with our finding of 5.4% at 25 minutes (see Table V).

It is important to relate any new diagnostic technique to methods in current use. We found a linear relation when the thyroid uptake of ^{99m}Tc was plotted against four different established ways of assessing thyroid function, the four-hour oral ¹³¹I uptake, the protein-bound iodine, the T-3 resin uptake, and the free thyroxine index, all of which were significant at the 0.1% level.

As the uptake of ^{99m}Tc is small in normal patients the test is, of course, of no value in the diagnosis of myxoedema, but we feel that it has several advantages over ¹³¹I in the diagnosis or exclusion of thyrotoxicosis. The radiation to the patient of 30 μ Ci ^{99m}Tc is about 1,000 times less than 5 μ Ci ¹³¹I (Goolden *et al.*, 1968), and for this reason its use is justifiable in children and in pregnancy. There is a considerable saving in both patient and in laboratory time with a test in which the uptake is measured after 20 minutes as opposed to four or six hours. ^{99m}Tc is readily obtainable and is cheap. If it is already being used for other purposes such as brain scans, the cost is negligible.

The technique we have described in which the thyroid uptake of ^{99m}Tc is measured with a scintillation detector is simple and gives satisfactory results in the diagnosis of thyrotoxicosis, and we are now using it routinely. If it is adopted in other centres we would advocate that each centre should establish its own values for normal subjects and thyrotoxic patients. The correction factor of 6% cannot necessarily be applied to other counters in different centres, and it is advisable that this be checked in each centre in the way we have described.

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Ferritin in the Serum of Normal Subjects and Patients with Iron Deficiency and Iron Overload

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Summary

The concentration of ferritin in serum gives a quantitative measure of the amount of storage iron in normal subjects and those with iron deficiency or overload. The mean level in normal men is 69 ng/ml, compared with 35 ng/ml in normal women. A concentration below 10 ng/ml is associated with a low transferrin saturation and iron-deficient erythropoiesis.

Introduction

Ferritin is found mainly in the cytoplasm of reticuloendothelial cells and liver cells. It is normally thought to be a storage compound from which iron is mobilized into the transferrin-bound plasma pool. A little ferritin is present in developing red cell precursors in the bone marrow. It has not previously been thought to appear in the plasma or extracellular fluid under normal conditions (Reissman and Dietrich, 1956; Aungst, 1966). Recently, however, a sensitive immunoradiometric assay has been described which has resulted in the detection of ferritin in normal serum (Addison *et al.*, 1972). Preliminary data on serum ferritin concentrations suggested that the level of circulating ferritin is related to body stores of iron and that the assay might provide a valuable method of screening subjects for subnormal or excessive storage levels.

This paper reports on serum concentrations in normal subjects, patients with iron deficiency anaemia, and patients with both primary and secondary iron overload.

Subjects and Methods

Normal Subjects.—Seventy-five unselected apparently healthy men aged between 18 and 65 years were examined. Blood samples were taken as part of a routine health screening

procedure in a Cardiff factory. Forty-four apparently healthy women members of staff at Velindre Hospital, Cardiff, were examined at the time that routine blood samples were being taken for screening purposes. Haematological criteria are shown in the Table. No marrow examinations were carried out in this group.

Haematological Data in Normal and Iron-Deficient Subjects. (Mean $\pm$ S.E., range in parentheses)

	No. of Subjects	Haemoglobin (g/100 ml)	Serum Iron (μ g/100 ml)	Transferrin Saturation (%)
Normal men	75	15.7 $\pm$ 0.1 (13.4-17.5)	123.5 $\pm$ 4.8 (44.0-220.0)	30.6 $\pm$ 1.3 (9.0-60.0)
Normal women	44	13.7 $\pm$ 0.18 (10.7-16.2)	94.9 $\pm$ 5.8 (28.0-196.0)	23.8 $\pm$ 1.8 (7.0-64.0)
Iron-deficient patients	21	9.1 $\pm$ 0.3 (5.6-12.6)	20.4 $\pm$ 1.7 (10.0-36.0)	4.3 $\pm$ 0.5 (2.0-11.0)

Iron deficiency Anaemia.—Twenty-one adults (17 women and four men) with untreated iron-deficiency anaemia were examined. The haematological criteria are shown in the Table. Bone marrow fragments were obtained by aspiration, and neither smears nor histological sections showed the presence of stainable iron.

Primary Haemochromatosis.—Eight patients with haemochromatosis in whom the diagnostic criteria included excessive iron deposits in liver biopsy samples and a differential ferroxamine test (Fielding, 1965) showing an increased amount of chelatable iron, F_v varying between 1,072 and 3,303 μ g ferroxamine/kg body weight. The mean serum iron in this group was 246.5 $\pm$ 23.1 mg/100 ml, and the mean transferrin saturation 88.3 $\pm$ 4.2%.

Refractory Anaemia.—Thirteen patients with primary refractory anaemia, all but one of whom had been treated with blood transfusion. In a number of cases more than one sample was taken from the patient at widely differing times so that the effects of increase in iron load could be seen. A total of 24 samples were obtained. The mean haemoglobin concentration in this group was 8.9 $\pm$ 0.6 g/100 ml, mean serum iron 171.8 $\pm$ 16.8 mg/100 ml, and the mean transferrin saturation 68.1 $\pm$ 6.5%.

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