This would seem to indicate that pulsatile flow in the veins of the leg is a prerequisite for effective prophylaxis. However, the method by which intermittent compression prevents thrombosis is still unknown. We envisage that each compression empties the venous system of the leg, particularly the large sinuses in the soleus muscle in which thrombosis most commonly arises (Gibbs, 1957). During anaesthesia the veins of the soleus muscle seem to be functionally isolated (Clark *et al.*, 1965). In addition, venous blood flow is markedly depressed by premedicant drugs and even more so by the induction of anaesthesia (Clark and Cotton, 1968). A low venous flow and stagnant blood in the soleal sinuses seems to favour the development of thrombosis. The effect of intermittent compression would be to alternately empty the sinuses and then to allow them to fill.

The results of our two trials of foot pedalling and intermittent compression are most encouraging. If the two series are grouped together, then in a total of 86 patients thrombosis has occurred in 24 control legs—an incidence of 27.9%. Similarly thrombosis has occurred only in five legs which were either pedalled or squeezed—an incidence of only 5.8%. These combined results show that there is now no doubt that reducing stasis of venous blood in the calf is a potent ($P < 0.01$) measure in the prevention of deep venous thrombosis. Further-

more, the pulsatility of the femoral vein flow is a clearer reflection of the degree of venous stasis occurring in the calf than the mean level of the flow.

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Use of $^{99}\text{Tc}^{\text{m}}$ for the Routine Assessment of Thyroid Function

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Summary

$^{99}\text{Tc}^{\text{m}}$ -pertechnetate is concentrated in the thyroid in the same way as iodide but it does not become organically bound. The uptake of $^{99}\text{Tc}^{\text{m}}$ is a measure of the thyroid trap, and this measurement is satisfactory as a routine test in the diagnosis of thyrotoxicosis. The reproducibility of the method is such that suppression tests can be carried out when necessary even when uptake is within the normal range of 0.4-3%. $^{99}\text{Tc}^{\text{m}}$ gives a low radiation dose to the thyroid and has certain other advantages over radioactive isotopes of iodine for early thyroid uptake measurements. It is particularly suitable when serial tests of thyroid function are required during treatment with an antithyroid drug.

Introduction

The measurement of thyroid uptake with radioactive iodine has been accepted as a simple and useful test of thyroid function. $^{99}\text{Tc}^{\text{m}}$ in the form of pertechnetate is concentrated in the thyroid in the same way as iodide, and the uptake of this radioisotope can be used as an index of thyroid activity (Andros *et al.*, 1965). It is relevant to consider therefore whether $^{99}\text{Tc}^{\text{m}}$ is likely to have any advantages over the various radioactive isotopes of iodine which are currently available.

Recent work has suggested that it is possible to predict which patients are likely to obtain a remission with antithyroid drug therapy by carrying out tests of thyroid function during treatment. About 50% of patients given carbimazole and L-triiodothyronine (T-3) showed suppression of thyroid uptake within three to six months of starting treatment (Alexander *et al.*, 1966, 1967). Suppression in these patients was tested by measuring thyroid uptake 20 minutes after an intravenous dose of ^{131}I . The likelihood of remission was found to be high in patients whose thyroid uptake was suppressed under these circumstances.

When serial tests of thyroid function are required during treatment it is advantageous to use a test that measures the ability of the thyroid to trap or concentrate iodide, because this function is not directly affected by drugs such as carbimazole which act at a later stage in thyroid hormone biosynthesis. $^{99}\text{Tc}^{\text{m}}$, which is concentrated in the thyroid but does not become organically bound, is very suitable for this purpose. We originally developed a method for measuring $^{99}\text{Tc}^{\text{m}}$ uptake in order to follow the progress of patients being treated with an antithyroid drug. Experience, however, has shown that it is a simple and reliable test of thyroid function and we now use it routinely in place of an early radioiodine uptake measurement.

Methods and Patients

Measurement of Uptake of $^{99}\text{Tc}^{\text{m}}$ by Thyroid.—The uptake of $^{99}\text{Tc}^{\text{m}}$ was determined by a method which is based on the use of scanning equipment and which is described in greater detail elsewhere (Williams *et al.*, 1971). The dose of $^{99}\text{Tc}^{\text{m}}$ (0.5 mCi) was measured with the detectors of a dual head scanner and was then given intravenously. A scan was started 20 minutes later. The number of dots per unit area in two regions immediately above and below the thyroid region was determined,

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and this information was used to derive a value for extrathyroidal radioactivity in the rectangular area containing the thyroid image. Further corrections were made for the thickness of the patient's neck, the decay of the isotope, and the speed of the scanner. The uptake in the thyroid was expressed as a percentage of the injected dose.

Though the results described in this paper have been obtained with a dual detector method it has been shown that the uptake can be measured without any loss of accuracy with a single detector scanner (Williams *et al.*, 1971).

The uptake of $^{99}\text{Tc}^{\text{m}}$ by the thyroid was measured in 18 normal volunteers and in 100 patients with thyrotoxicosis. For the past year this measurement was made in all patients suspected of being thyrotoxic. The diagnosis of thyrotoxicosis was made on clinical grounds and confirmed by protein-bound iodine (P.B.I.) and T-3 uptake measurements. $^{99}\text{Tc}^{\text{m}}$ uptake has also been measured in 30 patients who were eventually shown to be euthyroid. Most of these had a non-toxic goitre.

Suppression tests were carried out in 34 patients. The test consisted of an initial $^{99}\text{Tc}^{\text{m}}$ uptake measurement which was repeated after the administration of 120 μg of T-3 daily for a week. Twenty of the patients were thyrotoxic and some were being maintained on carbimazole while the test was carried out. The remaining 14 either had a non-toxic goitre or were in remission after treatment with an antithyroid drug.

Serial measurements of $^{99}\text{Tc}^{\text{m}}$ uptake were carried out in a group of patients undergoing medical treatment for thyrotoxicosis. They were given carbimazole in an appropriate dose with the addition of T-3 80 μg daily after the first month. Measurements were carried out immediately before and at intervals during treatment. Treatment was stopped if the $^{99}\text{Tc}^{\text{m}}$ uptake fell to within the normal range but was otherwise continued for a period of 18 months. Further measurements were carried out at intervals after the antithyroid drug had been stopped.

Results

Uptake Measurements in Normal Subjects and Patients with Thyroid Disorders.—Values for $^{99}\text{Tc}^{\text{m}}$ uptake in the normal subjects and in patients with thyroid disorders are shown in Fig. 1. The mean value in normal subjects was $1.6\% \pm \text{S.D. } 0.7\%$. Six of the thyrotoxic patients had normal values and seven of those with non-toxic goitre had values above the upper limit

FIG. 1—Values for $^{99}\text{Tc}^{\text{m}}$ uptake in normal subjects (18), patients with non-toxic goitre (30), and patients with thyrotoxicosis (100).

of the normal range. In 20 patients uptake was measured on two consecutive days. Values in these patients ranged from 0.8 to 22%. The average difference in uptake between the two measurements was 0.63%, which is a measure of the reproducibility of the method (Williams *et al.*, 1971).

Suppression Tests.—The results of the suppression tests are shown in the Table. None of the thyrotoxic patients showed a fall in uptake in excess of 15% of the initial uptake. In several

T-3 Suppression Tests with $^{99}\text{Tc}^{\text{m}}$ Uptake Measurements. Values Expressed as Percentage of Administered Dose

Euthyroid Patients		Thyrotoxic Patients	
Before T-3	After T-3	Before T-3	After T-3
0.9	0.1	1.7	1.9
1.0	0.0	1.8	2.1
1.4	0.2	2.0	2.2
2.1	0.7	2.1	3.1
2.3	0.4	2.2	1.9
3.0	0.4	2.3	2.3
3.3	0.3	2.3	1.9
3.4	0.5	3.1	4.5
3.6	1.5	3.5	3.0
4.1	0.4	3.8	3.5
5.0	1.6	4.3	4.7
5.6	2.0	5.0	4.2
8.4	1.7	7.5	7.0
8.6	2.0	7.5	7.2
		8.3	9.4
		8.4	7.4
		9.0	8.9
		12.0	15.3
		17.0	23.0
		18.9	21.4

patients the second value was higher than the first and in some cases this difference is significant. Thyroid uptake was suppressed in the patients with non-toxic goitre and in the four thyrotoxic patients who were in remission at the time the test was carried out. According to our data a fall in thyroid uptake of at least 50% of the initial value can be expected in non-toxic patients, and if this is used as an index of suppression the thyrotoxic patients can be readily distinguished from the euthyroid group.

SERIAL MEASUREMENTS IN PATIENTS UNDERGOING TREATMENT

The sequential changes in $^{99}\text{Tc}^{\text{m}}$ uptake in patients being treated with carbimazole are of interest but they have proved less useful in predicting the outcome of treatment than was anticipated. If thyroid uptake shows a progressive and consistent fall to within the normal range the likelihood of remission is high. This type of response is shown in Fig. 2. In this patient treatment with carbimazole and T-3 was discontinued after eight months. Within a month $^{99}\text{Tc}^{\text{m}}$ uptake had reverted to its pretreatment level. Further tests carried out two, three, and four months after stopping treatment showed a return towards normal. At the end of this time a T-3 suppression test caused the uptake to fall to within the normal range. Nine months later the uptake was still just above the upper limit of the normal range but normal suppression was again demonstrable. Two years after stopping treatment this patient was euthyroid, in-vitro tests were normal, and the response to T-3 suppression was also normal.

A normal suppression test does seem to indicate a state of remission but it may be only temporary and a relapse may occur within the space of a year or so. This sequence of events is shown in Fig. 3. Treatment with carbimazole was discontinued in this patient after 11 months. The rebound in uptake and subsequent suppression with T-3 were consistent with a remission. Thyroid status and P.B.I. remained normal for a year but after a further six months the uptake failed to suppress with T-3. Six months later the patient was clinically thyrotoxic and all thyroid function tests were indicative of hyperthyroidism.

Patients who fail to achieve a normal value are likely to

relapse soon, but here again there are exceptions. Some patients showing this type of response have remained euthyroid for a year or more after discontinuation of treatment.

FIG. 2—Serial $^{99}\text{Tc}^{\text{m}}$ uptake and P.B.I. measurements in a patient during and after treatment with carbimazole and T-3. This patient was in remission two years after stopping treatment.

FIG. 3—Serial $^{99}\text{Tc}^{\text{m}}$ uptake and P.B.I. measurements in a patient during and after treatment with carbimazole and T-3. Suppression was demonstrable in this patient at the time she stopped taking carbimazole but she relapsed 18 months later.

Discussion

The main problem associated with an early thyroid uptake measurement is that of finding a relatively simple and convenient method of correction for extrathyroidal radioactivity. Methods of measuring $^{99}\text{Tc}^{\text{m}}$ uptake are based on the use of scanning equipment (Andros *et al.*, 1965; Shimmins *et al.*, 1968; Atkins and Richards, 1968; de Garreta *et al.*, 1968). Such methods depend on the net difference in dot density between

the thyroidal and extrathyroidal regions at the time of measurement and are not based on assumptions about changes in extrathyroidal radioactivity with time. In a situation where the concentration of radioactivity in the gland may not be greatly in excess of that in the surrounding tissues, and where the proximity of the salivary glands is a complicating factor, the determination of thyroid uptake by a scanning method is probably more accurate than any other.

One advantage of $^{99}\text{Tc}^{\text{m}}$ is that it gives a small radiation dose to the thyroid gland. This, assuming an uptake of 2%, amounts to 0.2 rad/mCi administered. $^{99}\text{Tc}^{\text{m}}$ is acceptable therefore when in-vivo tests are required in children or pregnant women. Other radioisotopes which give a radiation dose comparable to that from $^{99}\text{Tc}^{\text{m}}$ and which are suitable for an early uptake measurement are ^{132}I and ^{123}I (Goolden *et al.*, 1968). ^{132}I , however, emits high-energy gamma rays, which preclude the use of a scanner, and this introduces problems associated with correction for extrathyroidal activity. ^{123}I would be satisfactory from a scanning and radiation dose viewpoint but this radioisotope is not yet widely available. There is one other difficulty which might arise if ^{123}I uptake were to be measured by a scanning method. With this radioisotope the rate of uptake will be increased and maintained for a long period because organic binding of iodine is taking place. The effect of this will be to introduce errors associated with the precise timing of the measurement. These errors are much less important when $^{99}\text{Tc}^{\text{m}}$ is being used because the uptake has usually reached a maximum value within 15 to 20 minutes.

There are difficulties in interpreting radioiodine uptake measurements in patients who are being treated with drugs which depend for their therapeutic effect on interference with the organic binding of iodine. It has been claimed that early thyroid uptake measurements are unaffected by such drugs and that they can be used to measure the thyroid iodide concentrating mechanism or trap (Thomas *et al.*, 1960; Koutras and Sfontouris, 1966). Whether or not this is so will depend on the rate at which trapped iodide becomes bound, on the time at which the measurement is made, and on the extent to which organic binding of iodine is impaired by the antithyroid drug.

Berson and Yalow (1955) examined in some detail the kinetics of trapping and binding. They concluded from their studies that binding took place with great rapidity and that iodide once trapped became bound almost instantaneously. In support of their findings it can be readily shown that perchlorate prevents any further accumulation of radioiodine by the thyroid but produces no demonstrable loss of radioactivity from the gland even when given intravenously. These observations suggest that in the unblocked thyroid gland early uptake measurements are essentially measurements of iodide already bound, though the earlier the measurement is made the more it will approximate to a measurement of the thyroid trap.

Radioiodine can be used to measure the thyroid trap provided organic binding is completely inhibited, but complete inhibition is not necessary for therapeutic control in patients who are being treated with an antithyroid drug. Hence a measurement at 20 minutes represents partly organically bound iodine and partly trapped iodide. It is not certain, therefore, what is being measured if radioiodine is used in these circumstances, particularly if measurements before treatment are compared with those made during treatment.

The studies of Ibbertson *et al.* (1971) are relevant to this problem. These workers measured thyroid clearance at varying intervals during the first 20 minutes after an intravenous dose of radioiodine. The same measurements were repeated after two weeks' treatment with carbimazole. The earliest clearance, which was made between 0 and 5 minutes, showed no significant fall, but clearances at later times did fall after treatment; the later the time of measurement, the greater the fall. This differential effect on thyroid clearance in relation to the time of the measurement is consistent with the known action of carbimazole on organic binding; that is to say, the later the measurement is

made, the more it will be influenced by organic binding. This means that a fall in the 20-minute uptake during treatment with carbimazole is due partly to impairment of organic binding, and this effect must be taken into account if conclusions on thyroid suppression are based on this measurement. Of interest in this context are some recent observations by Shimmins *et al.* (1971), who found that the 20-minute uptake of ^{131}I fell by about 20% as soon as treatment with carbimazole was started.

Attempts to predict the outcome of antithyroid drug treatment on the basis of thyroid suppressibility have met with limited success (Alexander *et al.*, 1970; Goolden *et al.*, 1971; Lowry *et al.*, 1971). Suppression is not necessarily indicative of long-term remission, and patients who fail to suppress do not always relapse when treatment is discontinued. Despite these limitations the examination of thyroid function during treatment may sometimes be helpful, and for this purpose $^{99}\text{Tc}^{\text{m}}$ uptake would seem to be the most appropriate method.

In our experience $^{99}\text{Tc}^{\text{m}}$ uptake measurements have proved very satisfactory for the routine assessment of thyroid function. In the absence of a direct comparison it cannot be said that they are any more efficient than early radioiodine uptake tests in differentiating between euthyroid and hyperthyroid individuals, but we think it unlikely that such a comparison would show any great difference. Points in favour of $^{99}\text{Tc}^{\text{m}}$ are that it gives a small radiation dose to the thyroid and that tests can be repeated at short time intervals. Furthermore, techniques for measuring the uptake of this radioisotope allow accurate correction for extrathyroidal activity, an essential requirement for any early thyroid uptake measurement. The reproducibility of the method described is such that suppression tests can be used when necessary even when thyroid uptake is within the normal

range. Finally, $^{99}\text{Tc}^{\text{m}}$ is particularly well suited for the assessment of thyroid function in patients being treated with an antithyroid drug.

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Pyrantel Embonate in Treatment of Hookworm Infestation

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Summary

The efficacy of pyrantel embonate (1,4,5,6-tetrahydro-1-methyl-2-(*trans*-2-(2-thienyl)-vinyl)-pyrimidine embonic acid salt; Combantrin) was evaluated in 60 cases of hookworm infestation. They were divided into six groups of 10 cases. Pyrantel embonate was administered orally, in dosage schedules (randomized) of 100, 75, 50, 20, 15, and 10 mg/kg of body weight. The stool examination for hookworm ova and coproculture were positive in each case. The predominant species was *Ancylostoma duodenale* (in 58 patients). After treatment with pyrantel embonate the stool examination for hookworm ova and coproculture were negative on the 10th and 15th days in each group. The blood levels of the drug were significantly higher in patients receiving 100 and 75 mg/kg body weight. In groups A and B one patient experienced nausea and vomiting on the day of administration of drug. There were no abnormal changes in liver function

tests or blood urea levels in any of the groups. Hence the optimum single dose of the drug effective against hookworm infestation is 10 mg/kg body weight, and further studies are required to evaluate the minimum effective dose of pyrantel embonate.

Introduction

Pyrantel embonate (Pamoate, Combantrin) is a 1,4,5,6-tetrahydro-1-methyl-2-(*trans*-2-(2-thienyl)-vinyl)-pyrimidine embonic acid salt. It is a yellow crystalline solid, with a molecular weight of 594.7. It has the molecular formula $\text{C}_{24}\text{H}_{30}\text{O}_6\text{N}_2$ and the structural formula shown in the Diagram. It has been shown

to be very effective against pinworm, roundworm, and hookworm of animals (Austin *et al.*, 1966; Cornwell and Hones, 1968; Howes and Lynch, 1967). The present study was under-

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