RADIOIODINE TRACER TESTS IN THE DIAGNOSIS OF HYPERTHYROIDISM

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The use of radioiodine, ^{131}I , has now an established place as an aid in the diagnosis of hyperthyroidism, but there is no agreement on which radioiodine test is best for this purpose. Many indices of thyroid function have been proposed which variously involve the measurement, either serial or at fixed times after the administration of the radioisotope, of its accumulation by the thyroid, excretion by the kidneys, and concentration in whole blood, blood plasma, and saliva.

Indices dependent on measurements of the radioiodine content in the thyroid or in blood are considered preferable to those dependent on urinary excretion because of the problems involved, particularly for out-patients, in urine collection over set periods of time.

Almost all of the radioiodine tests advanced in the literature will distinguish between the frankly thyrotoxic patient and the normal subject, but the real usefulness of a test must lie in its ability to aid the diagnosis in clinically borderline cases, and in its simplicity.

It is often difficult to assess the relative merits of particular proposed indices of thyroid function, as the clinical material varies so widely from one group of workers to another. However, most of the more promising radioiodine indices have been compared with each other, the B.M.R., and the biochemical determination of protein-bound iodine (P.B.I.) by the Royal Melbourne Hospital group (Clarke and Aujard, 1954; Madigan and King, 1954; Winikoff, 1954; Clarke, Sherriff, and Winikoff, 1955) and by others (Goodwin, Macgregor, Miller, and Wayne, 1951; Fryers, 1956; McConahey, Owen, and Keating, 1956).

From the studies in Melbourne it has been concluded that the best single index of thyroid function is the biochemical determination of P.B.I., which separates both the hyperthyroid and hypothyroid groups from the normal or euthyroid group with a high degree of accuracy. Between 90% and 95% of the patients in each group, including a large number of clinically borderline cases, have been correctly classified by this index.

The determination of P.B.I., however, is technically difficult on account of the very low levels of iodine to be measured, and demands the utmost care in keeping the laboratory and apparatus completely free from iodine contamination. For this reason it has been hoped that the use of radioiodine, which is readily detected by its beta and gamma emanations, would provide a simpler index of thyroid activity.

The best radioiodine indices in the Royal Melbourne Hospital studies referred to above have been shown to be

the measurement of plasma protein-bound radioiodine 48 hours after administration of the tracer dose (48-hour P.B. ^{131}I) and a measurement dependent on the early uptake of radioiodine by the thyroid.

The 48-hour P.B. ^{131}I index is the one proposed by Goodwin *et al.* (1951), who have shown that the rapid removal of the radioiodine as iodide from the plasma, and its early reappearance in hormonal form in hyperthyroid patients, can best be distinguished from the much slower process in euthyroid patients 48 hours after the administration of the tracer dose. It is a convenient index in that it does not require intravenous administration of the isotope, but it does necessitate the patient's attendance a second time, and, furthermore, since the measurement of the 24-hour percentage retention of radioiodine by the gland is considered useful in assessing the size of the therapeutic dose in those cases subsequently treated with radioiodine (Fairley, Holman, and King, 1956), patients often have to attend the hospital three days in succession, the first day for the administration of the tracer dose and early thyroid uptake measurements, the second day for a 24-hour percentage thyroidal retention measurement in case subsequent radioiodine therapy is prescribed, and the third day for a blood sample for the 48-hour P.B. ^{131}I determination.

Several early uptake tests have been suggested, and all appear reasonably reliable. The thyroid clearance test of Myant, Pochin, and Goldie (1949), however, is laborious in that it involves serial measurements over the gland and the measurement of radioiodine in the blood plasma; the uptake rate factor of Oddie, Meschan, and Wortham (1955) involves measurements of thyroidal radioiodine at 1, 4, and 24 hours; while the thigh/neck clearance test of Foote and MacLagan (1951) and the uptake rate factors of the earlier studies at the Royal Melbourne Hospital also depend on serial measurements.

Pochin (1950) was the first to observe that a simple but efficient test would be an early comparison of the counting rate over the neck with that over the thigh following the administration of a tracer dose of radioiodine, and Rundle, Seldon, and Indyk (1956) have also found such an index to be useful. In thyrotoxicosis the thyroid rapidly takes up radioiodine from the circulating plasma, so the early neck counts will become higher than normal and the thigh counts will become lower than normal, resulting in the neck/thigh ratio being greatly increased.

In the series of cases reported here the thyroidal uptake and the neck/thigh ratio have been determined two hours after oral administration of the tracer dose, the patient having had nothing to eat for the three hours before the test. The time interval of two hours was chosen because it was considered that by that time the amount of radioiodine secreted from the thyroid and the effect of variations in the absorption rates of radioiodine from the intestinal tract would be small.

The percentage content of radioiodine in the thyroid at 24 hours, which is used in many centres as an index of thyroid function, has not been found to have diagnostic significance in the Royal Melbourne Hospital Unit. In some patients the radioiodine content of the thyroid falls greatly between 2 hours and 24 hours, and the 24-hour measurement is considered useful as a measure of the degree of retention of radioiodine by the gland, which is taken into account when assessing

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the size of the therapeutic dose of radioiodine required. This measurement is here referred to as the 24-hour percentage thyroidal retention.

Technique

Certain dietary factors, medications, and special radiographic procedures involving substances containing iodine are known to influence the thyroidal uptake and turnover of radioiodine. In order that the dietary influence shall be minimal a diet which avoids foods with a high iodine content, such as fish foods, is prescribed for one week before the test. With regard to medication, thiourylene derivatives and carbimazole are discontinued for a minimum period of two weeks, and iodine preparations and thyroid for at least four weeks prior to the tracer test.

A tracer dose of 20 μ c of radioiodine (^{131}I), carrier-free, is administered orally, the patient having had nothing to eat for the previous three hours. Two hours after administration measurements are made of the radioiodine content of the neck and thigh, using paired G10Pb geiger counters as previously described (Clarke and Aujard, 1954).

Since the accumulation of iodine by tissues other than the thyroid and kidneys is relatively small, it has been assumed that the ^{131}I content of the tissue of the neck, excluding the thyroid, is approximately equal to the ^{131}I content of a similar volume of tissue of the thigh. The geometrical arrangements of the counters in the neck and thigh units are such that the response of the thigh counters to a distributed source of ^{131}I (as in the thigh) is three times the response of the neck counters to a similar source, hence thyroid counting rate = neck counting rate $\times \frac{1}{3}$ thigh counting rate and the neck/thigh ratio, which is here taken to mean

^{131}I content of the tissue of the neck including thyroid

^{131}I content of a similar volume of tissue of the thigh

will be equal to
$$\frac{\text{Neck counting rate}}{\frac{1}{3} \text{ thigh counting rate}}$$

In those cases where radioiodine therapy is a considered possibility similar measurements are made at 24 hours.

At 48 hours a blood sample is taken for the determination of P.B. ^{131}I , which is expressed as a percentage of the dose per litre of plasma. The details of the method are given below. The limits for the two-hour uptake, the two-hour neck/thigh ratio, and the 48-hour P.B. ^{131}I determined in this study are given in Table I. The same criteria have been adopted in the clinical assessment of thyrotoxicosis as have been previously described from this unit (Madigan and King, 1954).

Determination of 48-hour P.B. ^{131}I

Two-millilitre samples of plasma are used. The plasma proteins are precipitated by adding 6 ml. of 10% trichloroacetic acid, after which the suspension is centrifuged

and the supernatant liquid poured off. The precipitate is washed twice with 6 ml. of trichloroacetic acid, centrifuged, and the supernatant poured off. To the precipitate is now added 0.5 ml. of 2N sodium carbonate and 0.1 ml. of "teepol" (a commercial wetting agent) and the mixture is agitated with a glass rod until all has dissolved. It is then transferred quantitatively to an aluminium pan, dried gently by means of an infra-red lamp, counted by means of an EHM2 mica-window geiger counter, and compared with a standard radioiodine source.

Results

This study covers all the patients who were referred to the radioiodine unit of the Royal Melbourne Hospital for investigation, and who were given subsequent radioiodine tracer tests during the 15-months period August, 1956, to November, 1957. Some of these were frankly thyrotoxic patients for whom tracer tests were required for the determination of the 24-hour percentage thyroidal retention of radioiodine used in the assessment of the radioiodine therapy dose, but these results are not considered in the final analysis.

Altogether, 156 consecutive tracer tests were carried out on 139 patients. Twelve tests on 12 patients have been excluded from the analysis, as it has not been possible to assign a final diagnosis in these cases. A further 44 tests have been excluded either because medication had not been discontinued for a sufficiently long period, or because the patient was considered to be frankly toxic.

The results of the remaining 100 tracer tests on 96 clinically borderline patients considered free from influencing medication are given in Table II. These 100 tests include 61 in which no known influencing medication had been given at all, 3 post-operative, 17 post- ^{131}I therapy (minimum time interval since therapy being three months), and 19 others in which medication had been discontinued for longer than the prescribed period. In 52 tests the final classification was hyperthyroid and in 48 tests it was euthyroid. The final classification was decided after further observation and in some cases after a trial period of medication.

For various reasons not all the three radioiodine indices—that is, the two-hour uptake, the two-hour neck/thigh ratio,

TABLE I.—Limits for the Three ^{131}I Indices Presented

Classification	Two-Hour Thyroidal Uptake %	Two-Hour Neck/Thigh Ratio	48-Hour P.B. ^{131}I % Dose/Litre of Plasma
Hyperthyroid	≥ 55	≥ 50	≥ 0.5
Indeterminate	$> 50 - < 55$	$> 35 - < 50$	$> 0.45 - < 0.5$
Euthyroid	≤ 50 (lower limit uncertain)	≤ 35 (lower limit uncertain)	$0 - < 0.45$

TABLE II.—Results of 100 ^{131}I Tracer Tests on 96 Clinically Borderline Cases Considered Free from Influencing Medication

Final Diagnosis	No. of Tests	Two-Hour Thyroidal Uptake			2-Hour Neck/Thigh Ratio			48-Hour P.B. ^{131}I		
		Correctly Classified	Indeterminate	Incorrectly Classified	Correctly Classified	Indeterminate	Incorrectly Classified	Correctly Classified	Indeterminate	Incorrectly Classified
Hyperthyroid	34	30	—	4	32	1	1	31	1	2
Post ^{131}I therapy	10	9	—	1	9	—	1	10	—	—
Euthyroid	33	27	—	6	27	—	6	26	—	7
Post ^{131}I therapy	2	1	—	1	1	—	1	—	—	2
Hyperthyroid	3	2	—	1	2	—	1	—	—	—
Post ^{131}I therapy	3	3	—	—	3	—	—	—	—	—
Euthyroid	8	7	—	1	7	—	1	—	—	—
Post ^{131}I therapy	1	—	—	1	—	—	1	—	—	—
Hyperthyroid	2	2	—	—	—	—	—	2	—	—
Euthyroid	3	2	1	—	—	—	—	3	—	—
Post ^{131}I therapy	1	1	—	—	—	—	—	—	—	1
Totals	39	34	—	5	34	1	2	33	1	2
Hyperthyroid	13	12	—	1	12	—	1	10	—	—
Post ^{131}I therapy	44	36	1	7	34	—	7	29	—	7
Euthyroid	4	2	—	2	1	—	2	—	—	3

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