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WHOLE BODY COUNTER IN ROUTINE TESTS OF HYPERTHYROIDISM USING IODINE 131

by

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It was clear from the papers presented at the 'Symposium on Whole Body Counting' (I.A.E.A. 1962) that most of the associated instrumental and development problems had been overcome, and that whole body counting techniques were already being applied to clinical problems. Much credit must be given to the early workers who used high pressure ionization chambers with a sensitivity approaching the natural γ-activity of the body and who were largely concerned with the body retention of thorium and radium products (SIEVERT 1950, BURCH 1952, BURCH & SPIERS 1953, RUNDO 1955). Great stimulus for this work arose from the radiologic protection problems associated with the ingestion or inhalation of fission fall-out products and contamination from nuclear establishments. The estimate of body burdens and the time constants of retention became of world wide importance. Technologic progress with scintillators and photomultipliers occurred at the same time (MARSHALL & COLTMAN 1947, BELL 1948, HOFSTADTER 1948). The development of large volumes of liquid phosphors for neutrino studies (COWAN et coll. 1953) led to highly sensitive whole body counters using nearly 4π geometry (ANDERSON 1957). Thallium-activated sodium iodide crystals were used by MARINELLI

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(1956), and RUNDO (1958), and plastic scintillators by BIRD & BURCH (1958). A thorough investigation of the means of reducing NaI (Tl) background counts with a steel room was done by MILLER et coll. (1956). The use of chalk as a cheaper shielding material was described by TROTT et coll. (1963). A survey of whole body counters that were in operation during 1962 (MEHL & RUNDO 1963; I.A.E.A. 1964) indicates that the largest use was for investigation of occupational contamination (DOLPHIN, MEGAW & RUNDO 1962).

Uses of iodine 131. Whole body counters that are capable of measuring the natural potassium 40 content of subjects offer the advantage in clinical studies of using radioisotope tracer techniques with very small administered doses of radiation, and also of avoiding the difficulties of complete collection of excreta over long periods.

Perhaps the most widespread and frequent use of radioisotopes in non-malignant conditions is the investigation of hyperthyroidism with ^{131}I, and it is natural that the possible application of whole body counters to this work should be assessed with the aim of reducing the radiological exposure. Earlier reports (LUSHBAUGH 1961, LUSHBAUGH & HALE 1962, LUSHBAUGH 1963) showed that the thyroid in small animals and man could be studied by total body activity measurements. The main disadvantage of using very small doses of ^{131}I is that the plasma protein-bound radioiodine (PBI-131) cannot be measured and thyroid mapping cannot be performed. However, the PBI-131 is sometimes misleading and the plasma butanol-extractable iodine (BEI-127) could be used with advantage in its place, while thyroid mapping is of value only in a small number of special cases. A common method of reducing the radiological dose to the thyroid is to use ^{132}I. WAYNE, KOUTRAS & ALEXANDER (1964) suggested that the 2 1/2-hour thyroid uptake is less influenced by renal clearance than the 24-hour uptake, but it is more generally accepted that there is a wide equivocal range for early uptake measurements (HOBBS et coll. 1963). Also there is always some ^{131}I impurity with the ^{132}I which increases the radiological dose.

In a 25-g thyroid, with peak uptake of 30 %, the average dose in euthyroid subjects is 1.6 rad per microcurie of administered ^{131}I, and 46 millirad per microcurie of administered iodine 132 (using the effective absorbed energy per disintegration as given by the I.C.R.P. 1959 Book of Recommendations and assuming an effective diameter of 3 cm). It is desirable to reduce these doses as much as possible in most groups of patients, particularly in women of child-bearing age, all young people, children, pregnant mothers and babies. The metabolism of iodine in the mammary glands, the ovaries and the placenta is adapted to conserve the iodine of the foetus or the newborn which makes it

particularly susceptible to damage (HODGES et coll. 1955; HALL & MYANT 1956; POTTER et coll. 1959; GROSVENOR 1960; BROWN-GRANT 1961).

It is attempted to show in the present investigation that a large reduction in dose is possible for thyroid studies in adults with the aid of a whole body counter. Two techniques are described. The first is performed with a scanning technique to determine the total body retention of ^{131}I. The second is performed with a fixed crystal technique similar to a conventional thyroid uptake measurement, except that two large uncollimated crystals are used in a low background steel room.

Scanning technique

The urinary excretion of radioiodine has been used as a clinical test of thyroid function with considerable success (FRASER et coll. 1953). The radioiodine excreted in the sweat is negligible (HARDEN & ALEXANDER 1963), and the loss in the faeces is very small (MYANT 1956). Therefore a retention study of radioiodine with a whole body counter will be the converse of a study with urinary collections. The main problem in estimating the total body burden of ^{131}I with a whole body counter is the variation of the geometry of different subjects and the change in distribution of the isotope in the same subject with time. Ideally any distribution of ^{131}I should give the same sensitivity in all subjects, but unfortunately this is far from the case. Allowance has to be made for the shielding effect of the body, and the counting geometry at best can only approximate to 4π geometry. CEDERQUIST & LIDÉN (1961) showed that the ^{131}I retention can be more accurately measured by scanning than by using a sitting chair geometry.

The object of this investigation was to determine whether total body measurements in adults would give as reliable a guide to the thyroid peak uptake as that measured by a conventional thyroid uptake technique. If this was found to be true, it was also important to see how the discriminating power of the peak uptake compared with the total information of peak uptake, PBI-131, and in some cases the uptake of ^{131}I triiodothyronine (T_3) by red cells.

Apparatus. A scanning type whole-body-counter, NE8102, was used, (made by Nuclear Enterprises (G.B.) Ltd, Edinburgh) and installed in their six-inch thick steel room type SR-2 of length 245 cm, width 168 cm and height 183 cm. Two 6×4 inch crystals were used, one above and one below a couch. The maximum possible length of scan was 168 cm and this was used for all the subjects in this investigation. Matching of the gain of the two heads and the overall gain of the system was maintained with the aid of a multichannel analyser and a cobalt 60 source.

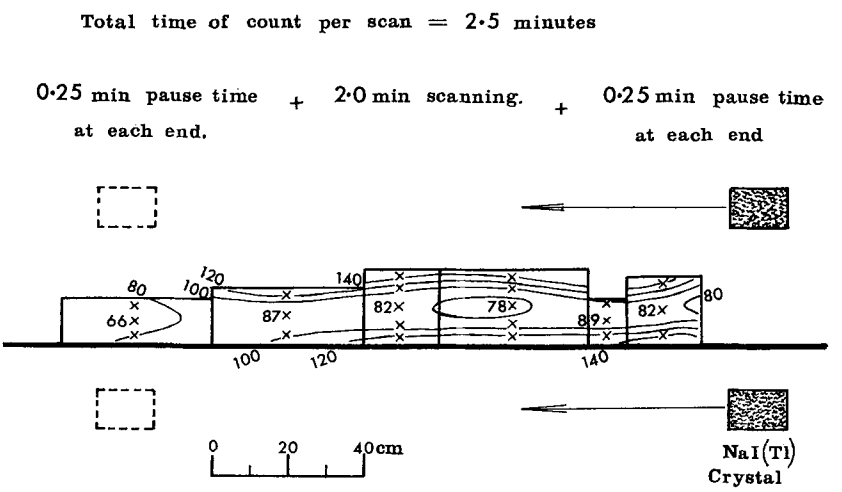

Fig. 1. Relative positions of a human phantom and crystals for scanning to determine the total body iodine 131. Isocount curves in the sagittal plane of the body are also shown; 100 % is taken as the sensitivity of the same source distributed evenly throughout the volume of the phantom. The isocount curves were interpolated from measurements made in the positions marked with a cross.

The subject lay supine as shown in Fig. 1, with the top of the head 15 cm inside the start of the scan, although this positioning was not critical. In order to correct for the limited length of the scanning distance, a pause time of 0.25 min was used at both ends of the scan with a scanning time of 2 min at 84 cm/min, giving a total counting time of 2 1/2 min each scan. This is similar to the technique used by WORTHLEY (1962).

Method. One hundred and twelve patients attending for routine ^{131}I thyroid uptake measurements were given 20 μCi ^{131}I with distilled water by mouth (sodium iodide 131 in dilute sodium thiosulphate solution, carrier-free, supplied by the Radiochemical Centre, Amersham, England) and were then counted in the total body counter within ten minutes of ingestion of the dose while the iodine was still largely confined to the stomach (SMALL et coll. 1961). They were allowed a light breakfast (TURELL et coll. 1958, found that a light breakfast did not affect the 3-hour thyroid uptake) but they were previously cautioned against taking any food with a high iodine content. Total body counts were repeated at 24 hours and 48 hours, and 64 of the patients were also measured at 96 hours after ingestion. Thyroid uptake measurements were made at 4 hours, 24 hours, 48 hours, and in the fewer cases at 96 hours. They all had 48-hour PBI-131 measurements and some also had the red cell uptake of iodine 131 triiodothyronine estimated (HAMOLSKY et coll. 1959, GOOLDEN et coll. 1962).

Table 1

Simple linear regression equations for thyroid peak uptake and total body retention of ^{131}I. The 48 hour retention gives the best correlation with thyroid peak uptake.

Time after ingestion of ^{131}I	Percent peak uptake (Y) as dependent variable		Per cent total body retention(X) as dependent variable		r	P
	Linear regression equation	S_Y	Linear regression equation	S_X		
24 hours	$Y = 1.15X - 14.0$	9.6	$X = 19.2 + 0.72Y$	7.6	0.91	$< 10^{-6}$
48 hours	$Y = 1.07X - 5.0$	8.5	$X = 10.5 + 0.81Y$	7.4	0.93	$< 10^{-6}$
96 hours	$Y = 5.6 + 0.95X$	11.5	$X = 10.9 + 0.76Y$	10.2	0.85	$< 10^{-6}$

S_Y and S_X = standard error of estimate; P = probability using student's t test; r = coefficient of correlation.

A single scan was used in the whole body counter with a 2 1/2 min count. However, the 20 μCi ^{131}I involved a very high count rate in the whole body counter, and a correction had to be applied for the dead time of the counter. A single channel analyser was used with a relatively wide channel width from 270 to 450 keV. The overall dead time of the counting system was found to be 5 microsecond per count. A number of subjects had profile counts done on the whole body counter to estimate the true dead time correction, and it was found that this could be estimated to within 1 % from the integral counts.

The sensitivity of a point source of ^{131}I in the sagittal plane of a water-filled polythene phantom having dimensions recommended by BUSH (1949) is shown in Fig. 1. The 100 % isocount curve is taken as the sensitivity that would be obtained if the point source was evenly distributed throughout the phantom. The values actually measured are shown by crosses and the isocount curves have been interpolated from them. The sentitivity of the thyroid is close to the sensitivity from an evenly distibuted source throughout the body. Hence the total body counts, even with much of the ^{131}I as extrathyroidal iodine, may be taken as a measure of retention, provided the extrathyroidal radioiodine is homogeneously distributed. However, the sensitivity of ^{131}I in the stomach was less than in the thyroid.

The ratio of the thyroid to stomach sensitivity was estimated in thirty euthyroid patients who attended for the 96-hour count. It was assumed that at this time 5 % of the total body ^{131}I was extrathyroidal (BERSON & YALOW 1954). No significant difference was found between the mean thyroid to stomach sensitivity ratio in men and women, and a value of 1.23 was used for

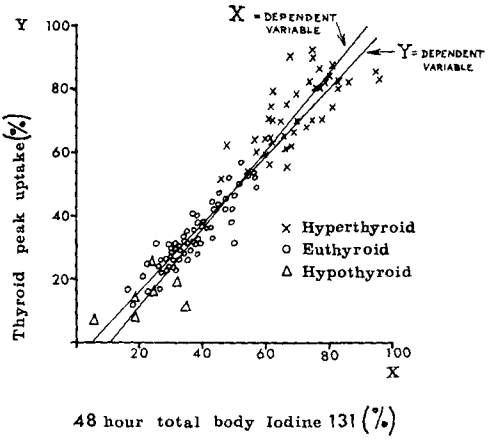

Fig. 2. Scatter diagram showing thyroid peak uptake and the 48-hour total body retention of ^{131}I. The simple linear regression lines, whose equations are given in Table 1, are also shown.

both sexes in all the 112 cases. There was no correlation between the weight to height ratio, and the sensitivity of ^{131}I in the stomach, the thyroid, and the ratio of thyroid to stomach sensitivity. This implies that the average body diameter of an adult subject does not give any clear indication of the shielding effect of the body with this particular geometry. The variation of the sensitivity of ^{131}I in the stomach, the thyroid, and the ratio of thyroid-to-stomach sensitivity, all had a standard deviation of distribution of 13 %. This was taken as evidence that no greater error is involved when the subject is counted within 10 minutes of ingestion, and weighted by a factor of 1.23 for the 100 % retention, than if the administered dose is accurately measured before ingestion and the percentage retention calculated from the average thyroid sensitivity. Hence all total body retentions were calculated by the former method in this investigation.

As an additional check that the method of weighting did not involve additional errors, 15 patients had their 48-hour retention calculated by the method of weighting, and also by using the average thyroid sensitivity. The coefficient of correlation with peak uptake was $+ 0.94$ and $P < 10^{-6}$ with each method. It appears that the shielding properties of the body for activities in the thyroid and the stomach are correlated in a way which is not simply represented by the weight to height ratio.

Mean sensitivities with standard error of the mean for a single scan and counting time of 2 1/2 min are:

Stomach: 25.9 $\pm$ 0.7 counts/nanocurie iodine 131/scan

Thyroid: 31.9 $\pm$ 0.9 counts/nanocurie iodine 131/scan

Background (room plus subject): 1 385 counts/scan.

Table 2

Arithmetic mean values for thyroid peak uptake, 24-hour thyroid uptake, and 24, 48, and 96-hour total body retention of ^{131}I (R-24, R-48 and R-96), with the standard deviation (σ), assuming a normal distribution. The limits where there is an equal chance of a false negative as a false positive ($x \pm A\sigma$) are also shown. The value P is the percentage overlap at this limit. $A = \frac{x_2 - x_1}{\sigma_1 + \sigma_2}$ where x_1 and x_2 are the means of the two groups.

	Hyperthyroid		Euthyroid		Hypothyroid		Hyperthyroid and euthyroid		Hypothyroid and euthyroid	
	Mean	σ	Mean	σ	Mean	σ	$x \pm A\sigma$	P	$x \pm A\sigma$	P
No. of subjects	42		63		7					
Per cent peak uptake	72.2	10.9	33.4	11.6	14.3	5.9	53.4	4.2	20.8	13.8.
Thyroid uptake at 24 hours (%)	68.9	9.7	31.5	9.5	13.6	7.0	50.0	2.6	21.2	14.0
R-24	72.7	11.1	41.6	9.2	36.0	11.2	55.7	6.3	39.1	39.2
R-48	70.0	11.0	36.9	9.9	21.4	11.9	52.6	5.7	29.9	23.9
R-96	66.9	11.6	35.8	11.4	15.0	12.0	51.2	8.9	25.7	18.7

Results

The correlations between the 24, 48, and 96-hour retentions (R-24, R-48, R-96) and the peak uptake were calculated with the simple linear regression equations and are shown in Table 1. Fig 2 is a scatter diagram showing the 48-hour values. The grouping of hyperthyroid and euthyroid subjects was based when possible on the thyroid peak uptake, PBI-131 and T_3 measurements; and when these were conflicting the clinical picture was also taken into consideration. The diagnosis of hypothyroidism was based only on clinical grounds, and only mild hypothyroid cases happened to be included.

The 24, 48 and 96-hour retentions all show significant correlation coefficients with the peak uptake, $r = 0.91$, 0.93 and 0.85, respectively, all with a probability $P < 10^{-6}$. The correlation for 48-hour retention is the best, probably because most of the inorganic iodine 131, and little of the organic iodine 131, had been lost from the body in hyperthyroid subjects. These results were also analysed by a method used by KUHNE et coll. (1955) and BRINKLEY et coll. (1957), where as a measure of reliability a normal distribution was assumed in the hyperthyroid, euthyroid and hypothyroid groups, and an index of 'percentage overlap' calculated. The values of retention and uptake, where there is an equal likelihood of false negatives as of false positives, are shown in Table 2

Table 3

The 48-hour total body retention (R-48) of 11 patients who were tested with 0.1 μCi ^{131}I together with other investigations

Case	Date	Per cent thyroid peak uptake	Per cent R-48 with 0.1 μCi ^{131}I	Per cent R-48 with 20 μCi ^{131}I	Per cent PBI-131 per litre	Per cent T_3
1. Euthyroid: large gain in weight	16.3.64	21	34	27	< 0.05	
2. Euthyroid: tremor & nervousness	6.4.64	26	31	33	< 0.05	
3. Hypothyroid	6.4.64	7	10	6	< 0.05	
4. Euthyroid: slight tachycardia	27.4.64	26	37	37	< 0.05	
5. Hyperthyroid	4.5.64	82	76	75	1.94	
6. Hyperthyroid	8.6.64	61	60	68	0.13	
7. Euthyroid: anxiety state	6.11.63		27			
8. Euthyroid: six months pregnant, exophthalmic, ophthalmoplegia	27.1.64	20	31		< 0.05	12
9. Euthyroid: boy 8 years, anorexia & nervousness	10.2.64		16			20
10. Euthyroid: breast feeding her baby	27.4.64		43			16
11. Hyperthyroid	8.6.64	82	82			22

as $x \pm A\sigma$, with the probability of making a false diagnosis with this limit shown as P, the 'percentage overlap'. As the peak uptake has been a major factor in the grouping of the patients, P cannot be used to compare the discriminating power of the thyroid uptake measurements and the retention values. BRINKLEY et coll. (1957) showed that if the diagnosis is based entirely on clinical follow-up studies, the probability of a false diagnosis based on thyroid peak uptake is very much greater than our values of P. However, P can be used to compare the relative reliability of thyroid 24-hour uptake, the peak uptake and the combined use of the peak uptake, PBI-131 and T_3 tests. Also the relative reliability of R-24, R-48 and R-96 can be compared.

From Table 2, the 24-hour thyroid uptake is just as reliable an index of hyperthyroidism as the peak uptake, and the 48-hour retention is a little more reliable than the 24-hour retention. The discrimination for hypothyroidism is poorer with the retention values than the thyroid uptake measurements, R-96 is a little better than R-24 and R-48.

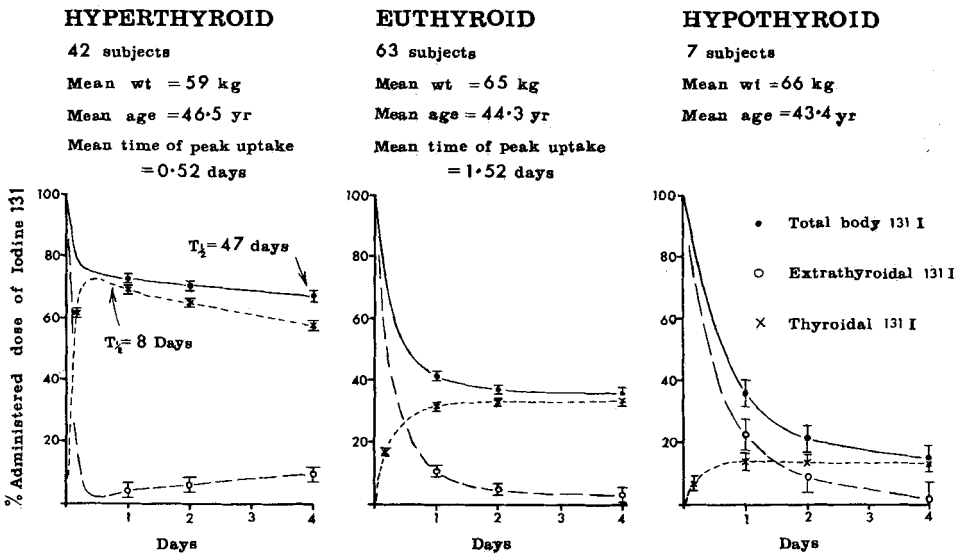

Fig. 3. Arithmetical mean values for thyroidal, extrathyroidal and total body iodine 131. Times of actual measurements are shown; the extrathyroidal ^{131}I was derived from the difference of the other two curves. The standard errors of the mean are shown.

To obtain the maximum information from the retention values, the ratio $(R\text{-}48)^2/R\text{-}24$ was investigated as this represents the product of the 48-hour retention and an index for the gradient of the curve between 24 and 48 hours. Unfortunately this ratio was found to be no improvement over the simple R-48 value and, although it gave some promise as an improvement for discriminating hypothyroidism over the R-48 value, it was no better than the R-96 value.

It is felt that these results cast considerable doubt on the advisability of using any urine collection technique for investigating hypothyroidism. The limits of normal thyroid peak uptake were given as 20 % and 55 % by BRINKLEY et coll. (1957), which leads to 23 % and 56 % as the limits for 48-hour total body retention of iodine 131 in normals. Using the upper limit of 56 % gives a probability of 2.7 % false positives and 10.2 % false negatives.

The mean total body retention and thyroid content of ^{131}I in the three groups of patients is shown in Fig. 3. The extrathyroidal ^{131}I is taken as the difference between the other two curves. The lower renal clearance in hypothyroid subjects (MCCONAHYE et coll. 1951, HLAD & BRICKER 1954, WAYNE, KOUTRAS & ALEXANDER 1964) accounts for the improvement in diagnosis of hypothyroidism with 96-hour retention compared with the 24 and 48-hour retentions. The mean extrathyroidal ^{131}I in euthyroid subjects at 24 hours is

Table 4

Standard deviation of counting — Administered dose is assumed to be 0.1 μCi ^{131}I with a 5-min scanning count

Per cent total body retention at 48 hours	Per cent standard deviation from counting statistics	Per cent total body retention at 48 hours with expected standard deviation of counting with 0.1 μCi ^{131}I and 5-min scanning
80	2.0	80 ± 1.6
60	2.4	60 ± 1.4
40	3.3	40 ± 1.3
20	5.7	20 ± 1.2
10	10.7	10 ± 1.1
5	20.4	5 ± 1.0

Background (room + subject) = 2 770 counts per 5 min scanning. Subject = 63.8 counts per nanocurie ^{131}I in the thyroid per 5 min scanning.

10 %, which compares with 14 % found by GOODWIN (1953) with urine collections. The peak uptake occurs on average at about 12 hours after administration in hyperthyroid patients in agreement with MALAMOS et coll. (1959), while in euthyroid subjects the peak is not reached until after 24 hours; this probably accounts for the slightly better discrimination with 24-hour thyroid uptake than the peak uptake measurements.

The average loss in thyroidal ^{131}I in hyperthyroidism from the peak uptake to the 24-hour uptake is 3.5 % of the administered activity, with an initial average half life of 8 days; a little of this may be inorganic iodide (ROSENBERG et coll. 1960). Although an average of 8 % of the administered activity is released from the thyroid by 48 hours in hyperthyroid subjects, only 3.5 % of the administered activity is lost from the body. The average total body biological half life of organic iodine in hyperthyroid subjects was 47 days as taken by the tangent to the curve at 96 hours. Hence the loss of thyroidal ^{131}I from the body is relatively slow even in hyperthyroid subjects; the shortest half life found was 18 days. STERLING & CHODOS (1956), found the turnover rate of thyroxine to be 16.9 % per day in hyperthyroidism, but most of the liberated iodine will be reabsorbed in the thyroid, while the thyroxine excreted via the bile into the faeces is small (MYANT & POCHIN 1950, MYANT 1956).

In some patients, a 4-hour total body measurement was also made, but calibration was difficult because of the extrathyroidal iodide concentrating mechanisms of the salivary gastro-enteric cycle and the kidneys, all of which play an important role in the distribution of ^{131}I at this time after administration

Table 5

Simple linear regression equation of thyroid peak uptake (Y) and the count rate in the whole body counter (X) with the crystals stationary over the thyroid

	Per cent peak uptake (Y) as dependent variable	S_y	r	P
Simple linear regression equation	$Y = -4.0 + 1.88 \times 10^{-3}X$	8.1 %	0.93	$< 10^{-6}$

r = coefficient of correlation; P = probability using 'student's t' test; S_y = standard error of estimate.

(PIRCHER et coll. 1960, BROWN-GRANT 1961, HAYS & SOLOMON 1961, ULLBERG & EWALDSSON 1964). LUSHBAUGH (1963) suggested the extrapolation of the retention to zero time as an index of thyroid activity; however, unless the retention curve is extended for a prolonged length of time there will be a tendency to overestimate the thyroid uptake in euthyroid subjects.

In order to confirm that the dead time corrections applied with 20 μCi ^{131}I were correct, and also to see if a large reduction in administered elemental iodine changed the ^{131}I thyroid uptake due to possible extrathyroid exchange processes, eleven subjects were tested in the whole body counter with 0.1 μCi ^{131}I using the same carrier-free iodine 131 from Amersham. The subjects were allowed a light breakfast and were warned against ingesting high iodine content foods as before. The subject's body background was determined before the ingestion of the radioiodine, and the total counting time was 5 minutes consisting of 2 scans of the body. Six of these subjects were retested a week later with a 20 μCi dose of ^{131}I, and both total body counting and conventional thyroid uptake measurements were made. The results are shown in Table 3. In cases 1 to 6 inclusive, the coefficient of correlation between R-48 in both tests was $r = 0.98$ with $P < 10^{-6}$ (using the student's t/test distribution). The results of R-48 in cases 7 to 11 inclusive on 0.1 μCi ^{131}I were also clinically acceptable.

It had been recommended that if carrier-free ^{131}I is used for thyroid tests, stable iodine 127 should be added to the stock, but should not exceed one microgram of iodine (I.A.E.A. 1960). CURTIS & FERTMAN (1949) considered the optimum daily dietary intake of iodine to be about 200 micrograms. However, the close correlation between the 0.1 μCi and the 20 μCi ^{131}I retention values indicates that there is probably no need to add stable iodine 127 to the 0.1 μCi doses of iodine 131, although it has a very high specific activity of 20 to 30 curies per milligram of iodine and is nearly a true carrier-free solution. It

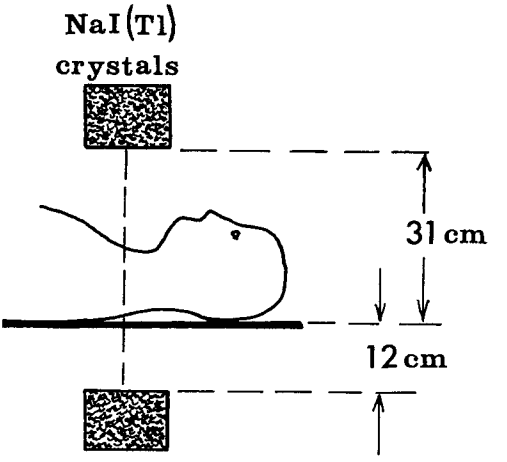

Fig. 4. Positioning of the crystals for stationary count over the thyroid, centred with a perspex former midway between the laryngeal prominence and the suprasternal notch.

should be added that all patients with dentures were asked to remove them for ingestion of the iodine 131.

Table 4 gives the expected standard deviation with 0.1 μCi ^{131}I administered with different fractional body retentions. These are calculated from the counting statistics for a 5-min scanning count and do not include the errors of the method. It can be seen that these errors are less than $\pm$ 2 % of the administered dose, i. e. they are small compared with the probable errors of the method.

Fixed crystals technique

A very complete review of conventional ^{131}I uptake measurements has been done by BRUCER (1959). With special γ-sensitive Geiger-Müller counters or NaI(Tl) crystals, doses of 1.0 μCi ^{131}I can be employed without a low background room (MORTON et coll. 1951). Using NaI(Tl) crystals very close to the thyroid burdens of 20 picocuries ^{131}I may be measured with a 30-min count for radiological protection work (LAURER et coll. 1963), and a more accurate estimate of thyroid uptake has been done with doses of 0.1 μCi of iodine 131 and iodine 125 to obtain the effective depth of the thyroid (VAN DILLA et coll. 1964). However, both these techniques are unsuitable for routine clinical use. With our two uncollimated crystals stationary and opposing through the thyroid as shown in Fig. 4, the sensitivity of evenly distributed iodine 131 in the whole body phantom was 16 % of the sensitivity of ^{131}I in the thyroid. This together with the close correlation of peak uptake and the 24-hour uptake and the small amount of extrathyroidal ^{131}I at 24 hours in hyperthyroid and euthyroid subjects, encouraged the investigation of the correlation of count

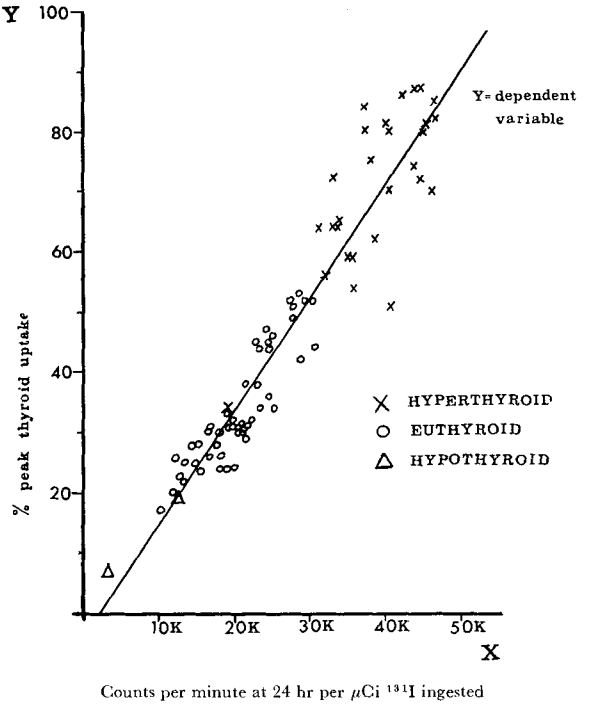

Fig. 5. Scatter diagram showing correlation between count rate at 24 hours with crystals stationary over the thyroid and thyroid peak uptake. The simple linear correlation equation is given in Table 5.

rate at 24 hours, using the uncollimated crystals stationary and opposed through the thyroid, with the peak uptake.

Method. Positioning of the crystals was obtained by using a perspex former and centering the crystals midway between the laryngeal prominence and the suprasternal notch. There was only a 2 % variation in the sensitivity of a 20 g and 85 g thyroid in a wax phantom; also, there was only a 2 % variation as the sagittal neck diameter changed from 10 to 14 cm. The sensitivity of this method was 55.2 counts/min/nanocurie iodine 131 in the thyroid, and with a dose of 20 μCi ^{131}I a dead time correction of up to 8 % was required. Only a one-minute-count was necessary. The contribution of counts from the body could have been reduced by using 1 cm thick lead shielding around the crystals; however, as most total body counters are designed without lead collimation it was considered part of the interest of the investigation to see whether this was necessary for the diagnosis of hyperthyroidism.

Table 6

Expected increase in the predicted 24-hour thyroid uptake, and standard deviation of the counts using 0.02 μCi ^{131}I and a 5-min count

Per cent true 24-hour thyroid uptake	Per cent possible extrathyroidal iodine 131	Estimate of uptake with uncollimated crystals
80	5	81 ± 1.6
60	5	61 ± 1.4
40	10	42 ± 1.1
20	15	22 ± 0.8
10	25	14 ± 0.5

Background (room + subject) = 2 660 counts/5 min; thyroid sensitivity = 276 counts/nanocurie/5 min; extrathyroidal sensitivity = 44 counts/nonocurie/5 min.

Eighty-one patients attending for routine iodine 131 thyroid uptake measurements were also counted in the total body counter at 24 hours with the crystals stationary over the thyroid. Some of the patients were also involved in the previous investigation, and they were all given 20 μCi of ^{131}I under the same conditions, and had the PBI-131 and sometimes the T_3 measurements as before.

Results

The results are shown in Fig. 5 and Table 5: the coefficient of simple linear correlation $r = 0.93$, and the probability $P < 10^{-6}$. The thyroid peak uptake can be derived from the count rate shown in Fig. 5, using the peak uptake as the dependent variable.

Table 6 shows the probable contribution to the counts from the body with various 24-hour thyroid uptakes. For hyperthyroid and euthyroid subjects the contribution is very small, but for hypothyroid subjects the contribution is large enough to prevent this technique from being discriminating for hypothyroidism. This table also gives the standard deviation to be expected from the counting statistics using 0.02 μCi ^{131}I and a 5-min count. These errors are less than ± 2 % of the administered dose in each example.

Discussion

From both these investigations it is clear that very small doses of iodine 131 can be reliably used for a discriminating test between hyperthyroid and euthyroid adult subjects with the aid of two large uncollimated crystals and a low background steel room, using either a scanning technique or stationary

crystals. These techniques are not very discriminating for hypothyroidism, largely due to the low renal clearance of iodide, which both increases the extrathyroidal iodine 131 and also results in a higher peak uptake in the thyroid. Some improvement may be obtained by prolonging the period of study for hypothyroidism.

An advantage of the scanning technique is that it is self-calibrating once the ratio of stomach to thyroid sensitivity has been determined. It may also have advantages for patients where the thyroid is retrosternal. The fixed crystal technique had the advantage of greater sensitivity but requires careful calibration.

The scanning technique should be particularly suitable for small children and babies where calibration with a conventional thyroid measurement is difficult. The correction factor for body shielding must be modified. Experiments with phantoms have indicated that the factor varies directly but slowly with the bodyweight, down to about 10 kg, and then more rapidly approaches unity as the bodyweight approaches zero. This factor can be interpolated without introducing an unacceptable error.

The standard errors of estimate for both techniques are of the order of $\pm$ 8 % of the administered dose. However, the true standard deviation of these techniques is smaller than the calculated standard error of estimate as the random error of the thyroid uptake measurements contributes to the standard error of estimate. The standard deviation for the conventional thyroid uptake measurements and the two whole body counter techniques are probably of the order of $\pm$ 6 % of the administered dose.

Patients' reactions to being confined in a steel room vary but only a small number are unduly concerned, and only two from approximately 150 patients refused to be shut in the room. A great deal of importance must be attached to the approach of the nursing staff; a simple explanation of the necessity of the steel room, the assurance given by a lead-glass window and a push-button alarm bell, a radio playing, and a light interior décor all do much to calm the more anxious patient. A true claustrophobic could not be shut in the steel room, with any amount of camouflage, without heavy sedation. Two claustrophobics who were shut in the room were perfectly composed until the doors were shut but then they gave no thought to the alarm bell and tried desperately to open the doors from within. It is clearly important that a watchful eye should be kept for these subjects although they are very few in number.

The use of thyroid uptake tests has probably been disappointing in their ability to distinguish borderline hyperthyroid subjects, for frequently the most difficult clinical picture also presents a borderline thyroid uptake measurement.

The thyroid uptake depends to a large extent on renal clearance, which varies from subject to subject (MYANT et coll. 1950). In hyperthyroid subjects the renal clearance is elevated and the thyroid uptake will not fully indicate the increased thyroidal clearance.

The use of less than 1 μCi ^{131}I excludes the measurement of PBI-131; however, this test is highly dependent on the size of the thyroidal iodine pool, and reduction in the size of this pool often occurs in just the cases where additional confirmation is required, e.g. after radioiodine therapy, after partial thyroidectomy and in autoimmune thyroiditis (DONIACH & HUDSON 1957, WAYNE, KOUTRAS & ALEXANDER 1964). BRINKLEY et coll. (1957) found only a small improvement in discrimination by using PBI-131 as well as thyroid peak uptake. In the first investigation reported in this paper, the use of 55 % peak uptake as the upper limit of normal gave 3.1 % false positives and 5.7 % false negatives, basing the diagnosis on peak uptake and PBI-131 measurements, which indicates that the PBI-131 does not give very much extra useful information.

FRASER (1956) suggested that the combination of B.M.R., PBI-127 and peak uptake would supply the most discriminating information. Both plasma protein bound iodine (PBI-127) (BLACKBURN et coll. 1955) and plasma butanol extractable iodine (BEI-127) (POSNER 1961) are useful tests particularly in mild hypothyroid subjects, although they are not necessarily an index of hormonal activity as the level of binding proteins affect the hormone transfer (ROBBINS & RALL 1960). The BEI-127 has the advantage of representing only the iodine of the thyroxine-like compounds. BEI-127 values for infants have been given by MAN et coll. (1952) and PBI-127 values for infants by DANOWSKI et coll. (1951). Hence it is suggested that adequate additional information to the peak uptake could be supplied without using radioactive techniques.

The amount of iodine 131 impurity in iodine 132, obtained from sodium tellurite absorbed on an alumina column, depends on the age and frequency of milking. We have found that over a 14-day period from the date of dispatch from Amersham, the iodine 131 can vary from 0.2 to 2.0 % of the activity of the iodine 132. These ^{131}I activities are of the same order as those required for thyroid studies in a whole body counter. Average background radiation is approximately 3 millirad/11-day period, and the average dose to the thyroid from 0.1 μCi ^{131}I administered, in euthyroid subjects, is approximately 160 millirad over an 11-day mean time, while 20 μCi ^{132}I administered gives an average of 920 millirad over a mean time of about 4 hours.

The possibility of obtaining evidence of a threshold level of radiological damage is getting more remote, as there is a consistent accumulation of evidence that somatic and genetic damage occurs at very low dose rates. Such is the

lack of adequate knowledge in this important field that the major recommendations for occupational exposure are based largely on judgement and the practicality of reducing radiological exposure. Even background radiation must be considered as incurring a definite statistical hazard, small for the individual but prominent for a large population (cf. 'Hazards to man of nuclear and allied radiations', Reports to the Medical Research Council 1956 and 1960; LEWIS 1957, WALLACE & DOBZHANSKY 1960).

There is much evidence of detrimental effects of radiation at high dose rates, and we must assume that the same effects are applicable at lower dose rates although the statistical risks to the individual are reduced and repair processes may improve the situation. Evidence of the induction of papillary and follicular carcinomas and benign adenomas have been reported in the rat thyroid after administration of iodine 131 (DONIACH 1953, POTTER et coll. 1960). Also, there can be no sharp distinction between benign and malignant tumours in the thyroid (WILLIS 1960). External irradiation of the thyroid produces a certain risk of subsequent development of malignant tumours, and the thyroid of infants and children is known to be more sensitive to radiation than the adult thyroid (see p. 961 Brit. med. J. Vol. 2 (1958); BEACH & DOLPHIN 1962). The probability of inducing leukaemia by iodine 131 is small but cannot be ignored (COURT-BROWN & DOLL 1957; POCHIN 1960; HEYSSEL et coll. 1960; LEWALLEN & GODWIN 1963). Chromosome abnormalities have been observed in peripheral leukocytes after ^{131}I therapy for hyperthyroidism (NOFAL & BEIERWALTES 1964).

An important aspect of this problem is the difficulty of assessing the radiation dosage to the thyroid from ^{131}I as the inhomogeneity of radioiodine in the thyroid will produce high spots of dosage. There is inhomogeneity in the specific activity of ^{131}I in the thyroid, as part of the thyroidal iodine pool turns over more rapidly than the rest (TRIANTAPHYLLIDIS 1958). The average thyroid size in children is smaller than in the adult (HALNAN 1964), but the mean uptake in normal children is the same as in adults (OLINER et coll. 1957). Iodine may be concentrated in the mammalian ovary, particularly during the phase of follicular development (BROWN-GRANT 1961). A large fraction of radioiodine can be excreted in the milk of the lactating mother (MILLER & WEETCH 1955, HALL & MYANT 1956, POTTER et coll. 1959, GROSVENOR 1960). These factors indicate particular caution in women of child-bearing age and children.

Out of 112 patients in the first investigation, 63 were euthyroid. MALAMOS et coll. (1959) describes thyroid tests on 1 000 subjects, of which 492 were euthyroid. The incidence of anxiety states and probably the incidence of hyperthyroidism associated with earlier mental stress is likely to increase as the pace of life continues to quicken. This will mean an increase in the demand to

discriminate between anxiety states and hyperthyrodism, and hence an increase in the demand for iodine 131 tests.

All these considerations should encourage a reduction of radiation exposure that does not involve a restriction of important clinical information to the individual.

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SUMMARY

With the aid of a whole-body-counter and a low background steel room, a discriminating test for hyperthyroidism in adults may be performed with 0.1 μCi iodine 131 using the total body retention at 48 hours as an index of thyroid function. It is suggested that reduction of the administered dose is desirable in many patients, particularly with the increasing use of iodine 131 for routine tests in subjects most susceptible to radiological hazards.

ZUSAMMENFASSUNG

Mit Hilfe eines Ganzkörperzählers und bei Anwendung einer Spezialkammer aus Stahl um Hintergrund-Strahlung zu vermindern kann ein Unterscheidungstest für Hyperthyreoidismus an Erwachsenen mit 0.1 μCi ^{131}J gemacht werden. Die Gesamtkörperretention bei 48 Stunden wurde als der Index für die Funktion der Thyreoidea angewendet. Die Verminderung der Dosis ist bei vielen Patienten wünschenswert, nachdem ^{131}J häufiger zu Routine-Untersuchungen verwendet wird und bei sehr empfindlichen Patienten zu Röntgenschäden führen kann.

RÉSUMÉ

La rétention corporelle totale à 48 heures, considérée comme indice de la fonction thyroïdienne, et mesurée grâce à un compteur total pour l'homme et à une chambre en acier à faible mouvement propre, permet de faire une épreuve de discrimination de l'hyperthyroïdie chez l'adulte avec 0,1 μCi de ^{131}I. L'auteur pense qu'il est souhaitable de réduire la dose administrée à de nombreux malades, en particulier en raison de l'emploi croissant de ^{131}I pour des examens systématiques chez des sujets très sensibles aux dangers des radiations.

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