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THE DETERMINATION OF THYROIDAL AND RENAL PLASMA I^{131} CLEARANCE RATES AS A ROUTINE DIAGNOSTIC TEST OF THYROID DYSFUNCTION [1, 2]

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INTRODUCTION

Since the early investigations of Hertz, Roberts and Evans (1) and Hamilton (2–4), various methods of estimating the radioiodine accumulating capacity of the thyroid gland have been employed as diagnostic clinical tests as well as in physiological studies. The most common procedures have involved the determination of the 24 hour thyroid uptake (5–7) or the total 24, 48, or 72 hour urinary excretion (8–10) of radioiodine following its oral administration. While these methods have provided an additional diagnostic tool for the evaluation of thyroid function, equivocal results have been obtained in about 10% of the cases in most series. Furthermore, where renal function is impaired, values characteristic of hyperthyroidism have been observed in the presence of normal thyroid function (10).

Measurements of the rate of disappearance from the blood (11) or the rate of urinary excretion (12, 13) or uptake by the thyroid (13–15) of radioiodine have proved to be involved procedures and have not satisfactorily eliminated overlapping, although the frequency of borderline cases has been reduced.

The relative and indirect nature of all these methods has been emphasized in a recent review (16) and in other reports (14) by the group at the Mayo Clinic. They have concluded (16), in agreement with Myant, Pochin and Goldie (17), that the clearance of I^{131} from the blood by the thyroid is probably the most reliable index of the iodine accumulating function of the gland. Present techniques, however, have made this determination a complicated procedure, precluding its more widespread use.

It is the purpose of this paper to present a simple, expedient method of obtaining the thyroidal and renal plasma iodide clearances without the necessity of performing analyses of blood samples.

Studies of the clearance rates in 87 euthyroid, 18 hyperthyroid and five hypothyroid subjects and a comparison with the 24 hour thyroid uptake and renal excretion values are presented. The significance of these studies in relation to the results obtained by other methods of measurement of the iodine accumulating capacity of the thyroid is discussed.

METHODS

Subjects of the study were patients of the Veterans Administration Hospital, Bronx, New York. All cases in which there was a history of recent iodine administration in any form were excluded from the study.

For routine diagnostic testing, doses of 25–50 μc carrier free I^{131} as KI in 2–8 ml of sterile isotonic saline solution were administered intravenously over a 10–25 second period. Calibration of the syringes revealed an accuracy of ±3% or better. For the special time-concentration studies, doses of 100–750 μc were administered. Doses of more than 150 μc were restricted to patients with carcinoma or with hyperthyroidism for whom the therapeutic use of I^{131} was planned.

The Geiger counters were standardized for I^{131} against a Braestrup type ionization chamber which was initially calibrated in terms of the "New York millicurie" which at the present time is equal to 0.85 Oak Ridge millicurie.

In vivo counting over the thyroid was performed with an RCL bismuth gamma counter, which at nine inches from the thyroid, had a sensitivity of 105 C/M/μc I^{131} over a background of approximately 60 C/M, as determined by calibration against a dummy source of known activity immersed in a paraffin filled phantom neck. The counter tube was attached to a scaling circuit whose output fed into a Streeter-Amet register, which automatically printed the cumulative counts at one minute intervals. The arrangement and shielding of the apparatus is shown in Figure 1. Because of the wide window in the counter shield and long sensitive region of the tube (five inches),

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[1] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[2] Presented, in part, at the Clinical Research Meeting, New York Academy of Medicine, April 5, 1951.

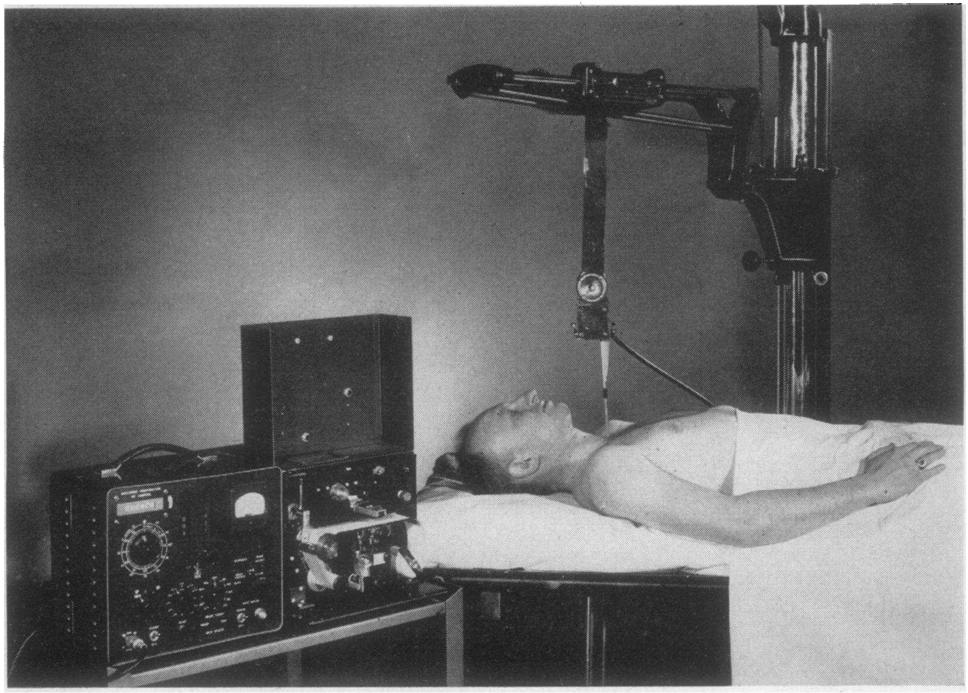

FIG. 1. APPARATUS FOR MEASURING THYROID UPTAKE

the variation of counting rate with distance from the neck followed more closely an inverse linear rather than an inverse square relation and approximated $1/r^{1.3}$. Therefore, an error of ¼ to ½ inch in the estimation of the depth of the thyroid within the neck produced an error of only 3½% to 7% in the counting rate due to activity in the thyroid at the standard nine inch distance.

Radioactivity of the administered doses and in the urine and blood samples was assayed in Marinelli beakers placed around 1 inch lead shielded RCL bismuth walled or tetramethyl lead silver walled glass Geiger counters with sensitivities of 4500 and 479 C/M/μc I^{131}, respectively.

Determination of clearance rates

Since the thyroidal plasma I^{131} clearance is defined as the volume of plasma cleared of I^{131} per minute by the thyroid gland, its evaluation requires the measurement of the uptake of I^{131} and a knowledge of the average plasma concentration over the same time period. Similar considerations obtain for the renal clearance. The first half hour following intravenous injection of the isotope has been selected for the clearance determination. Thus

$$\text{Plasma } I^{131} \text{ clearance}_{\text{thyroid}} = \frac{\tfrac{1}{2} \text{ hour thyroid uptake } I^{131}}{\text{average plasma concentration } I^{311} \times 30} \qquad (1a)$$

$$\text{Plasma } I^{131} \text{ clearance}_{\text{renal}} = \frac{\tfrac{1}{2} \text{ hour renal excretion } I^{131}}{\text{average plasma concentration } I^{131} \times 30} \qquad (1b)$$

In the following sections discussion of the measurement of the half hour thyroid uptake and renal excretion is followed by a consideration of the plasma I^{131} concentration determinations.

A. Determination of thyroid uptake and renal excretion

Because of a number of objections to the common use of thigh measurements in correcting for changing extrathyroidal activity in the neck, the following method for determining the thyroid uptake was introduced.

Prior to the injection a background reading is obtained with the counter over the patient's neck. The counting rate at one minute intervals is then recorded for 33 minutes from the time of injection, following which the patient empties his bladder into a bottle free of radioactivity. A five minute delay time in urinary formation and passage is assumed. For example, a urine specimen passed at 35 minutes is considered to represent the 30 minute excretion. Since the accuracy of the renal clearance is only of secondary interest, catheterization is considered unnecessary.

The counting rate obtained over the neck during the first minute or two following injection is a measure of the activity of radioiodine in the blood and extravascular spaces, since, at this time, only a fraction of the radioiodine can have been removed by the thyroid except in cases of marked hyperthyroidism. This activity has been termed the initial extrathyroidal level. In hyperthyroidism the activity obtained during the first minute has been accepted as the initial extrathyroidal level because of the rapid increase in counting rate during the first few minutes in these cases. Any error in the tissue level estimation in the hyperthyroid cases is of little consequence compared to the total half hour thyroid uptake. In non-hyperthyroid cases the activity of the second minute has been taken as the initial extrathyroidal level since at this time mixing in the blood stream is virtually complete. Although commonly equal to the counting rate of the first minute, the counting rate during the second minute is not infrequently slightly lower than that during the first minute. The reason for this can be appreciated when it is realized that a large number of counts may be recorded during the first few seconds due to the high activity of the concentrated injected material as it first enters the base of the neck through the great veins draining the site of injection.

The counting rate over the neck after any significant period of time is a measure of the activity within the thyroid gland as well as that still remaining in the blood and extrathyroidal tissues of the neck. Thyroid uptake of I^{131} may be calculated as follows:

Let Th = μc I^{131} collected by the thyroid during the first 30 minutes
U = μc I^{131} excreted in the urine during the first 30 minutes
D = dose injected in μc I^{131}
O = observed increase in activity over the neck in μc I^{131} during the first 30 minutes
E = initial extrathyroidal activity in the neck in μc I^{131}, less background value prior to injection.

E thus represents the activity of I^{131} in the extrathyroidal tissues of the neck before any significant removal by the thyroid and kidneys has occurred.

The thyroid uptake must have increased at the end of the measurement period by the sum of the observed increase in the activity of the neck and the fall in the level of activity of extrathyroidal I^{131} in that part of the neck "seen" by the counter. The extrathyroidal changes include the changes in concentration in the blood and extracellular spaces of the thyroid gland itself. At the end of the measuring period, the dose still circulating and in the tissue spaces throughout the body will have decreased by the amount picked up in the thyroid and excreted in the urine since minute amounts that may be concentrated above the general tissue level in other organs are negligible. The fractional fall in the general tissue level may then be expressed as $\frac{\text{Th} + \text{U}}{\text{D}}$. The fall in the extrathyroidal activity of the neck is therefore $\frac{(\text{Th} + \text{U})}{\text{D}}\text{E}$.

Then

$$\text{Th} = \text{O} + \frac{(\text{Th} + \text{U})}{\text{D}}\text{E}.$$

Solving for Th,

$$\text{Th} = \frac{\text{OD} + \text{EU}}{\text{D} - \text{E}}. \qquad (2)$$

The value of E is usually less than 10% of the activity of the dose and the urinary excretion usually not more than three times the increase in activity over the neck except in cases of hypothyroidism. It may be noted, then, that any error in urinary collection or measurement produces only a fraction of that error in the determination of the thyroid uptake. In hyperthyroidism, where the thyroid uptake is two to ten times the urinary excretion, the latter may be neglected entirely for practical purposes.

The total 30 minute urinary excretion is measured and the activity assayed as described above.

B. Determination of the average plasma I^{131} concentration during the 30 minute period following injection

Ideally, the plasma concentration should be kept at a constant level during the period of clearance determination. Owing to long continued change of space of iodide dilution as discussed below, maintenance of an unchanging concentration by constant intravenous drip would not only be difficult, but also undesirable, because of the larger dose required.[3] It is, however, equally valid to determine the average plasma concentration of I^{131} over the period of time of measurement of thyroid uptake and renal excretion, even though the concentration is changing.

The plasma concentration of I^{131} at any time following its administration is dependent upon the space into which it has been distributed and the extent to which it has been removed from circulation by the thyroid and kidneys. (Amounts fixed in other organs are negligible.) These two variables are discussed independently below. At the outset, however, a general consideration of the problem is pertinent.

The plasma concentration at any time, t, may be expressed as follows:

$$(\text{Plasma } I^{131} \text{ conc.})_t = D_t \cdot C_t, \qquad (3)$$

where

D_t = dose retained at any time, t,

$C_t = \frac{\text{fraction of dose retained}}{\text{ml plasma}}$ at the same time.

The dose retained at any time is the administered dose less that removed by the thyroid and kidneys up to that time.

The average plasma I^{131} concentration over any time interval following administration of the isotope can then be formulated:

$$(\text{Average plasma } I^{131} \text{ conc.})_{O-T} = \frac{\int_O^T (D_t \cdot C_t)\,dt}{T}. \qquad (4)$$

The integral of the product of the two factors D_t and C_t approximates the product of the integrals of each factor as one or both approach a constant. Thus:

$$\frac{\int_O^T (D_t \cdot C_t)\,dt}{T} \cong \frac{\int_O^T D_t\,dt}{T} \cdot \frac{\int_O^T C_t\,dt}{T}. \qquad (5)$$

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[3] In hyperthyroidism, this procedure would require separate determination of hormonal and inorganic iodide in the plasma, since, by the time complete mixing of I^{131} in the body has occurred (usually three or more hours) a significant amount of I^{131} may have re-entered the circulation in the form of hormonal iodide after having been taken up by the thyroid. Furthermore, for the same reason, determination of thyroid uptake would be in error because of the I^{131} leaving the gland after being incorporated into hormone.

The first integral term on the right hand side of equation *5* is the average dose retained while the second expresses the average plasma concentration in terms of the fraction of the dose retained. The change in C_t with time is therefore dependent only on the change of space of dilution. These two terms have been evaluated separately and the error involved in the approximation considered subsequently.

1. Evaluation of average dose retained. A close approximation to the value of the integrated average dose retained is given by the following:[4]

$$\bar{D}_{0-T} = \frac{\int_0^T D_t\,dt}{T} \cong \frac{D_0(1-e^{-\lambda T})}{\lambda T}, \qquad (6)$$

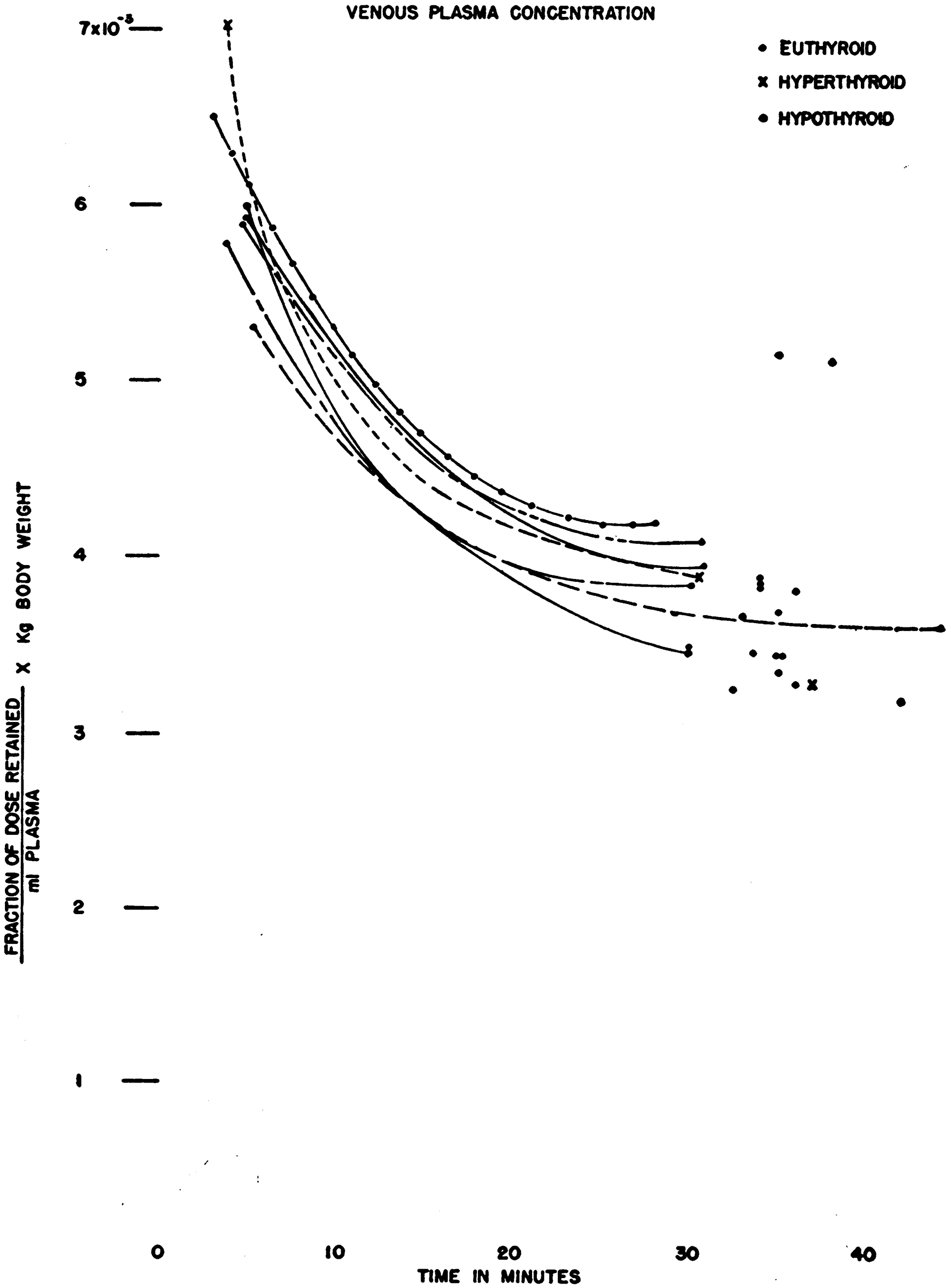

FIG. 2. VENOUS PLASMA I^{131} CONCENTRATION-TIME CURVES

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[4] See Appendix A.

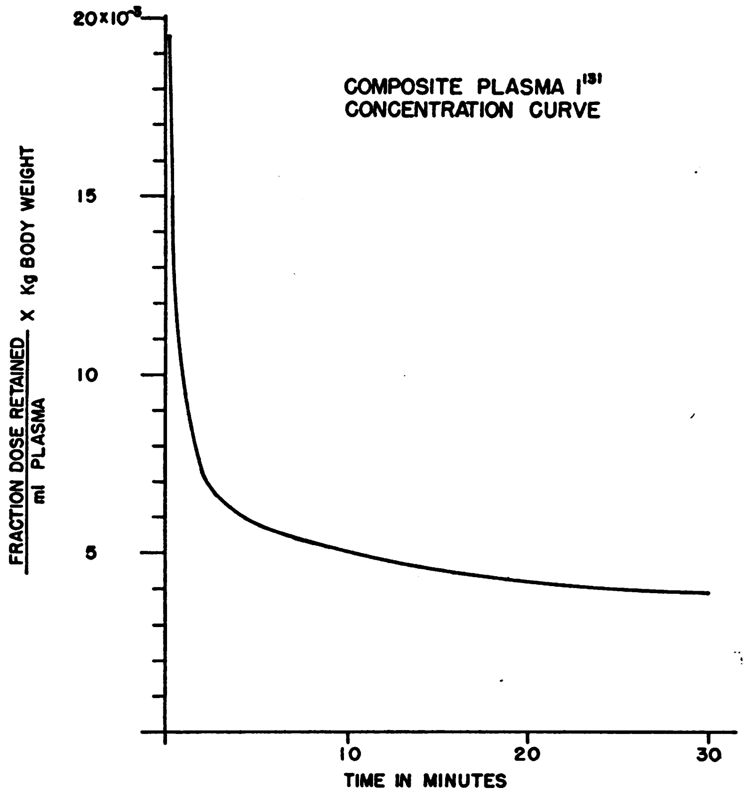

FIG. 3. COMPOSITE PLASMA I^{131} CONCENTRATION-TIME CURVES

Points during the first three minutes were obtained from arterial sample assays.

where $\bar{D}_{O-T}$ = Average dose retained over time interval O–T
D_O = Dose I^{131} administered
T = Time in minutes
λ = Average fraction of the dose removed per unit time. The evaluation of this term is discussed in Appendix A.

While this expression can be evaluated in a number of ways, it may be desirable for the sake of mathematical expediency to approximate the average dose retained by taking the arithmetic mean of the dose administered and the dose retained at the end of the period of measurement.[5]

$$\bar{D}_{O-T} \cong \frac{D_O + D_T}{2} \cong D_O - \tfrac{1}{2}(Th_T + U_T), \qquad (7)$$

where D_T = Dose retained at time $T = D_O - (Th_T + U_T)$
Th_T = Thyroid uptake at time T
U_T = Total renal excretion at time T.

2. Evaluation of average C_t. As shown subsequently $\frac{\int^T C_t\,dt}{T}$, when T = 30 minutes, has been found to be quite constantly related to body weight in non-edematous subjects and to have the value of $\frac{5 \times 10^{-3}}{\text{body weight}_{kg}}$ in units of $\frac{\text{fraction of dose retained}}{\text{ml plasma}}$.

3. Derivation of final clearance formulae. Both integrals on the right hand side of equation *5* have now been separately evaluated. Substituting these values in equation *5* for T = 30 minutes gives:

$$(\text{Av. plasma } I^{131} \text{ conc.})_{O-\frac{1}{2}hr} = \bar{D}_{O-\frac{1}{2}hr} \cdot \frac{5 \times 10^{-3}}{\text{body weight}_{kg}}.$$

Substituting back in the original clearance equations *1a* and *1b*:

$$\text{Plasma } I^{131} \text{ clearance}_{\text{thyroid}} = \frac{\frac{1}{2} \text{ hour thyroid uptake}}{\bar{D}_{O-\frac{1}{2}hr} \times \frac{5 \times 10^{-3}}{\text{body weight}_{kg}} \times 30} = \frac{\frac{1}{2}\text{ hour thyroid uptake} \times .20 \times 10^3 \times \text{body weight}_{kg}}{\bar{D}_{O-\frac{1}{2}hr} \times 30}. \qquad (8)$$

$$\text{Plasma } I^{131} \text{ clearance}_{\text{renal}} = \frac{\frac{1}{2}\text{ hour renal excretion} \times .20 \times 10^3 \times \text{body weight}_{kg}}{\bar{D}_{O-\frac{1}{2}hr} \times 30}. \qquad (9)$$

The average dose retained over the first half hour ($\bar{D}_{O-\frac{1}{2}hr}$) may be calculated from equation *6* or *7*.

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[5] See Appendix B.

CONSIDERATIONS OF I^{131} DISTRIBUTION IN THE DETERMINATION OF PLASMA CONCENTRATION

A. Change of plasma I^{131} concentration due to change of space of iodide dilution during the first half hour

During the first half hour following intravenous administration, the I^{131} space of dilution increases rapidly due to entrance of I^{131} into red blood cells, diffusion into extracellular fluid spaces and penetration of the body cellular tissues.

In order to determine the change in concentration of I^{131} due to the change of space of dilution with time, multiple venous blood assays were performed during the 30 minute period following injection of I^{131} in seven subjects including one subject with Graves' disease and one with post-thyroidectomy myxedema. The activity in the plasma and frequently also in the red blood cells was determined at four to five points during this time period after administration of I^{131}. To account for the variation of the space of I^{131} dilution with body size, $C_t \times$ body weight$_{kg}$ has been plotted as a function of time (Figure 2). The dose retained at each point was calculated by subtracting from the dose administered the amount picked up by the thyroid plus that excreted in the urine up to that time. The thyroid gland is exposed to a concentration of I^{131} approximating that in the arterial blood and it may take two to three minutes for the venous blood to approach the arterial concentration. Therefore the arterial plasma concentration was assayed at half minute intervals during the first three minutes following intravenous administration of the isotope, in order to permit a more accurate extrapolation back to zero time for the concentration of plasma I^{131} to which the thyroid is exposed. The areas under the curves thus obtained were measured with a planimeter. The maximum variation from the mean area was found to be about 3%.

In 17 other subjects, including one patient with Graves' disease, single points at 30–40 minutes were obtained. When all these points were extrapolated along a typical curve to the 30 minute time, the maximum variation of 22 of the 24 30-minute points was less than 11% from the mean. The mean concentration over the first half hour varied less than the concentration at 30 minutes since the relative spread was greater at the end of the time interval and because the curves crossed each other to a certain extent. It is quite possible that the two exceptional points represent technical errors due to low counting rates or slight contamination rather than true deviations.

TABLE I

Three hour iodide space

Patient	3 hour iodide space *% body weight*
85	36.1
29	31.2
86	45.4
82	42.0

Figure 3 shows the composite time-concentration curve, including the results of the arterial plasma assays during the first three minutes. The area under this curve divided by the time interval, 30 minutes, is then the mean concentration over the first half hour expressed as $\frac{\text{fraction dose retained}}{\text{ml plasma}} \times \text{body weight}_{kg}$. Its value was found to be 5.0×10^{-3}. Thus

$$\frac{\int_0^T (C_t \cdot \text{body weight}_{kg})}{T} = 5 \times 10^{-3} \text{ in units of } \frac{\text{fract. dose ret.} \times \text{kg}}{\text{ml plasma}}.$$

Since body weight is a constant for any subject, then

$$\frac{\int_0^T C_t\,dt}{T} = \frac{5 \times 10^{-3}}{\text{body weight}_{kg}} \text{ in units of } \frac{\text{fract. dose ret.}}{\text{ml plasma}}.$$

This is the value of $\frac{\int_0^T C_t\,dt}{T}$ utilized in the clearance calculations described under methods.

B. "Iodide space"

The reciprocal of $\frac{\text{fraction dose retained}}{\text{ml plasma}}$ obviously represents the space of dilution. The reciprocal of any point along the curve in Figure 3 thus represents $\frac{\text{space in ml}}{\text{body weight in kg}}$, or taking a liter of plasma as equivalent to a kilogram, the space, in per cent of the body weight, through which the I^{131} would have had to be uniformly distributed in order to have given the experimentally obtained plasma concentration. In terms of any anatomical space in the body, this has no significance, since the I^{131} is not uniformly distributed between extracellular and intracellular tissues. For example, the plasma/red cell ratio of I^{131} has ranged between 1.6 and 1.8 for all determinations made between three minutes and three hours after injection. However, the "iodide space" may serve as a convenient mathematical expression for purposes of calculation of plasma concentration and gives a rough quantitative idea of the extent of distribution. At 30 minutes, in 22 of the 24 observations the mean and maximum range of the "iodide space" was 26 ± 2.8% of body weight in non-edematous subjects. However, at three hours the variation was much greater, the space ranging from 31 to 45% of the body weight (Table I). The average space over the first half hour was found to be 20% of the body weight.

In a patient with considerable nephrotic edema, the "space" at 30 minutes was 38% of his body weight compared to the normal of 26%. In a patient with cardiac edema the average "space" over the first half hour was 26% of his body weight compared to the normal of 20%. For accurate determinations in cases with significant edema it is therefore necessary to obtain several plasma assays during the first half hour, although the error introduced by using an estimated correction of the normal space does not influence the clearance values sufficiently to confuse the diagnosis when hyperthyroidism is present.

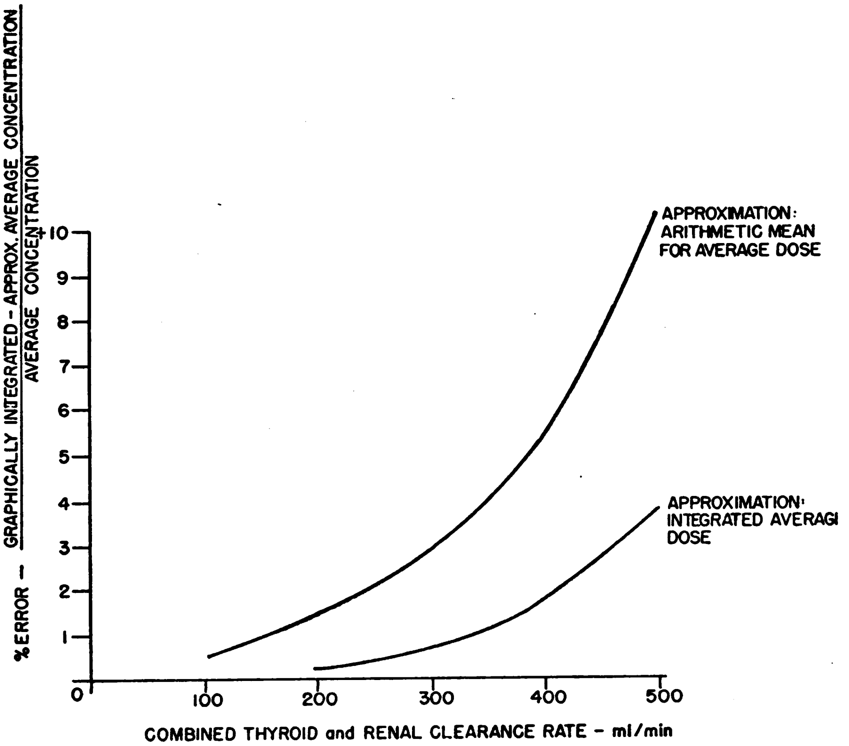

FIG. 4. PER CENT ERROR INVOLVED IN MATHEMATICAL APPROXIMATIONS AT DIFFERENT CLEARANCE RATES

See text

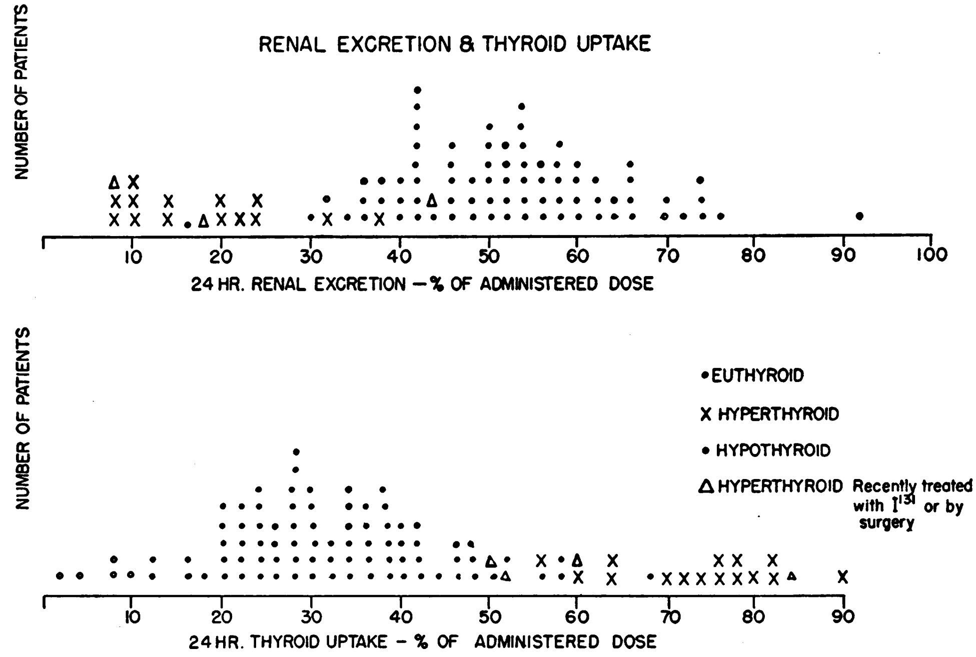

FIG. 5. FREQUENCY DISTRIBUTION OF 24 HOUR RENAL EXCRETION AND THYROID UPTAKE VALUES EXPRESSED AS PER CENT OF THE ADMINISTERED DOSE

TABLE II

Patient	Age	Sex	Height	W (*kg*)	Surface area (*m*²)	24 hour uptake (*% dose*)	24 hour excretion (*% dose*)	Plasma I^{131} clearance (*ml/min.*)		Plasma I^{131} clearance (*ml/min./1.73 m*²)	
								Thyroid	Renal	Thyroid	Renal
Euthyroidism											
1	26	M	6′	73.1	1.93	22.2	73.5	8.0	50.4	7.2	45.2
2		M	5′5″	60.5	1.65	57.4	41.7	29.3	10.6	30.7	11.1
3	35	M	5′9½″	75.5	1.91	68.0	31.0	44.2	14.3	40.0	12.9
4		M	5′11½″	71.5	1.90	28.4	60.4	15.4	25.0	14.0	22.7
5	39	M	5′11″	66.4	1.83	55.0		29.9	21.2	28.2	20.0
6	26	M	5′9″	77.2	1.92	15.0	76.0	6.3	54.0	5.7	48.7
7	28	M	5′11″	73.0	1.90	33.0	62.2	14.0	33.2	13.4	31.9
8	60	M	5′8″	63.2	1.73	27.2	73.4	8.9	37.4	8.9	37.4
9	58	M	5′11″	69.0	1.96	46.0	50.0	30.3	31.3	26.7	27.6
10	62	M	5′5½″	59.0	1.63	25.0	46.3	6.3	15.5	6.7	16.4
11	27	M	5′10″	53.0	1.64	30.0	41.8	14.8	44.0	15.6	46.4
12		M	5′3″	70.0	1.72	22.0	54.0	17.5	34.2	17.6	34.3
13		M	5′6″	68.5	1.76	35.0		38.4	28.1	37.8	27.6
14	31	M	5′10½″	73.0	1.90	13.0		11.6	44.0	10.5	40.0
15	25	M	5′11″	70.0	1.87	46.0	54.0	23.3	44.5	21.5	41.2
16	32	M	5′8″	54.0	1.61		52.0	37.9	28.6	40.8	30.8
17	29	M	5′9″	75.0	1.89	23.0	52.5	17.2	45.0	15.7	41.1
18	37	M	6′2″	83.4	2.08	48.8	51.2	20.0	24.1	16.6	20.0
19	32	M	5′8¾″	65.0	1.77	48.0	34.0	18.8	20.8	18.3	20.3
20	61	M	5′9″	64.5	1.77			22.6	23.2	22.0	22.6
21	61	M	5′9″	63.6	1.76	12.0	66.0	15.3	33.1	15.1	37.6
22	58	M	5′7½″	56.3	1.63	50.5		33.2	27.0	35.2	28.7
23	48	M	5′6″	49.0	1.53	42.0	50.0	27.9	21.0	31.5	23.8
24	42	M	5′8½″	79.5	1.88	41.0	60.0	42.0	54.0	38.7	49.7
25	28	M	6′1″	75.0	1.96	47.0	53.0	39.8	32.2	35.2	28.4
26	24	M	5′3″	61.6	1.62	25.0	53.0	19.1	51.2	20.4	54.6
27		M	5′7″	79.0	1.89			15.8	45.0	14.4	41.2
28	44	M	5′4½″	43.2	1.43	19.0	45.0	5.7	22.8	6.9	27.7
29	39	F	5′6¼″	63.8	1.71	31.4	58.3	15.2	29.8	15.4	30.2
30	51	M	6′0″	74.5	1.94	34.2	62.5	22.3	38.7	19.9	34.5
31	54	M	6′1¼″	75.5	1.99	39.0	55.0	25.7	44.2	22.3	38.4
32	42	M	5′3½″	76.0	1.79	28.0	57.0	27.4	52.2	26.5	50.5
33	45	M	5′6¾″	61.2	1.69	48.0	42.0	25.7	20.8	26.3	21.3
34	29	M	5′7½″	61.2	1.71			30.0	34.3	30.3	34.7
35	33	M	5′9¾″	88.3	2.05	38.6	55.0	25.4	52.0	21.4	43.9
36	46	M	5′11¼″	95.5	2.14	37.0	58.5	18.1	48.7	14.7	39.4
37	28	M	5′10½″	79.0	1.96	42.0	63.0	28.4	53.0	25.1	46.8
38	29	M	5′7″	80.0	1.90	22.0	50.0	7.8	31.2	7.1	28.4
39		M	5′8¼″	63.3	1.74	27.0	63.0	9.8	53.0	9.7	52.0
40	23	M	5′7″	69.5	1.79	38.0		29.8	41.5	28.8	40.0
41	62	M	5′9¼″	80.5	1.95	25.0	36.8	12.1	57.2	10.7	50.7
42	55	M	5′7½″	54.5	1.62	30.0	53.0	20.5	30.9	21.9	33.0
43	64	M	5′1¾″	74.5	1.74	30.0		12.9	20.1	12.8	20.0
44	34	M	6′0″	89.0	2.10	28.0	66.0	8.3	38.2	6.8	31.4
45	39	M	5′8″	84.0	1.96			7.7	57.1	6.8	50.5
46	26	M	5′11¾″	88.5	2.09	38.0	49.0	31.0	48.6	25.6	40.2
47	52	M	5′5½″	85.5	1.92	21.0	47.2	12.3	28.8	11.1	25.9
48	64	M	5′4″	57.3	1.59	22.0	60.0	13.5	42.5	14.7	46.2
49	40	M	5′8″	59.0	1.67	19.0		7.1	50.1	7.4	52.0
50	34	M	5′11½″	86.3	2.05	25.0	48.0	9.5	69.0	8.0	58.0
51	54	M	5′5½″	65.8	1.73	44.3	46.8	35.3	49.0	35.3	49.0
52	39	M	6′0″	86.3	2.07			9.2	49.1	7.7	41.0
53	27	M	5′8″	78.0	1.90	40.0	48.0	21.8	61.6	19.8	56.2
54	55	M	5′8″	60.5	1.82	36.0	50.0	17.4	21.6	16.5	20.6
55	30	M	5′5″	84.0	1.90	37.0	40.0	21.8	50.5	19.9	46.0
56	32	F	5′3½″	62.6	1.65	43.5	46.7	39.2	34.8	41.0	36.6
57	58	M	5′6″	81.5	1.87	28.0	57.0	8.1	29.5	7.5	27.3
58	30	M	5′8½″	75.9	1.89	37.5	53.0	21.0	48.2	19.2	44.3

TABLE II—*Continued*

Patient	Age	Sex	Height	W (*kg*)	Surface area (*m²*)	24 hour uptake (*% dose*)	24 hour excretion (*% dose*)	Plasma I^{131} clearance (*ml/min.*)		Plasma I^{131} clearance (*ml/min./1.73 m²*)	
								Thyroid	Renal	Thyroid	Renal
				Euthyroidism—*Continued*							
59	52	M	5'11"	68.5	1.86	20.0	59.0	15.8	18.5	14.7	17.2
60	17	F	5'2½"	57.6	1.57	42.5	45.4	17.0	21.2	18.7	23.4
61	45	M	5'11"	72.5	1.91	20.0	67.0	11.6	39.2	10.5	35.4
62	28	M	5'11"	88.0	2.07	23.0	50.0	8.8	35.2	7.4	29.4
63	41	M	5'6½"	75.0	1.84	25.0	60.0	24.0	42.7	22.5	40.1
64	45	F	5'7"	60.0	1.69	28.0	55.0	6.0	28.2	6.1	28.9
65	40	F	5'4"	64.5	1.68	33.9	57.7	20.6	34.8	21.2	35.8
66	44	M	5'9"	91.4	2.05	19.0	73.0	11.9	61.2	10.1	51.7
67	55	M	5'10½"	81.8	1.99	51.0		23.7	20.4	20.6	17.7
68	38	M	5'11"	66.0	1.83	34.0		21.8	33.6	20.6	31.7
69	28	M	5'11½"	89.0	2.09	37.6	42.0	24.0	38.2	19.8	31.5
70	41	F	5'5½"	79.6	1.86	57.6	42.0	40.4	51.0	37.6	47.5
71	55	M	5'7½"	59.0	1.68	35.0	65.0	3.6	25.0	3.7	25.8
72	59	M	5'6¾"	82.8	1.93	29.3	44.0	13.6	33.9	12.2	30.4
73	35	F	5'7½"	82.3	1.94	31.0		8.0	28.0	7.2	25.0
74	52	F	5'2"	45.4	1.42	29.0	56.0	8.6	15.4	10.5	18.7
75	28	M	5'10"	79.6	1.96	32.0	61.5	15.2	54.2	13.4	47.8
76	37	M	5'7"	64.5	1.73	30.0	53.0	16.8	51.6	16.8	51.6
77	32	F	5'5"	59.8	1.69	16.2	64.2	5.1	47.5	5.2	48.5
78	24	F	5'7½"	71.0	1.83	22.0	70.5	8.5	54.6	8.0	51.7
79	38	M	5'9"	91.0	2.04	23.6	58.7	14.6	52.0	12.4	46.1
80	26	M	5"9"	81.3	1.95			10.8	46.0	9.6	40.8
81	63	M	5'1¼"	48.2	1.44	27.2	40.4	10.0	16.1	12.0	19.3
82	56	M	5'4½"	66.0	1.70	36.9	54.3	19.1	30.4	19.4	30.9
83	60	M	5'9"	70.4	1.83	39.5	58.0	11.3	51.4	10.7	48.5
84	48	M	5'5½"	60.4	1.64	27.4	41.8	8.4	28.0	8.8	29.5
85	56	M	5'7"	47.6	1.54	25.5	55.2	8.1	28.0	9.1	31.5
86	31	M	5'2"	57.6	1.56	39.6	40.3	21.5	44.2	23.8	49.0
87	34	M	6'1"	69.5	1.91	35.1	54.2	21.2	30.2	19.2	27.3
				Hyperthyroidism							
1	45	M	5'4¾"	66.0	1.67	63.0	13.9	94.5	38.2	97.5	39.4
2	63	M	6'2"	51.4	1.70	82.0	24.0	73.5	19.0	75.0	19.3
3	33	M	5'9"	61.3	1.79	73.0	7.0	371.0	24.5	358.0	23.7
4	54	M	5'8"	69.0	1.81	70.0	20.0	345.0	24.8	330.0	23.7
5	34	M	5'10"	59.0	1.72	78.5	20.0	210.0	35.4	211.0	35.6
6	63	M	5'7½"	70.5	1.81	56.0	32.0	77.5		74.5	
7	55	M	5'5½"	64.6	1.71	64.0	38.0	82.0		83.0	
8	32	M	5'8½"	53.5	1.63	78.0	23.0	257.0	32.1	273.0	34.1
9	34	M	5'10"	60.0	1.73	71.0	14.0	115.0	15.6	115.0	15.6
10	54	M	5'4"	66.0	1.69			82.5	43.5	84.5	44.5
11	61	M	5'8"	60.5	1.70	75.8	10.4	74.0	5.1	75.5	5.2
12	37	M	5'9"	63.0	1.75	81.3	8.0	360.0	22.0	356.0	21.7
13	34	M	5'6½"	56.8	1.63	77.0	10.3	387.0	34.9	410.0	37.0
14	61	M	5'5"	52.0	1.54	80.0	10.0	206.0	23.2	232.0	25.0
15	45	M	5'11"	69.4	1.88	61.0	24.0	103.0	39.0	92.0	36.0
16	62	M	5'7"	67.5	1.77	90.0	11.0	523.0	52.0	512.0	51.0
17	25	F	5'8½"	81.8	1.95	81.0		229.0	60.0	203.0	53.3
18	63	F	5'4"	51.0	1.52	84.8	9.7	188.0	17.2	214.0	19.6
				Hypothyroidism							
1	47	F	5'1½"	70.0	1.69	3.0	73.0	1.2	39.2	1.2	40.0
2	23	M	5'10"	65.0	1.80	10.1	92.0	1.2	38.4	1.5	36.9
3	73	M	5'6½"	79.5	1.89	7.5	32.0	0	15.4	0	14.1
4		M	5'8"	66.0	1.77	7.7		4.2	9.3	4.1	9.1
5	55	M	5'5½"	64.5	1.70	2.9	70.0	3.2	33.8	3.2	34.0

It has been noted by others (17) that the "iodide space" in thyrotoxic patients may be increased over that found in normal subjects. This has not been observed in the few cases which we have studied. However, when the blood volume is markedly increased and edema associated with decompensated heart disease as a consequence of the toxic state is present, such an increase in the "iodide space" is to be expected. None of our hyperthyroid patients showed such changes.

C. Evaluation of errors introduced by approximations

In the section on Methods, several approximations were made in the mathematical treatment of the changes in concentration with time. The validity of the approximations made in equations *5*, *6*, and *7* under the conditions of the present study has been tested by graphic integration.

From the observed values of "iodide space" determined at minute intervals from the curve in Figure 3, calculated plasma concentration-time curves were obtained for combined thyroid and renal clearance rates of 100–500 ml/min. The mean concentrations over the first half hour determined by integrating the areas under these curves were then compared with the mean concentrations calculated from equation *5*. Both the approximate integrated dose retained (equation *6*) and the arithmetic mean dose retained (equation *7*) were employed in calculating the average concentrations from equation *5*. The per cent difference between the graphically integrated and the calculated average concentrations (*i.e.*, the error involved in the approximations under discussion) was then plotted as a function of the combined thyroid and renal clearance rates (Figure 4). At the highest combined clearance rate in euthyroidism (100 ml/min., see Table III) the error is negligible (less than 1%), if either the approximate integrated or the arithmetic mean dose retained is used to calculate the average concentration. At the second highest yet observed combined clearance rate (450 ml/min.) the error involved when the approximate integrated dose is used is only 2½–3% and is still less than 10% even when the arithmetic mean dose is accepted as the average dose retained.

For more accurate evaluation of the clearance rates in hyperthyroidism, correction for the approximations involved in the calculations of the average concentration may be obtained from Figure 4. The only approximation which is not corrected for is in using the average "iodide space" over the first half hour as 20% of body weight, but, as noted above, this has been observed to be strikingly constant in non-edematous subjects with a maximum probable range of ±10% from the mean.

RESULTS

A. 24 hour thyroid uptake and renal excretion values

In Table II are presented the clearance data and the 24 hour thyroid and urinary I^{131} accumulation values in 87 euthyroid, 18 untreated hyperthyroid and five hypothyroid subjects, four of whom were frankly myxedematous. Studies in five cases of hyperthyroidism recently treated with therapeutic doses of I^{131} or by subtotal resection, with only partial clinical success, are also included. All of these five patients shortly thereafter relapsed into full blown toxicity.

Figure 5 shows the frequency distribution of the 24 hour thyroid uptake and renal excretion values expressed as per cent of the administered dose. The range and average values for each clinical group are presented in Table III. While there is fairly good diagnostic separation of the clinical groups there remains a definite overlap with either test. The chart on renal excretion excludes 16 cases in which the urine collection was known to be incomplete. Since in any particular case, the reliability of a urine collection may be questioned, this measurement is even less suitable as a diagnostic test than might be inferred from the data pictured in Figure 5.

A thyroid uptake of 50% or more at the end of 24 hours has heretofore been accepted in this clinic and elsewhere as indicative of hyperthyroidism. Seven cases of euthyroidism are noted to fall in this range.

Excluding the cases in which the urine collection was known to be incomplete, an average of 87% of the administered dose was accounted for in the thyroid and urine at the end of 24 hours in the euthyroid subjects.

B. Half hour thyroid uptake curves

In contrast to the overlap between euthyroid and hyperthyroid cases in the 24 hour thyroid uptake measurements, the thyroid uptake curves during the first half hour reveal that a better differentiation is possible at this time (Figure 6).

TABLE III

Range and mean values for 24 hour thyroid uptake and renal excretion

Clinical state	Thyroid uptake (*% of dose*)		Renal excretion (*% of dose*)	
	Range	Mean	Range	Mean
Hyperthyroid	56.0–90.0	70.1	7.0–38.0	18.1
Euthyroid	12.0–68.0	33.0	31.0–76.0	53.7
Hypothyroid	2.9–10.1	6.2	32.0–92.0	66.8

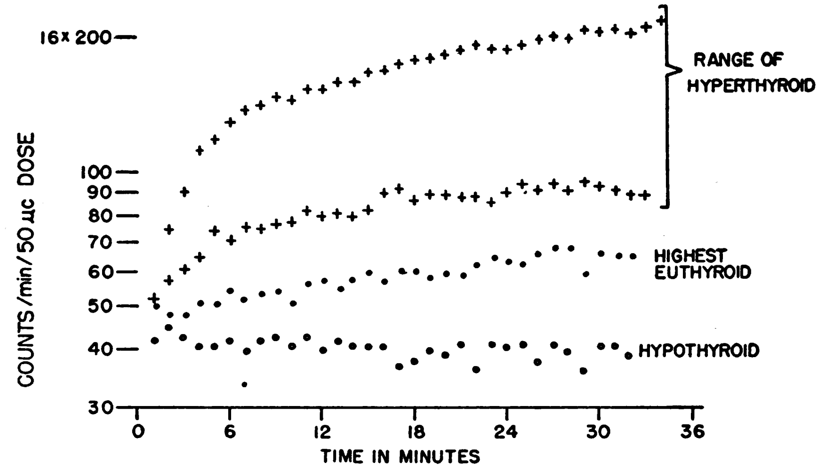

FIG. 6. COUNTING RATE OVER THE NECK DURING THE FIRST HALF HOUR FOLLOWING INTRAVENOUS ADMINISTRATION OF I^{131} TO PATIENTS IN DIFFERENT CLINICAL STATES

C. Thyroid and renal clearance values

The frequency distributions of the thyroid and renal clearances are shown in Figure 7. The clearance rates have been corrected to 1.73 m^2 surface area to facilitate comparison between different individuals. The range and mean values for each clinical group are presented in Table IV. There appears to be no real difference in renal clearance rates among the various clinical groups. It may be assumed that the iodide ion is readily filtered through the glomerulus. The clearance values are then consistent with the interpretation that the iodide is reabsorbed by the tubules. That the variations in renal clearance among normal individuals may be related to tubular mechanisms regulating the excretion of other electrolytes, particularly chloride, must be considered. This has not been investigated. It may be noted, however, that only the two lowest points obtained were associated with known renal disease.

In contrast to the distribution of the renal clearance values the thyroid clearances show a clearcut

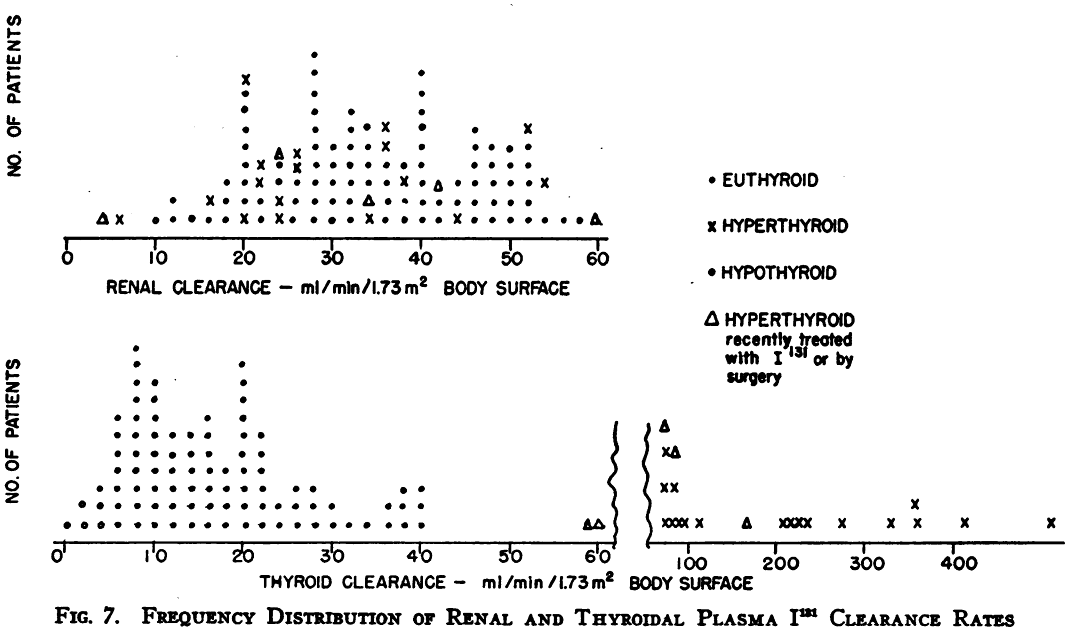

FIG. 7. FREQUENCY DISTRIBUTION OF RENAL AND THYROIDAL PLASMA I^{131} CLEARANCE RATES

TABLE IV

Range and mean values for thyroid and renal clearances

Clinical state	Thyroid clearance (*ml/min./1.73 m^2*)		Renal clearance (*ml/min./1.73 m^2*)	
	Range	Mean	Range	Mean
Hyperthyroid	74.5–512	210.5	5.2–53.3	30.3
Euthyroid	3.7– 41.0	17.7	11.1–58.0	35.6
Hypothyroid	0.0– 4.1	2.0	9.1–40.0	26.8

separation between euthyroid and hyperthyroid cases, with a less well-defined delineation between the euthyroid and hypothyroid cases. The lowest clearance rate observed in untreated hyperthyroidism was almost twice the highest euthyroid clearance. Even in the patients who were in partial clinical remission as a result of therapy and who shortly thereafter showed complete relapse, the clearance rates were significantly beyond the euthyroid range. In general the hyperthyroid patients with markedly enlarged glands showed the highest clearance rates.

The number of euthyroid cases is large enough to define reliably the expected range of normal. It is unlikely that a significant fraction of euthyroid clearance values will be found beyond this range. Owing to the small number of observations in hyperthyroid cases, it is possible that clearances below the present limit may occur. However, because of the marked separation between the clinical groups, it is unlikely that any significant degree of overlap will be encountered.

In order to evaluate the constancy of the thyroid clearance rate in the same individual, the values obtained from the half hour study were compared, in a small group of euthyroid subjects, with those obtained between one half hour and three hours following the administration of I^{131} (Table V). The clearance rates during the one-half hour to three hour period were calculated from the thyroid uptake values and the actual plasma concentrations during this time as determined by repeated plasma analyses. The relative constancy of the thyroid clearances observed here confirms the results of Myant, Pochin, and Goldie (17) in studies done over a longer period in two subjects. In one patient (No. 13) thyroid clearance determinations performed six weeks apart were almost identical.

TABLE V

Comparison of clearance values determined during the first half hour and during one-half to three hours

Patient	Thyroid clearance (*ml/min./1.73 m^2*)		Renal clearance (*ml/min./1.73 m^2*)	
	0–½ hour	½–3 hours	0–½ hour	½–3 hours
85	9.1	8.5	31.5	27.3
29	15.4	14.2	30.2	22.0
86	23.8	19.0	49.0	40.5
82	19.4	14.5	30.9	25.2

To further test the validity of the area measurements and the mathematical approximations previously considered, the clearance rates during the first and second 15 minute periods were compared with each other and with the overall 30 minute clearance rate in seven subjects (Table VI). The clearance rates during each 15 minute period were obtained in the same manner as the 30 minute clearance rates by determining the areas under each half of the curve in Figure 3. The average "iodide spaces" during the first and second 15 minute periods were found to be 16.5% and 24.8% of body weight respectively. In general, the agreement of the values is within the error of the measurements.

TABLE VI

Comparison of clearance values determined over different periods during first half hour

Patient	Thyroid clearance (*ml/min./1.73 m^2*)		
	0–¼ hour	¼–½ hour	0–½ hour
86	23.0	24.2	23.8
82	19.9	18.2	19.4
24	37.4	38.8	38.7
25	35.9	29.7	35.2
81	12.7	10.9	12.0
23	24.2	41.0	31.5
13—9/28/50			37.8
11/9/50	32.7	36.7	36.2

D. Correlation of thyroid/renal clearance ratios with 24 hour thyroid uptake/renal excretion ratios

Figure 8 shows the correlation of the 24 hour thyroid uptake/renal excretion ratios plotted against the thyroid/renal clearance ratios. In this figure are included the results of 118 studies in 89 subjects. Cases in which urinary collections were known to be incomplete have been excluded.

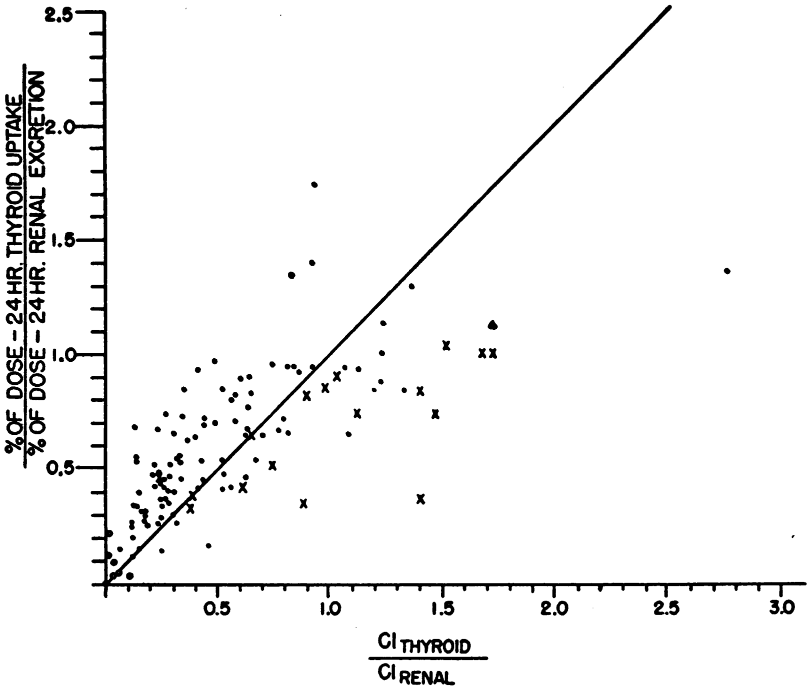

FIG. 8. CORRELATION BETWEEN 24 HOUR THYROID UPTAKE/RENAL EXCRETION RATIOS AND THYROID/RENAL CLEARANCE RATIOS

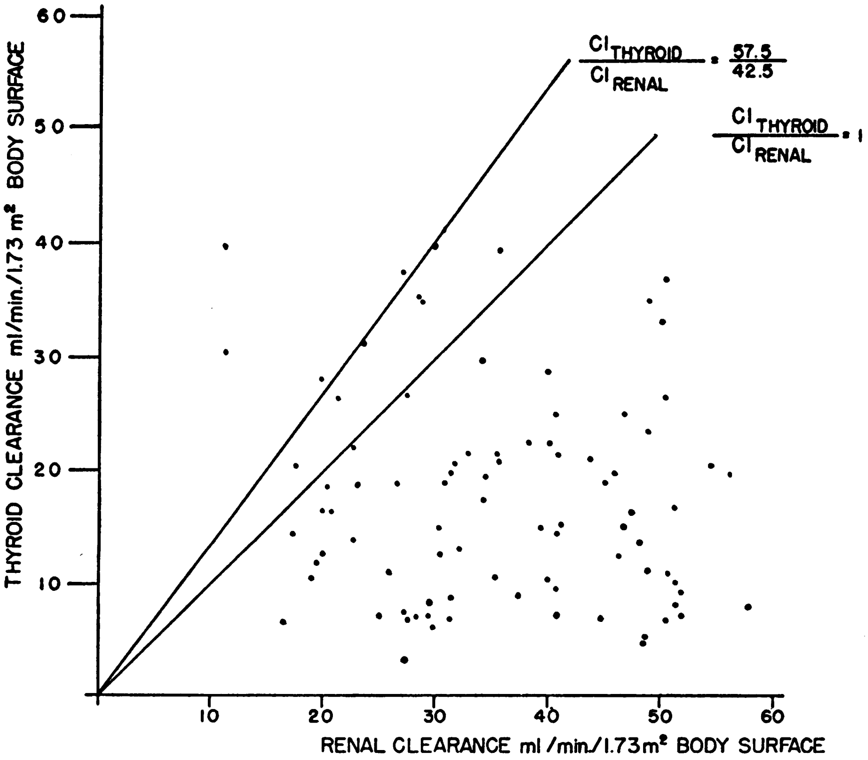

FIG. 9. CORRELATION BETWEEN THYROID CLEARANCE AND RENAL CLEARANCE RATES IN EUTHYROID CASES

In the hyperthyroid cases both ratios were divided by 10 in order to bring the points onto the same graph. While the correlation is good (4-fold r = 0.73), it should be noted that the majority of the euthyroid cases fall somewhat to the left of the 45° line through the origin. Since the evidence favors a constant thyroid clearance, this indicates that the average 24 hour renal clearance is slightly lower than that obtained during the test period. This is probably related to temporary alterations in renal function produced by changes in position and activity. In contrast, the points in all but one of the hyperthyroid cases fall to the right of the 45° line. Considering the increased rate of turnover of iodine in the hyperfunctioning gland, the finding of a 24 hour thyroid uptake/renal excretion ratio lower than the respective clearance ratio is not unexpected. Significant amounts of radioiodine may be released in an organically bound form within the 24 hour period. This results in an apparently lower thyroid uptake. Furthermore, some of the iodine previously accumulated by the thyroid may be excreted directly in organically bound form or as iodide resulting from metabolic destruction of the organic iodine compounds, thus leading to falsely high urinary excretion values.

E. Effect of renal clearance on thyroid uptake

To determine the effect of the renal factor on the thyroid uptake, the thyroid clearance rates were plotted against the renal clearance rates of the euthyroid cases as shown in Figure 9. There is no significant correlation between them (4-fold r = 0.1). The probability of the thyroid uptake exceeding the renal excretion at any time is represented by the per cent of points lying to the left of the 45° line intercepting the origin. Eleven cases or 12.6% fell into this position. This value then represents the expected frequency of a 24 hour thyroid uptake of 43.5% or greater, since at the end of 24 hours, an average of 87% of the dose was accounted for in the thyroid and urine. Thirteen cases or 16.2% of the actual 24 hour values fell in this range. Similarly the expected frequency of a thyroid uptake of 50% or more of the dose is indicated by the per cent of points to the left of the line whose slope is 50/37 or 57.5/42.5. Six points or 7% fell on or to the left of this line, corresponding exactly to the number of cases found to have a thyroid uptake of 50% or greater at the end of 24 hours.

DISCUSSION

Inquiry into the application of clearance methods to the study of thyroid function was initiated by the British group of workers, whose reports (17–20) represent the only major contributions in this field. These investigators calculated the clearance rates from data obtained by multiple assays of thyroid activity and plasma concentration over a period of several hours following administration of I^{131}. The clearance values of thyrotoxic patients observed by them showed a progressive fall with time to zero levels in five to seven hours. As may be seen from Table VII, which gives for different clearance rates the time required for removal by the thyroid and kidneys of half the dose, at high clearance rates virtually the entire dose may be removed within two hours or less. It should be also noted that in thyrotoxic patients, clearance values obtained more than an hour or two after administration of the dose may represent significant underestimations since at this time appreciable amounts of radioiodine are being released from the gland as hormone, compared to the reduced amounts entering the gland. These points emphasize the necessity for performing the measurements as early as possible when dealing with very active glands. Further, it is desirable to perform the en-

TABLE VII

Calculated removal of radioiodine based on an estimated constant 40% space in a 70 kg man

Combined clearance rates (*ml/min.*)	Half time for removal (*hours*)	% removed at 24 hours
10	32	40.3
20	16	64.4
30	10.7	78.8
40	8.0	87.3
50	6.4	92.4
60	5.3	95.6
70	4.6	97.3
80	4.0	98.4
90	3.6	99.0
100	3.2	99.4
200	1.6	99.99
300	1.1	
400	0.8	

Since, during the early period of time following the administration of the dose, the space is considerably smaller than the estimated 40%, the half time for removal will be appreciably less than the times given in the table above for the higher clearance rates; *e.g.*, the half time for removal at a combined clearance rate of 400 ml/min. is less than 20 minutes.

tire determination at a single sitting in order to avoid the inevitable errors inherent in repositioning the counter.

The thyroid clearance values obtained by Myant, Pochin and Goldie (17) in eight control subjects showed a range of 8 to 38 ml/min. with a mean value of 16 ml/min. Clearance rates in untreated thyrotoxic patients ranged from 198 to 1,390 ml/min. with a mean value of 486 ml/min. The renal clearance rates ranged from 11 to 46 ml/min. with a mean of 27 ml/min. No significant difference in the renal clearance rates between control and thyrotoxic subjects was observed. The only other figures on I^{131} clearance that have come to our attention are those given by Keating and associates (21) in eight cases and those of Stanley (22) in three cases. In the series of Keating and coworkers three euthyroid patients with nodular goiter had thyroid clearances varying from 2 to 13 ml/min., while five patients having exophthalmic goiter had clearances ranging from 20 to 228 ml/min. Our results are more in accord with those of the British workers (17) and show almost the identical range of normal values. This latter group has considered the influence of the extraction ratio on the clearance rate and has pointed out that not only must blood flow be considerably increased over the normal rate of 3½ to 6 ml per gram of tissue per minute (23) but also that extraction must be very nearly complete in markedly overactive glands.

The present study, in agreement with many others, reveals that approximately 9/10 of an administered dose can be accounted for within the thyroid gland and the urine at the end of 24 hours, when thyroid and kidneys are functioning normally. Measurements taken 24 hours or longer after administration of a tracer dose, therefore, do not give an estimate of the absolute level of thyroid function but only express the relationship between the thyroid and kidneys in their ability to clear the blood of iodide. From Table VII, it may be seen that at high renal clearance rates almost all of the dose is removed at 24 hours even in the absence of functioning thyroid tissue.

Since the thyroid clearance remains fairly constant, at least for periods of several hours to a day, the rate of thyroid uptake is necessarily influenced by the rate of renal clearance and the changes with time in the space of I^{131} distribution within the body. Measurements made on the thyroid alone do not take into account either of these factors. Determination of the changes in plasma concentration of I^{131} alone does not enable one to distinguish between removal by the thyroid and loss in the urine, nor does it permit evaluation of the changes of I^{131} space. Measurements of the rate of renal excretion, such as described by Keating, Power, Berkson, and Haines (12) eliminated the renal factor in the evaluation of thyroid function, but did not account for the changes in the space of I^{131} dilution with time as was well appreciated by the original workers.

All of these tests have the additional disadvantage of requiring multiple assays of one sort or another. A single thyroid uptake measurement at an early time, in a sense, gives an approximation to the rate of iodide accumulation and serves to give better diagnostic differentiation than 24 hour studies. For example even the half hour uptake curves alone shown in Figure 6 allow for a well marked separation between the euthyroid and hyperthyroid cases, although overlapping between euthyroid and hypothyroid cases was observed. Similarly, in a recent report (24) on a limited number of patients, multiple measurements of thyroid activity during the first hour following intravenous administration of the isotope permitted a good diagnostic differentiation between euthyroidism and hyperthyroidism.

Stanley (22) has shown that at low serum inorganic iodide levels the rate of accumulation of radioiodine is independent of the serum iodide concentration. In his cases, the I^{131} accumulation was depressed only when high serum levels were produced by administration of iodine. This evidence suggests that, in the untreated gland, it is the clearance rate and not the iodide accumulation rate which reflects the level of thyroid function.

The rate of stable iodide (I^{127}) accumulation by the thyroid may be readily calculated as the product of the I^{131} clearance rate and the plasma concentration of inorganic iodide (I^{127}). It has been shown by Taurog and Chaikoff (25) that, as early as 15 minutes after the injection of I^{131}, 95% of the radioactivity present in the thyroid is organically bound. Radioiodine administered to patients with Graves' disease is rapidly released into the blood stream as thyroxine (26). Radioiodine is also identifiable in the protein precipitable fraction of the serum of euthyroid subjects as early as a few hours following its administration (11). If all the iodide leaving the gland is in hormonal form and if the total iodine content of the gland is not changed significantly, then the rate of I^{127} accumulation by the thyroid is equal to the rate of hormone release expressed in terms of iodine content. Assuming a serum inorganic iodide concentration of approximately 1 $\mu g\%$ (22), then at the mean euthyroid clearance rate of 17.7 ml/min., the average daily hormone formation and release would amount to 255 μg iodine. This is equivalent to 0.39 mg thyroxine or 127 mg USP thyroid extract. While these figures are only approximations, they agree well with the values of Stanley (22) as regards I^{127} accumulation and with Greer's (27) estimates of thyroid extract equivalent produced daily. They are also close to the daily requirements of myxedematous patients.

Where significant amounts of iodine have been recently ingested or when drugs affecting thyroid function have been administered, these speculations lead to invalid conclusions. As an example it may be noted that in hyperthyroid patients under the influence of such drugs as propylthiouracil and tapazole, the clearance rates may remain considerably elevated (28), indicating continued ability of the thyroid temporarily to accumulate radioiodine. Since hormone formation is blocked by the drug, however, the iodide is rapidly released from the gland as such, and in this circumstance there is no direct relationship between the rate of iodine accumulation and the rate of hormone formation. Ideally, on theoretical grounds, the rate of hormone formation and utilization would be most likely to reflect the clinical state of thyroid function. No publications satisfactorily dealing with the direct solution of this problem have yet appeared. Some recent studies (29–31), reporting the level of organically bound I^{131} in the serum at various times following the administration of the isotope, have failed to take into consideration differences in the stable iodine content of the thyroids of different individuals and the time required to achieve constant specific activity within the body. In any event, this measurement alone does not give more than a first approximation to the rate of hormone formation.

SUMMARY AND CONCLUSIONS

1. The thyroidal and renal plasma I^{131} clearance rates may be obtained in non-edematous individuals with good approximation by a method which is suitable for routine diagnostic use and which does not require the analysis of blood samples. The method is based on an observed relationship of relative constancy between the body weight and the space of I^{131} dilution during the first half hour following intravenous administration of the isotope. The clearance rates are readily determined in a single 35 minute sitting from the assay of radioactivity in the neck and in a single urine specimen.

2. The clearance rates and the 24 hour thyroid uptake and renal excretion values for 87 euthyroid, 18 untreated hyperthyroid, five treated hyperthyroid and five hypothyroid patients are presented. Overlap between euthyroid and hyperthyroid 24 hour values was obtained. The lowest thyroidal clearance rate in hyperthyroidism was almost twice the highest rate in euthyroidism. From analysis of the clearance rates it is to be expected that approximately 7% of the 24 hour values of normal subjects will fall into the hyperthyroid range.

3. In euthyroidism and hyperthyroidism the clearance rates are such that at the end of 24 hours approximately 90% or more of the dose has been removed by the thyroid and kidneys. The fraction of the dose of radioiodine concentrated in the thyroid, especially at this time, is modified by a number of extraneous factors, chief of which is the rate of renal clearance. Since the thyroid clearance rate is independent of these factors it is the most direct and reliable index of the iodine accumulating function of the thyroid gland.

4. The relationship of the thyroidal I^{131} clearance rate to the rate of thyroid hormone formation is discussed.

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APPENDIX A

If the space of dilution and the rate of removal by the thyroid and kidneys remained constant the dose retained would decrease exponentially with time according to the formula:

$$D_t = D_O e^{-\lambda t}, \qquad (a)$$

where

D_t = dose retained at any time, t

D_O = the administered dose

λ = the constant fraction of the dose removed per unit time.

The relative constancy of the clearance rates over periods up to three hours has been verified in the present study confirming the findings of Myant, Pochin, and Goldie (17) in normals.

The average dose retained over any time interval could then be expressed as

$$\bar{D}_{O-T} = \frac{\int_O^T D_O e^{-\lambda t}\,dt}{T}, \qquad (b)$$

where $\bar{D}_{O-T}$ = average dose retained over time interval O − T. λ may be obtained from equation (*a*) as follows:

$$\lambda = \frac{-\ln \frac{D_T}{D_O}}{T}, \qquad (c)$$

where D_T = dose retained at time T.

Since the space of dilution is changing during the first half hour following injection, λ is a variable and these relationships do not hold as absolute equalities. However, the change in λ is such that for values of λT which are small compared to 1, the following approximation is valid. (See Figure 4.) Integrating (*b*) between the designated limits,

$$\bar{D}_{O-T} \cong \frac{D_O(1 - e^{-\lambda T})}{\lambda T}, \qquad (d)$$

where

$\bar{D}_{O-T}$ = approximated integrated dose retained

λ = average value obtained from (*c*).

APPENDIX B

That this approximation is valid for small values of λT can be shown as follows:

$$\bar{D}_{O-T} = \frac{\int_O^T D_O e^{-\lambda t}\,dt}{T} = \frac{D_O(1 - e^{-T\lambda})}{\lambda T}.$$

Expanding $(1 - e^{-\lambda T})$

$$\bar{D}_{O-T} = \frac{D_O}{\lambda T}\left\{1 - \left(1 - \lambda T + \frac{\lambda^2 T^2}{2!} - \frac{\lambda^3 T^3}{3!} + \cdots\right)\right\}$$

$$\bar{D}_{O-T} = \frac{D_O}{\lambda T}\left(\lambda T - \frac{\lambda^2 T^2}{2} + \frac{\lambda^3 T^3}{6} - \cdots\right)$$

$$\bar{D}_{O-T} = D_O - \frac{D_O \lambda T}{2} + \frac{D_O \lambda^2 T^2}{6} - \cdots.$$

Where λT is small compared to 1, the higher order terms can be neglected. Then

$$\bar{D}_{O-T} \cong D_O - \frac{D_O \lambda T}{2}.$$

But $D_O \lambda T$ approximates $D_O - D_T$ for small values of λT. Therefore

$$\bar{D}_{O-T} \cong \frac{D_O + D_T}{2}.$$

APPENDIX C

Sample protocol and calculations

No. 70 41 year old white woman 5'5½", 79.6 kg Surface area = 1.86 m^2. Dose 49.7 μc i.v. at 2:02 p.m., 1/22/51.

Time after injection	Activity in μc over neck
Background	.76 μc
1 minute	7.70 μc
2 minutes	7.47 μc
3 minutes	7.61 μc
—	—
29 minutes	9.75 μc
30 minutes	9.90 μc
31 minutes	9.90 μc

Urine passed at 2:36 p.m. (29 minute specimen) contained 4.25 μc.

Calculations

Initial extrathyroidal level in neck (E) = 7.47 μc − .76 μc = 6.71 μc.

Observed increase in activity over neck (O) = 9.90 μc − 7.47 μc = 2.43 μc.

29 minute urinary excretion (U) = 4.25 μc.

Dose administered (D) = 49.7 μc.

Substituting these values in equation 2:

Thyroid uptake (Th)

$$= \frac{(2.43)(49.7) + (6.71)(4.25)}{49.7 - 6.71} = 3.48\ \mu c.$$

Dose retained at end of half hour ($D_{\frac{1}{2}\,hr}$)

$$= 49.7 - (3.48 + 4.25)\ \mu c, \quad = 41.97\ \mu c.$$

Average dose retained ($\bar{D}_{O-\frac{1}{2}\,hr}$):

(a) Determination of arithmetic mean dose:

From equation 7: $\bar{D}_{O-\frac{1}{2}\,hr} = \frac{49.7 + 41.97}{2} = 45.8\ \mu c$

(b) Determination of approximate integrated dose:
From equation *c* in Appendix A:

$$\lambda T = -\ln\frac{41.97}{49.7} = 0.167$$

From equation *6*:

$$\bar{D}_{O-\frac{1}{2}\,hr} = \frac{49.7(1 - e^{-0.167})}{0.167} = 45.8\ \mu c.$$

Substituting the arithmetic mean dose from (*a*) in the final clearance formula (equation *8* or *9*)

$$Cl_{thyroid} = \frac{3.48}{45.8} \times \frac{.20 \times 10^3}{30} \times 79.6 = 40.4 \text{ ml/min.}$$
$$= 37.6 \text{ ml/min./1.73 m}^2$$

$$Cl_{renal} = \frac{4.25}{45.8} \times \frac{.20 \times 10^3}{29} \times 79.6 = 51 \text{ ml/min.}$$
$$= 47.5 \text{ ml/min./1.73m}^2$$

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