

THYROID FUNCTION ASSAY WITH RADIOIODINE. II. ROUTINE CALCULATION OF THYROIDAL AND RENAL RATE FACTORS¹

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In the preceding paper (1) mathematical equations and numerical data were presented describing the early movement of a test dose of radioiodine in the human body. The information given can be used directly to calculate thyroidal uptake and renal excretion rate factors (or clearance rates) from observed values of the fractions of the net dose in the neck, N , and urine E , without the need for any blood samples, but the process is rather too tedious for routine use. However, the procedure can be greatly simplified by making suitable charts relating N and E to the thyroidal, k_1 , and renal, k_2 , rate factors for selected *fixed* times t after injecting the test dose. Fixed time schedules are necessary because otherwise a large number of charts is required. For convenience the pertinent equations from the preceding paper (1) are repeated below:

$$k = k_1 + k_2 \quad (1)$$

$$k_1/k = \frac{N - N_0 V_n/V + E N_0 V_n/V}{N - N_0 V_n/V + E} \quad (2)$$

$$k\phi t = \ln \frac{1 - N_0 V_n/V}{1 - N - E} \quad (3)$$

All the symbols used are as defined in the preceding paper (1), namely:

E = The fraction of the original dose excreted by the kidneys up to time t minutes after injection.

$k \text{ min.}^{-1}$ = The average combined (thyroid plus kidneys) fractional rate of removal of radio-iodide from the iodide space during the time interval $t = 0$ to 30 minutes; that is, an average fraction k of the circulating iodide pool is removed each minute.

$k_1 \text{ min.}^{-1}$ = The average fractional rate of uptake by the thyroid from $t = 0$ to 30 minutes.

$k_2 \text{ min.}^{-1}$ = The average fractional rate of renal excretion from $t = 0$ to 30 minutes.

N = The fraction of the original dose observed in the neck by external counting at time t , including both thyroid and extra-thyroid tissues.

N_0 = The initial value of N at time $t = 0$ assuming instantaneous mixing of the dose with the circulating plasma.

$t \text{ min.}$ = The time from injection of the test dose.

$V \text{ ml.}$ = The volume of the total effective iodide space at time t .

$V_n N_0 \text{ ml.}$ = The apparent volume of iodide space, at time t , that is "observed" in the extra-thyroid neck tissues by the external counter.

ϕ = The average value of $1/V$ up to time t expressed as a fraction of the average up to $t = 30$ minutes.

The above three equations are all that are needed for the development of simple routine methods and charts, as will be shown in the following sections.

EXTRA-THYROIDAL RADIOIODINE CONTENT OF NECK TISSUES OBSERVED BY EXTERNAL COUNTER

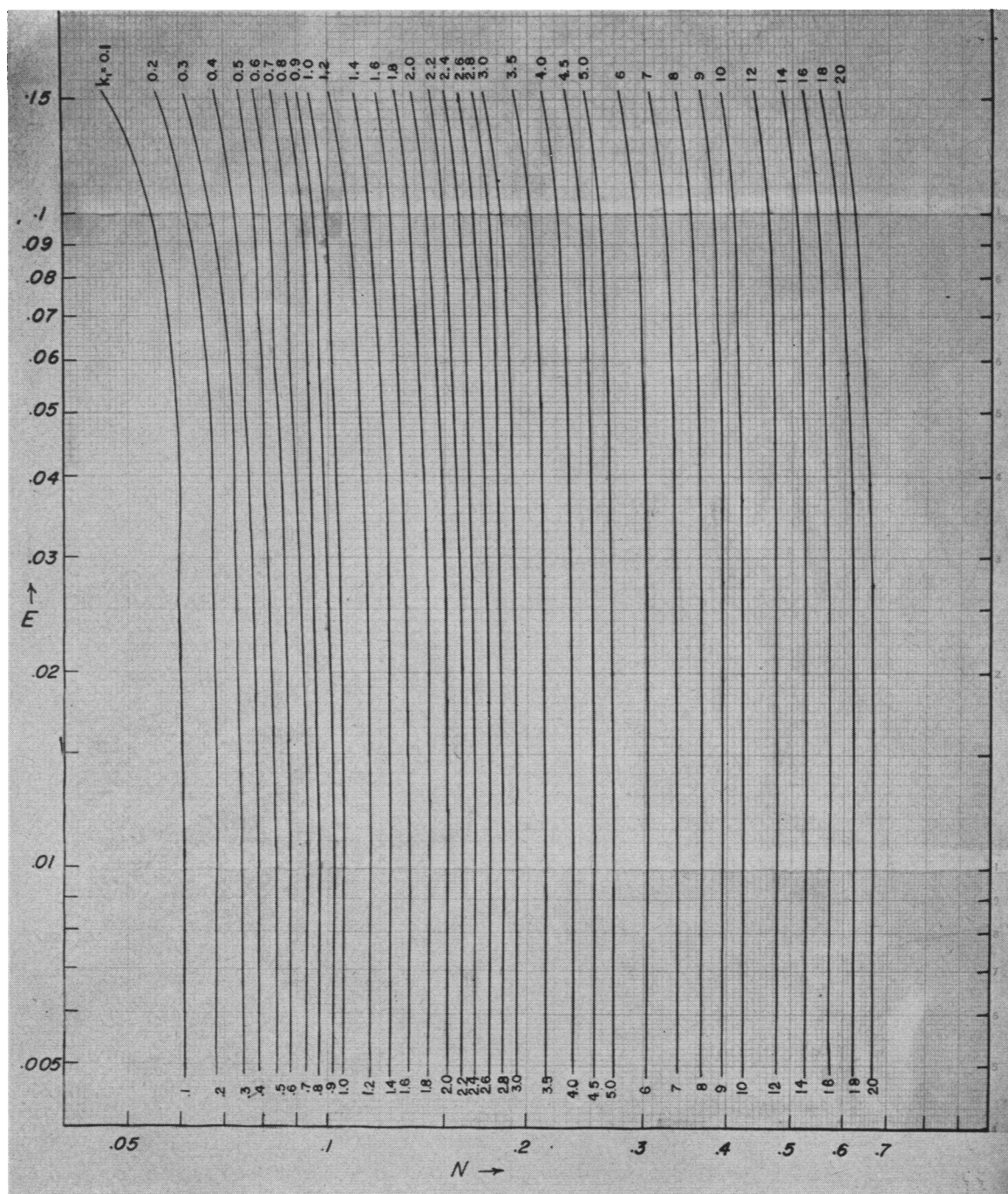
The term $N_0 V_n/V$ in equations (2) and (3) is derived from the fraction of the net dose observed in the extra-thyroidal neck tissues at time t , which has been shown (1) to be given by $\frac{N_0 V_n e^{-k\phi t}}{V}$. It has also been shown that V_n/V varies with time, but average smoothed values of this ratio have been tabulated in the form $\frac{V_n/V}{(V_n/V)_2}$ —where the denominator represents the value of V_n/V at exactly two minutes after injection.

If then, $N_0 V_n/V$ (at any particular time t) can be treated as a *constant* for all patients, equations (1), (2) and (3) can be represented on only one pair of charts connecting k_1 and k_2 with N and E for each selected time t ; but if $N_0 V_n/V$ varies too widely from patient to patient, a large number of pairs of charts must be constructed to cover the range of variation of this factor. Moreover, there is the additional advantage that if $N_0 V_n/V$ is known with sufficient accuracy for all patients, there will usually be no need to make an initial *in vivo* count over the neck immediately after injection.

Obviously variations from patient to patient

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FIG. 1. CHART FOR THYROIDAL RATE k_1 MEASURED AT ONE HOUR ($t = 60$)

become less troublesome when the extra-thyroidal tissue contribution $N_0 V_n/V$ is kept small by careful collimation of the external counter; to provide some data on this point we have measured the value of $N_0(V_n/V)_2$ —that is the extra-thyroidal neck tissue fraction two minutes after injection—in the same athyroid patient with four different

counting arrangements with the results presented in Table I.

The benefit derived from using a long collimator is apparent from the reduced value of the contribution of the neck tissues. In addition we have made observations on two series of different patients with long and short collimators, finding

mean values with standard deviations of the individual values set out in Table II.

Here again the long collimator gives more concordant results, and by using it for routine uptake studies $N_0(V_n/V)_2$ can be taken as 0.071, with a *maximum* expected variation of about ± 0.027 , for all cases except doubtful ones undergoing repeated tests; such cases occur sometimes when the numerical results of a first test lie close to the diagnostic borderline values separating euthyroid and hyperthyroid groups.

For the latter exceptional cases, or for collimators of different shape, it is necessary to deduce the individual values of N_0V_n/V from the initial and final total counts over the neck. This can be done by approximating equation (11) of the preceding paper for times t and two minutes, finally obtaining the approximate relation

$$N_0V_n/V = [\phi t N_2 - 4.3 N] / \left[\frac{\phi t (V_n/V)_2}{V_n/V} - 4.3 \right] \quad (4)$$

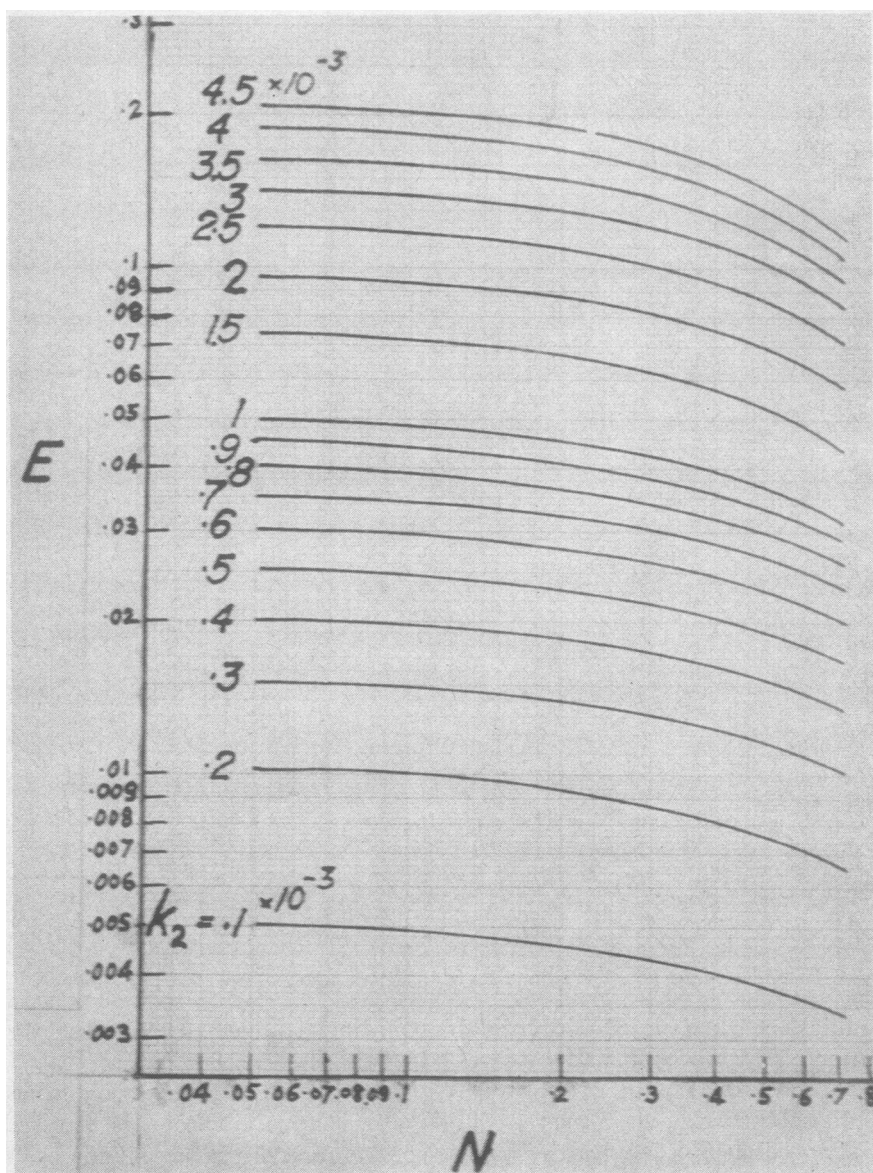


FIG. 2. CHART FOR RENAL RATE k_2 MEASURED AT ONE HOUR ($t = 60$ minutes)

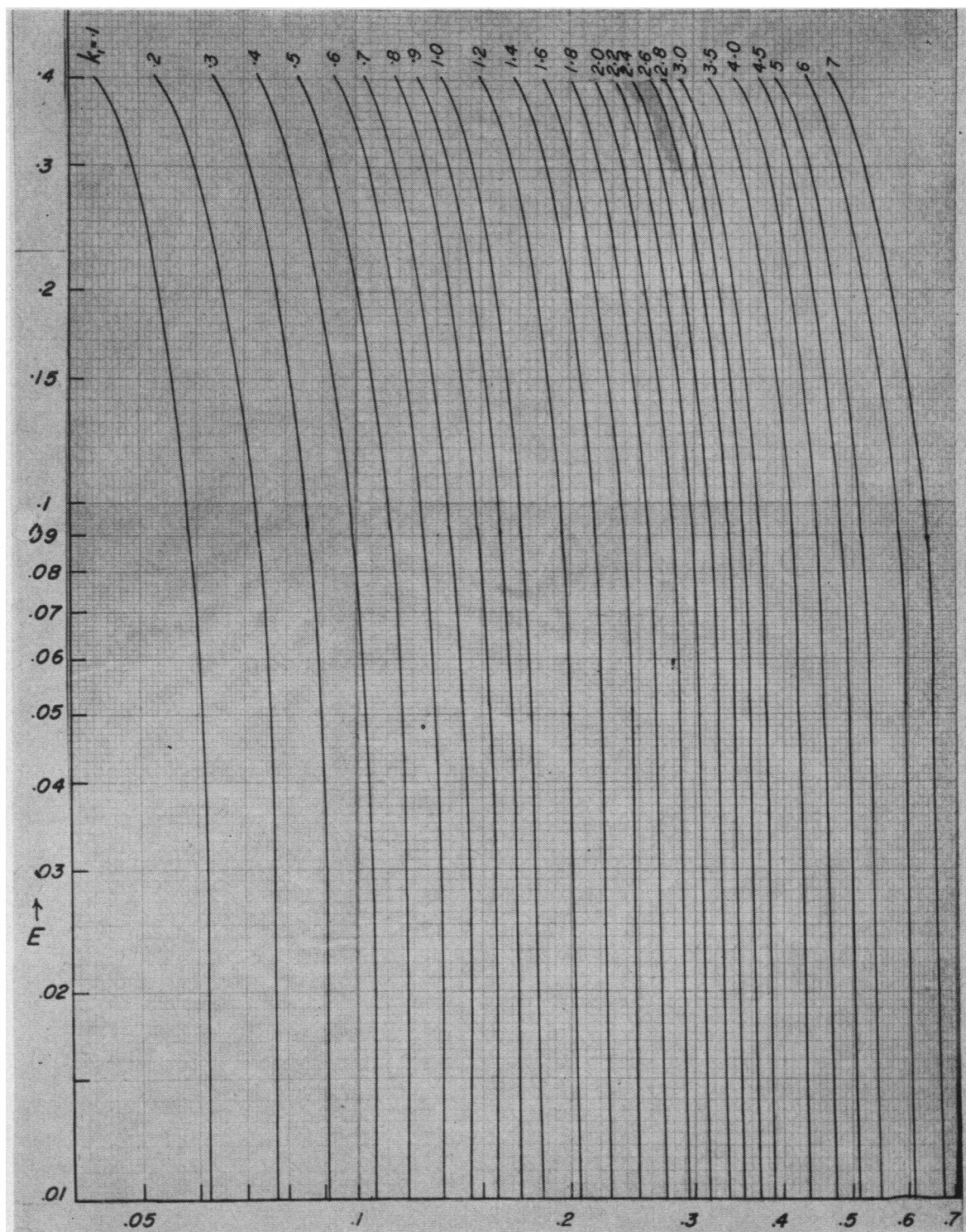


FIG. 3. CHART FOR THYROIDAL RATE k_1 MEASURED AT FOUR HOURS ($t = 240$)

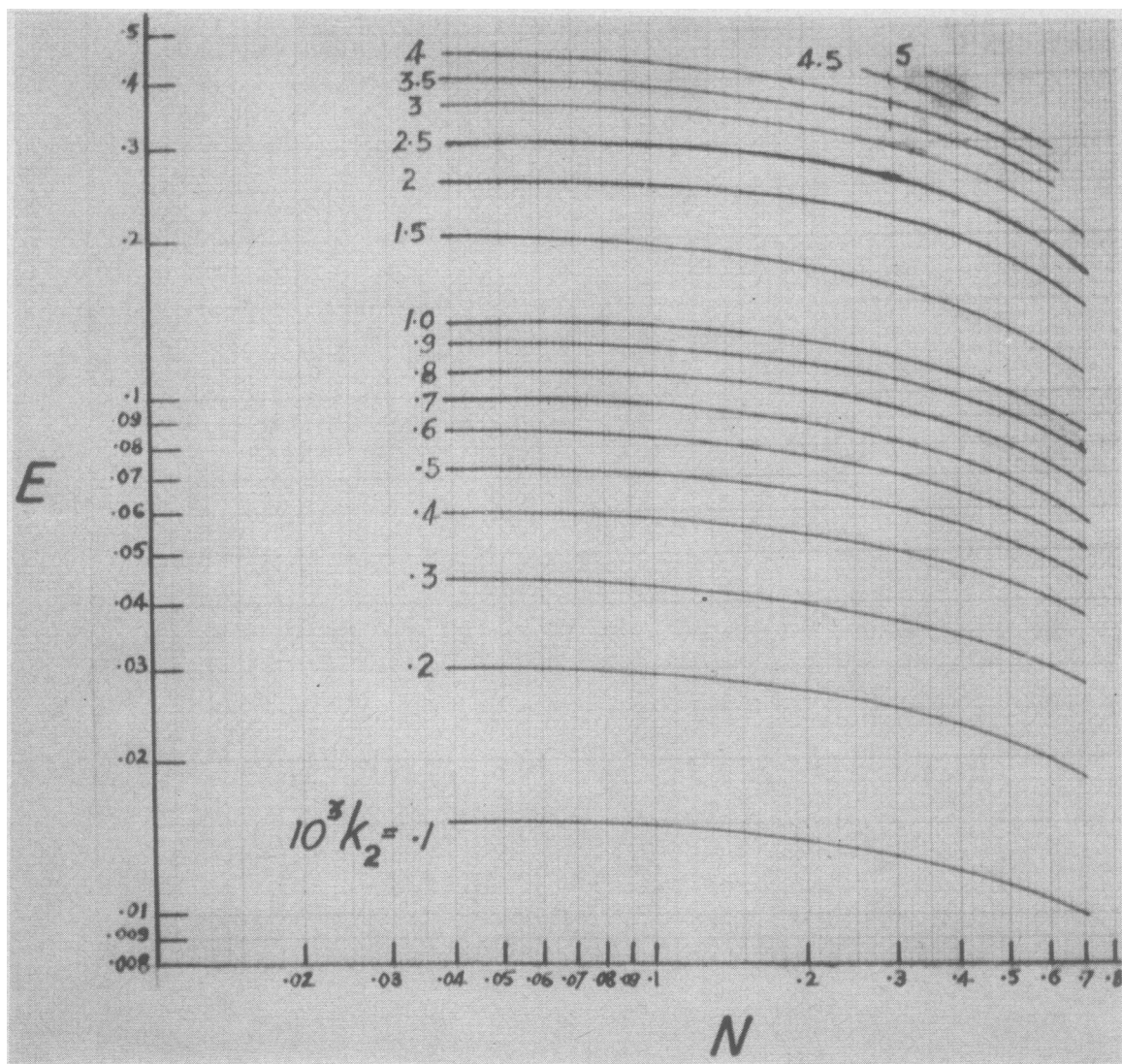
FIG. 4. CHART FOR RENAL RATE k_2 MEASURED AT FOUR HOURS ($t = 240$)

TABLE I

Counting arrangement	Estimated area of neck and torso observed, including penumbral region	Observed $N_0(V_n/V)_2$
Cylindrical Geiger counter in transverse position 15 cm. from skin; open type lead shield similar to arrangement of Werner, Quimby, and Schmidt (2)	550 cm. ²	.126
End window Geiger counter, 15 cm. from skin, in cylindrical lead shield of open type.	250 cm. ²	.106
Scintillation counter, 47 cm. from skin, short collimator as described earlier (1)	1000 cm. ²	.151
Scintillation counter, 47 cm. from skin, long collimator as described earlier (1)	200 cm. ²	.073

or, if the initial count is taken over the period 2 to 10 minutes

$$N_0 V_n / V = [\phi t N_{2,10} - 8.9 N] / \left[\frac{.95 \phi t (V_n/V)_2}{V_n/V} - 8.9 \right] \quad (5)$$

Thus, for example, if $t = 60$ minutes is the time selected for the second count, the tabu-

TABLE II

Collimator	Number of cases	$N_0(V_n/V)_2$		Standard deviation of individual readings
		Mean	Range	
Short	17	.146	.074-.272	.047
Long	24	.071	.046-.100	.013

lated values required are found in Table III of the preceding paper as $\phi t = 50.8$ minutes and

$$\frac{V_n/V}{(V_n/V)_2} = 0.84 \text{ so equation (5) reduces to}$$

$$N_0 V_n/V = 1.05 N_{2,10} - 0.184 N$$

Similar computations for other times lead to the coefficients listed in Table III.

In the routine case where $N_0(V_n/V)_2 = 0.071$ the derived figures for $N_0 V_n/V$ are those in the fourth column of Table III.

CHARTS FOR ROUTINE TESTS

Assuming that routine tests can be timed so that the middle of the period of the uptake ob-

servations is at a preselected time, charts are readily constructed to give k_1 and k_2 directly from the observed fractions N and E . Such charts for our long collimator have been derived

TABLE III
Data for finding $N_0 V_n/V$

Time t minutes		Formula for finding from two neck counts $N_0 V_n/V$	Mean $N_0 V_n/V$ with long collimator
First observation	Second observation		
2	30	$1.01 N_2 - 0.144 N$.062
2-10 (mean)	30	$1.28 N_{2,10} - 0.38 N$.062
2-10	60	$1.05 N_{2,10} - 0.184 N$.060
2-10	120	$0.91 N_{2,10} - 0.093 N$.056
2-10	240	$0.80 N_{2,10} - 0.048 N$.051
2-10	1,440	$0.56 N_{2,10} - 0.009 N$.037

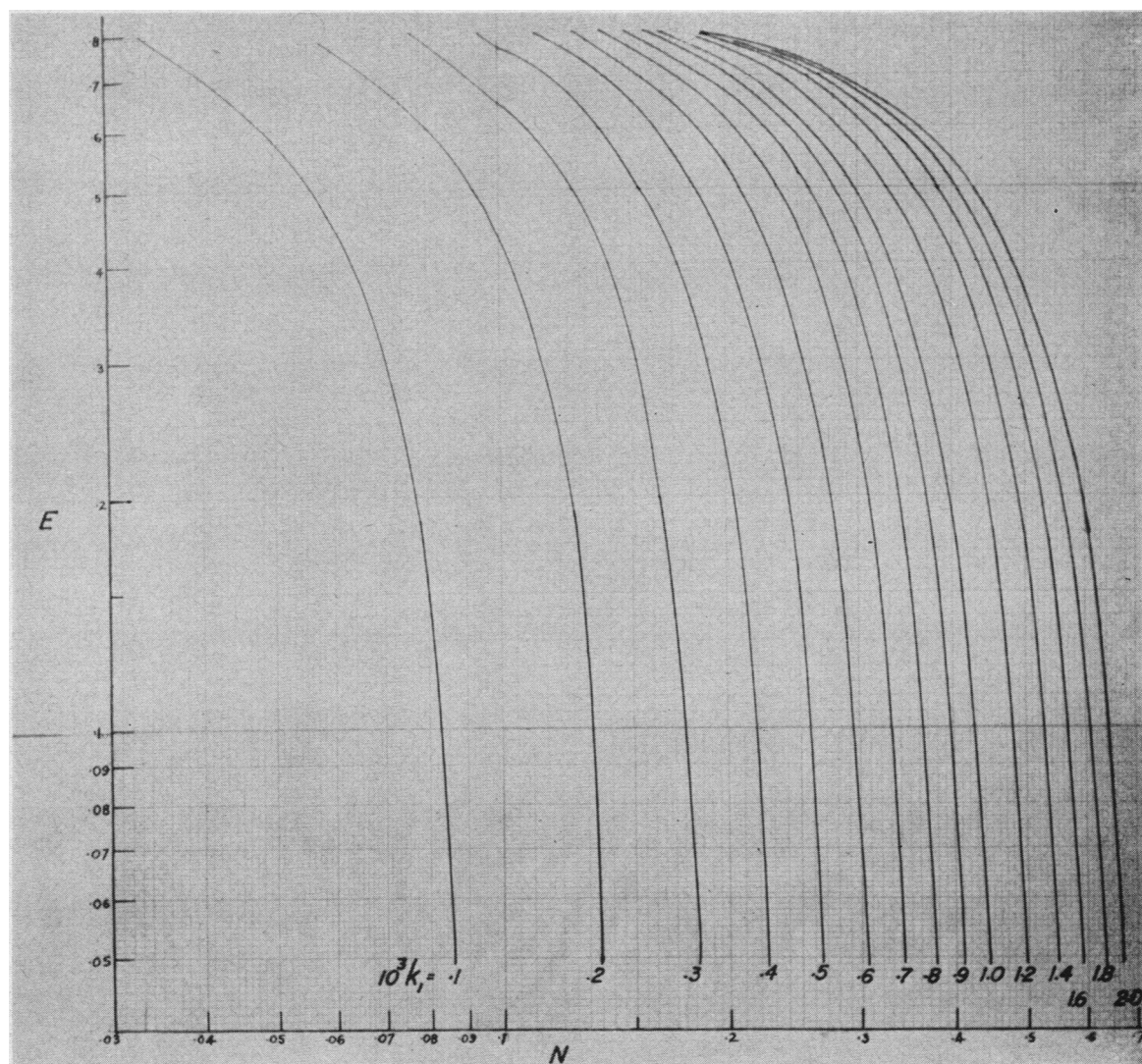
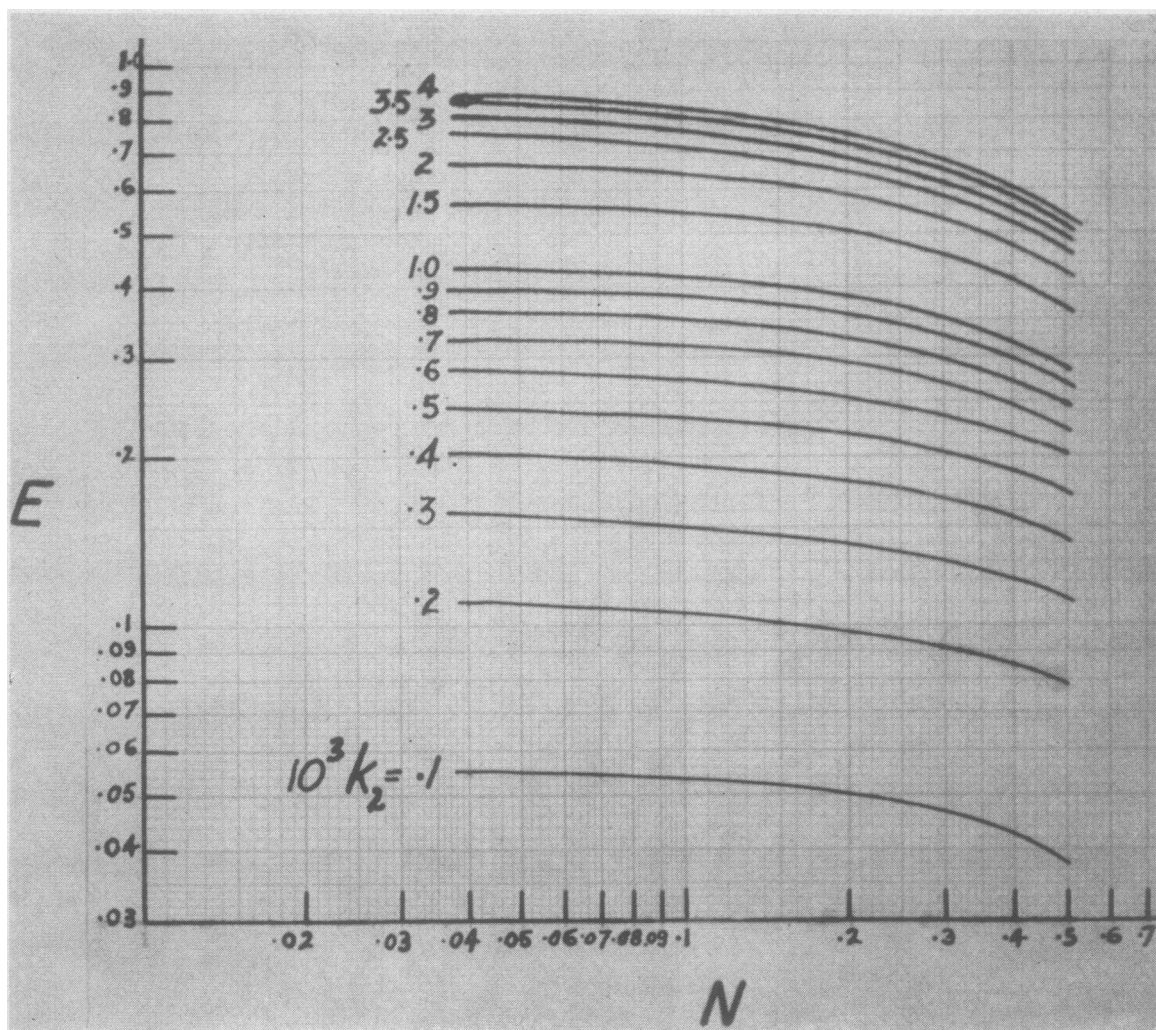


FIG. 5. CHART FOR THYROIDAL RATE k_1 MEASURED AT 24 HOURS ($t = 1,440$)

FIG. 6. CHART FOR RENAL RATE k_2 MEASURED AT 24 HOURS ($t = 1,440$)TABLE IV
Corrections for urine collection time *

Required t^\dagger	Actual collection time †	Correction factor for observed E	Required t^\dagger	Actual collection time †	Correction factor for observed E
60 (1 hour)	55	1.15	240 (4 hours)	230	1.06
	60	1.07		235	1.04
	65	1.00		240	1.02
	70	0.94		245	1.00
	75	0.89		250	0.98
	80	0.84		255	0.96
120 (2 hours)				260	0.95
	110	1.12	1,440 (24 hours)	1,400	1.03
	115	1.08		1,415	1.02
	120	1.04		1,430	1.01
	125	1.00		1,445	1.00
	130	0.97		1,460	0.99
	135	0.94		1,475	0.98
	140	0.92		1,490	0.97

* Note that 5 minutes' lag is allowed in urine accumulation, so that urine collected at, for example, 65 minutes, is assumed to be that excreted up to $t = 60$.

† All times in minutes from injection.

TABLE V
Solution of equation (3) for k at preselected times

$\frac{1 - N_0 V_n / V}{1 - N - E}$	$10^3 k \text{ min}^{-1}$				
	$\frac{1}{2}$ hour $t = 30$	1 hour 60	2 hours 120	4 hours 240	24 hours 1,440
1.00	0.00	0.00	0.00	0.00	0.00
1.05	1.63	0.96	0.56	0.33	0.09
1.10	3.18	1.88	1.10	0.64	0.17
1.15	4.7	2.75	1.61	0.94	0.25
1.20	6.1	3.59	2.10	1.23	0.32
1.25	7.4	4.4	2.56	1.51	0.39
1.30	8.7	5.2	3.02	1.77	0.46
1.35	10.0	5.9	3.45	2.03	0.53
1.40	11.2	6.6	3.87	2.27	0.59
1.45	12.4	7.3	4.3	2.51	0.66
1.50	13.5	8.0	4.7	2.74	0.72
1.55	14.6	8.6	5.0	2.96	0.77
1.60	15.7	9.3	5.4	3.17	0.83
1.65	16.7	9.9	5.8	3.38	0.89
1.70	17.7	10.4	6.1	3.58	0.94
1.75	18.6	11.0	6.4	3.78	0.99
1.80	19.6	11.6	6.8	3.97	1.04
1.85	20.5	12.1	7.1	4.2	1.09
1.90	21.4	12.6	7.4	4.3	1.13
1.95	22.3	13.2	7.7	4.5	1.18
2.00	23.1	13.6	8.0	4.7	1.23
2.1	24.7	14.6	8.5	5.0	1.31
2.2	26.3	15.5	9.1	5.3	1.39
2.3	27.8	16.4	9.6	5.6	1.47
2.4	29.2	17.2	10.1	5.9	1.55
2.5	30.5	18.0	10.5	6.2	1.62
2.6	31.9	18.8	11.0	6.4	1.69
2.7	33.1	19.6	11.4	6.7	1.76
2.8	34.3	20.3	11.8	7.0	1.82
2.9	35.5	21.0	12.2	7.2	1.88
3.0	36.6	21.6	12.6	7.4	1.94
3.1	37.7	22.3	13.0	7.6	2.00
3.2	38.8	22.9	13.4	7.9	2.06
3.3	39.8	23.5	13.7	8.1	2.11
3.4	41	24.1	14.1	8.3	2.16
3.5	42	24.7	14.4	8.5	2.21
3.6	43	25.2	14.7	8.6	2.26
3.7	44	25.8	15.0	8.8	2.31
3.8	44	26.3	15.3	9.0	2.36
3.9	45	26.8	15.6	9.2	2.41
4.0	46	27.3	15.9	9.4	2.45
4.2	48	28.3	16.5	9.7	2.54
4.4	49	29.2	17.0	10.0	2.62
4.6	51	30.1	17.5	10.3	2.70
4.8	52	30.9	18.0	10.6	2.77
5.0	54	31.7	18.5	10.9	2.84
5.5	57	33.6	19.6	11.5	3.01
6.0	60	35.3	20.6	12.1	3.17
6.5	62	36.9	21.5	12.6	3.31
7.0	65	38.3	22.4	13.1	3.44
8.0	69	41	23.9	14.0	3.68
9.0	73	43	25.3	14.8	3.88
10.0	77	45	26.5	15.6	4.1
12	83	49	28.6	16.8	4.4
14	88	52	30.3	17.8	4.7
16	92	55	31.9	18.7	4.9
18	96	57	33.2	19.5	5.1
20	100	59	34.4	20.2	5.3

from equations (1), (2), and (3) using the mean $N_0 V_n / V$ from Table III; they are shown in Figures 1 through 6, which give k_1 and k_2 for uptake times of 1, 4, and 24 hours ($t = 60, 240$ and 1440 minutes).

In using the charts it is assumed that the neck content N is measured over the ten-minute period from $t - 5$ to $t + 5$ minutes, and that E is measured with urine produced up to t but collected from the bladder at $t + 5$. If the urine is not collected at exactly this time a correction should be applied from Table IV.

NON-ROUTINE TESTS

In non-routine tests where previous results have been doubtful or where there is reason to suspect that $N_0 V_n / V$ may be well away from the expected average value, it is advisable to make initial counts over the neck during the period $t = 0$ to 10 minutes. This should always be done, if the final count is to be at 30 minutes because the average $N_0 V_n / V$ may not be precise enough for this short time of uptake.

Having found N , E , and N_2 or $N_{2,10}$, Table III enables $N_0 V_n / V$ to be calculated, ϕt is found from the figures tabulated earlier (1) so that equation (3) gives k , equation (2) gives k_1 and finally equation (1) gives k_2 .

To save time if t is kept to one of the selected values ($\frac{1}{2}$, 1, 2, 4, or 24 hours), the solution of equation (3) for the value of k may be found from Table V. These methods will become clear from the following examples.

EXAMPLES OF CALCULATIONS

Routine case at $t = 60$ minutes

Let the observed neck fraction, measured with the long collimator from $t = 55$ to 65 minutes, be $N = .235$, and the urine fraction collected at $t = 73$ minutes be .063.

From Table IV the corrected excretion fraction must be $E = .063 \times .91 = .057$.

With these values of N and E , Figures 1 and 2 give

$$k_1 = 4.2 \times 10^{-3} \text{ minute}^{-1}$$

$$k_2 = 1.3 \times 10^{-3} \text{ minute}^{-1}$$

Non-routine case at $t = 240$ minutes

Let $N_{2,10}$, measured over the period $t = 2$ to 10 minutes, have an average value of .095; N , observed from $t = 235$ to 245 minutes, be .106; and E , collected at $t = 250$ minutes, be .134.

From Table IV the corrected urine value is

$$E = .134 \times .98 = .131$$

From Table III, putting in values

$$N_0 V_n / V = .80 \times .095 - .048 \times .106 = .071$$

then

$$\frac{1 - N_0 V_n / V}{1 - N - E} = \frac{1 - .071}{1 - .106 - .131} = 1.22$$

and Table V gives $k = 1.34 \times 10^{-3}$ minute⁻¹. From equation (2)

$$k_1/k = \frac{.106 - .071 + .009}{.106 - .071 + .131} = .265$$

so that

$$k_1 = .265 \times 1.34 \times 10^{-3} = .35 \times 10^{-3} \text{ minute}^{-1}$$

and from equation (1)

$$k_2 = (1.34 - .35) \times 10^{-3} = .99 \times 10^{-3} \text{ minute}^{-1}$$

Non-routine case at $t = 190$ minutes

Let the measured fractions be $N_{2,10} = .083$, $N = .317$ and the urine collected at $t = 205$, $E = .188$. Because the time of observation, $t = 190$ minutes, is not covered by the charts or Table V, much more calculation is needed in this case.

First E is corrected from the presumed time of excretion (200 minutes) to the time of observation (190 minutes) by multiplying by the ratio of the corresponding ϕt values taken from the preceding paper (1). Thus the corrected value is

$$E = .188 \times 124/129 = .181$$

Then interpolating between the tabulated data of Table III

$$N_0 V_n/V = .86 N_{2,10} - .067 N = .050$$

Equation (2) with these values gives

$$k_1/k = \frac{.317 - .050 + .009}{.317 - .050 + .181} = .616$$

and equation (3) gives

$$k = \frac{2.303}{124} \log \frac{1 - .050}{1 - .317 - .181} = 5.1 \times 10^{-3} \text{ minute}^{-1}$$

so that

$$k_1 = .616 \times 5.1 \times 10^{-3} = 3.1 \times 10^{-3} \text{ minute}^{-1}$$

and

$$k_2 = 2.0 \times 10^{-3} \text{ minute}^{-1}$$

DISCUSSION

The method that has been described for calculating the rate constants k_1 and k_2 can be applied regardless of the type of measuring equipment used for uptake observations and urine assay; the charts (Figures 1 through 6), however, are only applicable to collimated counting arrangements with a low average factor $N_0(V_n/V)_2$ of about .07. When other wide-angle apparatus is employed it is necessary to observe the initial counts over the neck (or less preferably over the thigh) to find the correction for extra-thyroidal neck tissue.

Provided that sufficient counts are obtained for good statistical accuracy, and that the collimator is carefully positioned over the patient's gland, a fair degree of accuracy can be expected with the higher values of k_1 , if measurements are made one hour after injection. For low- k hypothyroid or cardiac cases, however, there will be little or no rise in the counts over the neck in one hour and we suggest that the four-hour read-

ings should be selected, and in very low cases an additional set of values should be measured at 24 hours also.

The fixing of diagnostic limits for the rate constants k_1 and k_2 depends upon a number of questions distinct from the more physical problems discussed above; in fixing such limits use can be made of some of the information already published by other groups, as will be shown in a later paper describing some of our own clinical results.

In the meantime it can be stated, from the information given in the preceding paper, that the thyroidal rate factor k_1 minute⁻¹ is related to the thyroidal clearance rate g ml. per minute, for a 70 Kg. patient, by the relation

$$k_1 = 10^{-3} g/16.3$$

This means that, if we take $g = 60$ ml. per minute as the approximate diagnostic borderline between euthyroid and hyperthyroid patients, the corresponding borderline value of k_1 will be around 3.7×10^{-3} minute⁻¹. Thus euthyroid values of k_1 will usually lie below this level, and there will be another not very distinct borderline between hypothyroid and euthyroid groups at about $k_1 = 2 \times 10^{-4}$ minute⁻¹.

SUMMARY

Based on a preceding paper, routine methods are developed for calculating thyroidal uptake and renal excretion rate factors from measured fractions of the dose of radioiodine observed at an early time t after administration.

Charts are included, for selected times t of 1, 4, and 24 hours, giving the rate factors directly from the experimental observations when uptake readings are made with good collimation to keep the extra-thyroidal neck tissue contribution low. Under these conditions such contribution is taken as a mean value for all patients and an uptake study normally requires only one observation over the thyroid gland and one urine assay.

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