Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 11 (1955)

Heft: 1-2

Artikel: Dynamic theory of the radioiodine investigation of thyroid function (confirmed by experiments)

Autor: Joyet, G. / Gautier, R.

DOI: https://doi.org/10.5169/seals-307210

C. D. 612.441

Betatron and Isotope Laboratory, Radiological Institute
Prof. H. R. Schinz, Zurich (Switzerland)

Dynamic Theory of the Radioiodine Investigation of Thyroid Function*

(Confirmed by experiments)

By **G. Joyet** and Mrs. **R. Gautier**

1. Introduction

As the direct measurement of the activity of the thyroid (uptake after 3, 6, 12 or 24 hours after administration) or the measurement of the urine excretion do not lead to a clear distinction between normal and pathological functions (see for instance *Ansell G.*, *MacGregor A.*, *Miller H.* and *Wayne E. J.* [1]) many attempts have been made in recent years to follow the *dynamics* of the miscellaneous movements of radioiodine in the organism after administration. The idea is that it is not the *static* state of uptake in the thyroid or the urine excretion at the usual predetermined times which can give a good representation of the *intensity* of the function, but it is the importance of the movements of radioiodine from the plasma to the thyroid and from the thyroid to the plasma which are determinant. The static uptake at a standard time is only a result of the combination of those different incoming and outgoing movements. Moreover, the uptake is strongly influenced by the very variable rate of urinary excretion and we will see that this rate probably has no significance at all for the biological intensity of the thyroid function. The notion of "thyroid clearance rate", as defined and measured by *Berson S. A.*, *Yalow R. S.*, *Sorrentino J.* and *Roswit B.* (2) is a very good attempt to determine the uptake rate of the radioiodine of the plasma by the thyroid during the first thirty minutes after intravenous injection, and gives a clear distinction between normal and pathological functions. It is probably because they administered the radioiodine orally and effected their measurements too late, that *Goodwin J. F.*, *MacGregor A. G.*, *Miller H.* and *Wayne E. J.* (3) found an appreciable degree of overlap of the thyroid clearance between thyrotoxicosis and euthyroid patients.

* The main idea of this paper was expressed at Lugano in a lecture delivered to the Soc. Helv. Sc. Nat. Sept. 1953 (29).

Some authors have clearly seen that only the mathematical analysis is able to tell us the importance of the diverse individual movements of iodine in the organism. It is this direction of research that we will chiefly consider here.

Oddie T. H. (4) developed a theory with five parameters (k_1 to k_5) and gives approximate solutions for the uptake and excretion curves. As the number of parameters is very high, he was compelled to make the assumption that the renal excretion rate is about constant ($k_5 = 0.06$), which in fact is not the case as we will see later, and that the flow rate k_2 of inorganic iodine from the thyroid to the plasma ought to be negligible. In a second paper with *Kaye Scott R.* (5), he pointed out that the initial uptake rate k_1 of radioiodine from the plasma to the thyroid "varies widely and does not promise to be of immediate diagnostic use". This assertion is explained by the fact that the radioiodine is administered orally and not intravenously, and is also submitted to the great variations of the digestive tract absorption. By analysing 25 uptake curves the authors demonstrate that the uptake in percentages at 24 hours, or the plateau height, is unreliable for diagnosing toxic thyroid conditions. They remark that the parameter k_4 which measures the fraction of organic iodine leaving the thyroid as hormone in unit time may be used to diagnose toxic conditions. We will compare these conclusions with our own later.

Rotblat J. and *Marcus R.* (6) consider that the avidity of the thyroid for inorganic iodine is the right indication of the state of the thyroid function. They develop a theory with four parameters: uptake rate by the thyroid λ_T, urinary excretion λ_U and two parameters λ_R and λ_B which characterize the movement from the plasma to the tissues and the inverse movement from the tissues to the plasma. It is the opinion of the authors that those movements are important too. But they do not consider the important flow of iodine from the thyroid to the plasma, which explains the fall of the uptake curve after the maximum. They proceed with *intravenous injection* and that permits the important assumption that initially the blood contains the whole quantity N_0 of the injected radioactive atoms. The authors manage to effect an exact integration and to find the functions for the activity of blood, thyroid, urine and tissues in terms of time. Each of these functions is described by two exponentials of which the exponential factors depend on the values of the four rates λ_T, λ_U, λ_R, and λ_B.

The authors do not analyse experimentally the uptake curve of the thyroid but the curve of urine excretion of which the analytical form is also represented by the addition of two exponentials. They show very

clearly that the analysis of the experimental curve during the first 24 hours enables the four factors λ to be determined. It is necessary to take numerous samples of urine during the first hours, preferably with a catheter, which complicates routine work. Their findings in 58 tests on 49 patients were:

Euthyroid (normal)	$\lambda_T = 0.10 \pm 25\%$ (standard deviation) per hour
Hyperthyroid	$\lambda_T = 0.37$ to 1.50 per hour,
Myxœdema (few cases)	$\lambda_T = 0.04$ per hour,

and they concluded that the correlation with the clinical diagnosis was very good.

It is necessary to outline these important results which we will compare with those of an entirely different method.

Haigh C. P. and *Reiss M.* (7, 8) in semi-empirical and theoretical considerations also affirm that a true measurement of the iodine avidity of the thyroid must be made *during the first hour after intravenous injection*. They, too, consider the slope ϱ of the ascension curve, which they record with a counter placed directly against the thyroid region, as determinant. But they "normalize" this slope in two ways which are difficult to understand. It is true that the ordinate C, at the origin, where the prolongation of the uptake curve cuts the ordinate, represents the relative activity of blood and tissues around the thyroid. It is also true that $k = \frac{\varrho}{C}$ would be constant on *one person* for different activities injected, measured with different geometries of the counter. But as C is very variable from one person to another and has no direct biological significance for the function, the values of k could not be compared from one patient to another. The attempt to "normalize" a second time k by dividing it by the total urinary excretion E is also not rational because C is not inversely proportional to E. C is a limit value at the initial time which is almost independent of the urinary excretion*. It is probably for that reason that *Haigh C. P.*, *Reiss C.*, and *Reiss J. M.* (9) found later several limitations to their method.

For *N. B. Myant* (10) the test of radioiodine is essentially a measure of the iodine-concentrating activity of the thyroid, and the *iodine clearance* rate is the best index for that measurement.

He considers a iodine space of V litres from which the thyroid "cleared" g ml/min. and the kidneys r ml/min. The concentration C in the iodine space decreases according to the law

* C is determined by anatomical and circulatory conditions and may vary from 1 to 30. It is clear that for a constant slope and different values of C on different patients k has no longer any significance.

$$C = C_0 e^{-\frac{g+r}{V}t}$$

where $\frac{g+r}{V}$ is the "disappearance rate" of *Keating* and co-workers. Both the cumulant totals of radioiodine in the thyroid G and urine R approach a maximum value exponentially,

$$G = \frac{g}{g+r}\left|1 - e^{-at}\right|$$

$$\text{and} \quad R = \frac{r}{g+r}\left|1 - e^{-at}\right|$$

The maximum uptake in the thyroid is equal to

$$\frac{g}{g+r}$$

and hence is dependent on the renal clearance. In these calculations the return of radioiodine from the thyroid to the blood is disregarded. The analytical form of the maximum of R explains why, experimentally (*Myant* et al. [11]), the total urinary excretion is not a sensitive test. A high thyroidal clearance rate g could be masked by a high renal clearance rate.

The foregoing is a summary of those papers only which deal with mathematical and theoretical considerations.

2. *The principal hypotheses of the theory*

This theory is based on the following assumptions which our experimental knowledge of the thyroid function generally permits us to accept as well established.

a) After *intravenous injection*, the solution is mixed with the whole plasma and with the extracellular liquid in a lapse of time of 5 to 10 minutes. This fact is clearly confirmed by the measurements of *Haigh C.* and *Reiss M.* (7) in the thyroid region and also by their experiments with ^{24}Na. *Morel F. F.* (12) has shown on the rabbit that the equilibrium with extracellular liquid after an injection of ^{24}Na is attained in about 6 minutes. The author obtained the same result with ion iodine (13). The extracellular ions Cl, Br and Na were previously studied in 1941 by *Hahn L.* and *Hevesy G.* (14), who also found a diffusion time of about 10 minutes in the extracellular fluid. He explained (*Hevesy G.* [15]) that the distribution by diffusion in the extracellular fluid is so fast, lasting a few seconds only, because of the very short distances between the capillaries.

b) When one proceeds by *oral administration*, penetration into the blood is very variable and reaches its maximum in a lapse of time ranging from 20 minutes to 2 hours or more. Fig. 1 shows the activities

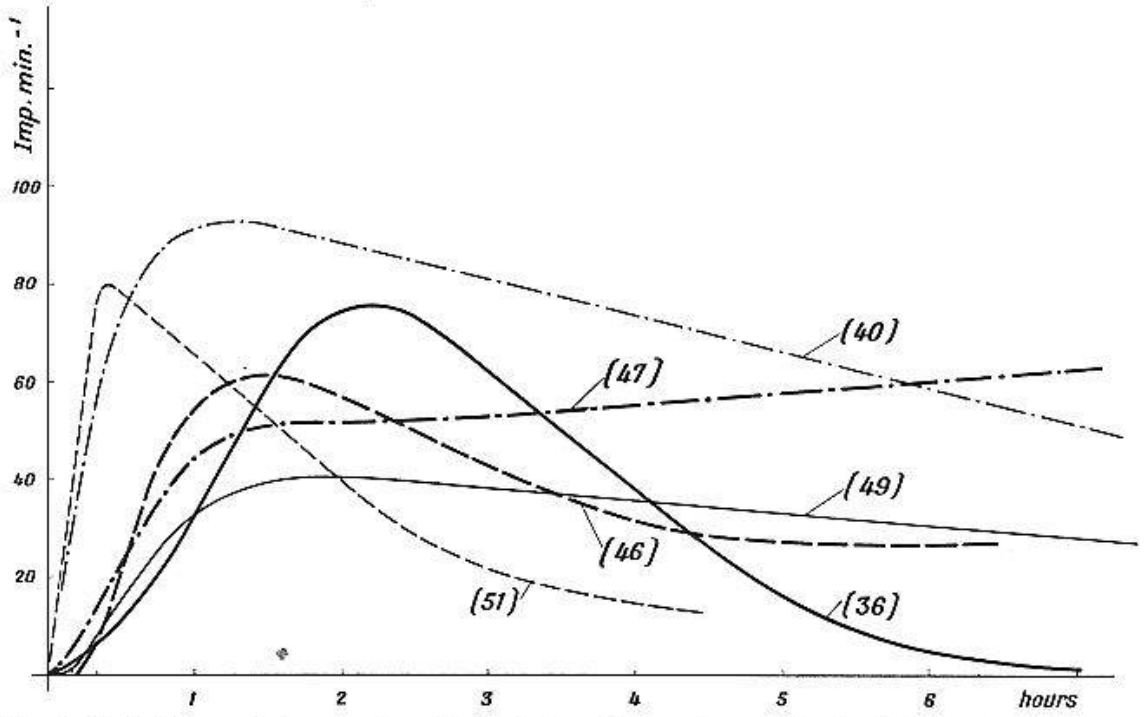

Fig. 1. Relative activity on the thigh of 6 patients after oral administration of 0.1 mC ^{131}I (counter equipped with cylindrical lead collimator).

measured on the thigh after oral administration in the morning on 6 fasting patients. When *clear initial conditions* must be obtained, as for the measurement of the uptake rate or for the clearance test, oral administration ought to be excluded and only the intravenous form should be accepted.

c) Hence, five to ten minutes after intravenous injection about 90% of the radioiodine has attained its equilibrium in the plasma and in the extracellular phase. The space occupied by the inorganic iodine in that phase is called "iodine space". Measurements of this space 30 minutes after injection were made by *Berson S. A.*, *Yalow R. S.*, *Sorrentino* and *Roswit B.* (2) and they found, as the mean value of 24 observations, $26 \pm 3\%$ of the total weight of human patients. This value is about the same as that of the "sodium space" determined by *Kaltreider* et al. (16) with ^{24}Na and thiocyanate. They found about 25% of body weight with both methods. Iodine and sodium, both extracellular elements at the beginning, fill nearly the same space in the same time immediately after injection.

Moreover, *Myant N. B.*, *Pochin E. E.* and *Goldie E.* (17) have shown experimentally on two normal and two thyrotoxic subjects that thyroid and kidneys remove radioiodine from the plasma at a rate proportional to the plasma concentration during the first hours after oral administration.This law is no longer valid later when thyroxine-like organic bound iodine appears in the plasma.

d) If we except the thyroid, it is not probable that iodine has another important cellular phase elsewhere in the organism. By performing necropsies on nine patients who received therapeutic doses of ^{131}I, *Trunnell J. B.* et al. (18) have shown that the specific activity of nearly all tissues (thyroid and cancer metastases excepted) is, on the average, lower than that of the blood. About fifty organs or tissues were examined. They found, for example, in mean relative values: blood 9.8, adrenal 8.3, ovary 6.9, kidney 4.7, liver 4.7, spleen 3.6, testes 3.3, muscle 2.2, posterior pituitary 1.6, anterior pituitary 0.4, etc. Only in one case, a patient who died two days after the administration of iodine, was the level of radioiodine higher in adrenal ($3\times$), in gall bladder ($2\times$), in spinal cord ($1.5\times$) than in blood.

In statistics of 13 euthyroids, 4 hypo- and 15 hyperfunctions, we have measured the maximum uptake of the ascension curve and the total urinary excretion after 4 days. The sum of these values was, to be sure, determined with a low precision of about 7%. But the mean value of the total for the 22 cases amounted to $95.7 \pm 2\%$. Hence no more than about 4% of the injected iodine disappears other than by urinary excretion or uptake in the thyroid. It is possible to show that after four days less than about 1% only is mixed with the plasmatic and extracellular inorganic iodine.

The conclusion is that we can consider, in a first approximation, the plasma and the intercellular phase for the inorganic iodine as a container in which the equilibrium of the densities is rapidly attained. Thus, it seems unnecessary to consider separately the double movement of inorganic iodine from the plasma to the tissues and vice versa.

Fig. 2 shows the relative activities on the thighs of seven patients after intravenous administration of 0.1 mC radioiodine. It is because they were dealing with an oral administration that *Tubiana M.* and *Sung S. S.* (19) assumed that the equilibrium is attained after 4 hours only. Here the maximum is always reached in less than one hour and 90% of the maximum in a lapse of time of no more than 10 minutes.

e) As we will see later, the total flow of iodine in organic, as in inorganic form from the thyroid to the plasma is very slow and reaches a few $^0/_{00}$ per hour of the total iodine contents of the gland. On the other hand, it is generally assumed that the thyroid does not take up the protein-bound iodine or the thyroxine from the plasma. As is shown by the papers of *Harsha W. N.* (20), *Horst W.* and *Rösler H.* (21) and *Rall J. E.* (22), it is only after four to ten days that the organic radioiodine reaches its maximum in the blood. The half-life of thyroxine is not unequivocally defined in the paper of *Benua R. S.*, *Albert A.*, and *Keating F. R.* (23),

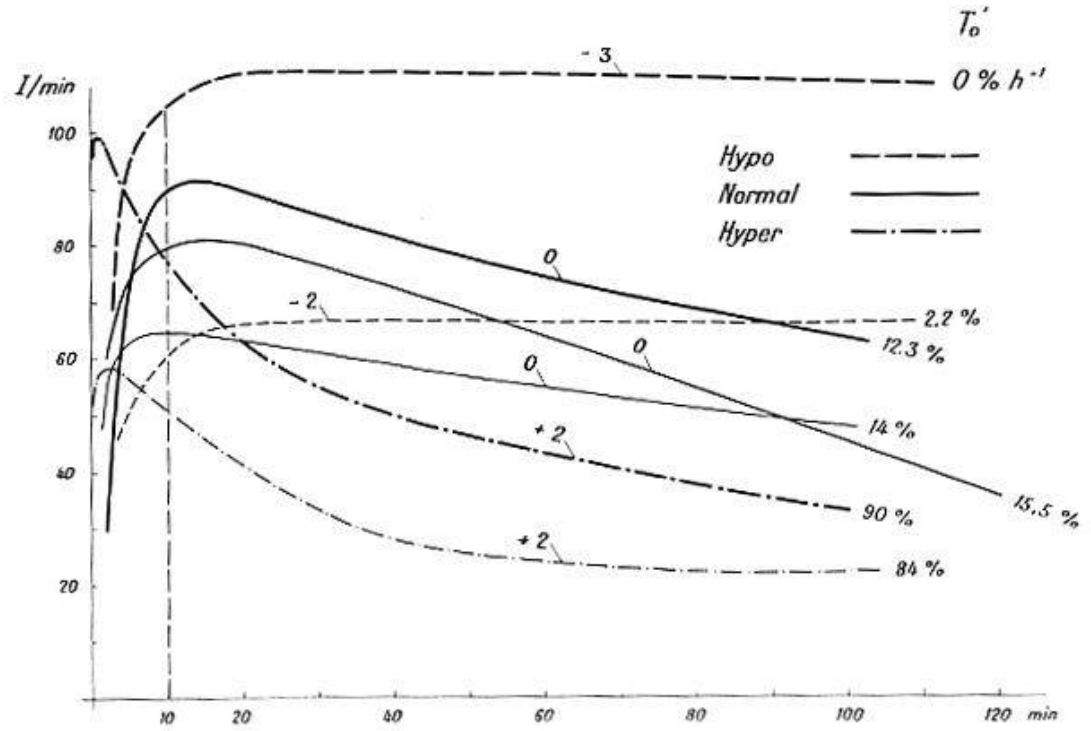

Fig. 2. Relative activity on the thigh of 7 patients after intravenous administration of 0.1 mC ^{131}I (counter equipped with cylindrical lead collimator). 0, +2, −2, etc. indicates the medical class of the function.

because they injected the man with a therapeutic and not with a tracer quantity. However, if we take their longer half-life and if, on the other hand, we take account of the curves of *Horst* et al. (21), we can assign to the thyroxine, which forms at least 90% of the protein-bound iodine (*Harsha W. N.* [20], *Horst* et al. [21], *Taurog A.*, *Chaikoff* and *Tong W.* [24]), a half-life of about 10 days. It is only in the case of a hyperfunction, that the half-life of thyroxine should be much shorter and the destruction products could be taken up again earlier by the thyroid or eliminated through the kidneys.

It has been shown by *Rall J. E.* (22) that the quantity of organic radioiodine excreted by the kidneys is very small and does not amount to more than 2% after three days in cases of hypofunction and normal function. Only in hyperthyroidism did the organic fraction (the Somogy precipitate) gradually attain up to 12 to 40% on the third day.

During the first days after administration in cases of euthyroid and hypofunction it is thus plausible to admit that the principal phenomena of renal excretion and thyroid uptake occur in the inorganic phase, and the organic phase for the two clearances may be disregarded in a first approximation.

f) It is clear that the quantity of radioisotope which flows per time unit from the plasma to the thyroid and from the plasma through the kidneys is proportional to the density of the isotope in the plasma. *Myant N. B.*, *Pochin E. E.*, and *Goldie E.* (25) have checked this asser-

tion on two normal and two thyrotoxic subjects. The law is valid for normal subjects between 1 and 6 hours, for thyrotoxic subjects between 0.5 and 3 hours after oral administration. For this, it is not necessary that the radioactive densities throughout the plasma and extracellular phase be constant, but only that a state of equilibrium be attained.

The assumption, which is always made in theoretical considerations, that the two flows of inorganic radioiodine from the plasma to the thyroid and the plasma through the kidneys are proportional to the whole iodine of the iodine space, is also entirely justified as long as the equilibrium time in the iodine space is short in proportion to the uptake rate by the thyroid or the excretion rate through the kidneys.

Another necessary assumption, which was made first by *Oddie T. H.* (4) and *Oddie T. H.* and *Kaye Scott R.* (5), and in another form recently by *Tubiana M.* and *Sung S. S.* (19), is that the fractions of organic or inorganic radioiodine leaving the thyroid for the plasma are both proportional to the whole contents of the thyroid in organic or inorganic radioiodine respectively. We, too, will employ a similar assumption, knowing very well that it is necessary but not at all evident. With excellent autoradiographs *Leblond C. P.* and *Gross J.* (26) have shown on rats how the flow of radioiodine from the outer margin of the colloid to the interior of the latter is rather slow. It takes about one day for the radioactivity to move uniformly through the colloid. We are no longer entitled to speak of a short equilibrium time as we do in the plasmatic and extracellular phase.

However, we will make in the following the necessary assumption that the flow of organic and inorganic radioiodine from the thyroid to the plasma is proportional to the whole activity of the gland, without understanding clearly what it means microscopically. This assumption is supported by the experiment of *Taurog* and *Chaikoff* (27) who have shown that, as early as 15 minutes after the injection of ^{131}I, 95% of the radioactivity present in the thyroid is organically bound.

3. *A three-parameter theory of the radioiodine test dynamics*

Let us first define the symbols:

S Whole activity of blood and extracellular liquid at any time (whole activity of iodine space).

S_0 Initial activity of the injected inorganic iodine ($S_0 = 1$ or 100%).

T Total activity of the thyroid at any time (organic and inorganic phase).

U Activity of the whole renal excretion of inorganic iodine from time 0 up to time t.

a Uptake rate parameter of the *inorganic iodine* of the iodine space through the thyroid.

η Excretion rate parameter of the *inorganic iodine* from the iodine space through the kidneys.

λ Flow rate parameter of the *organic and inorganic iodine* from the thyroid to the plasma.

We have now to consider the following flows of radioiodine at the time t during dt. These flows are given diagrammatically in fig. 3. Unlike *Rotblat* et al. (6), therefore, we do not consider the two movements from and to the tissues.

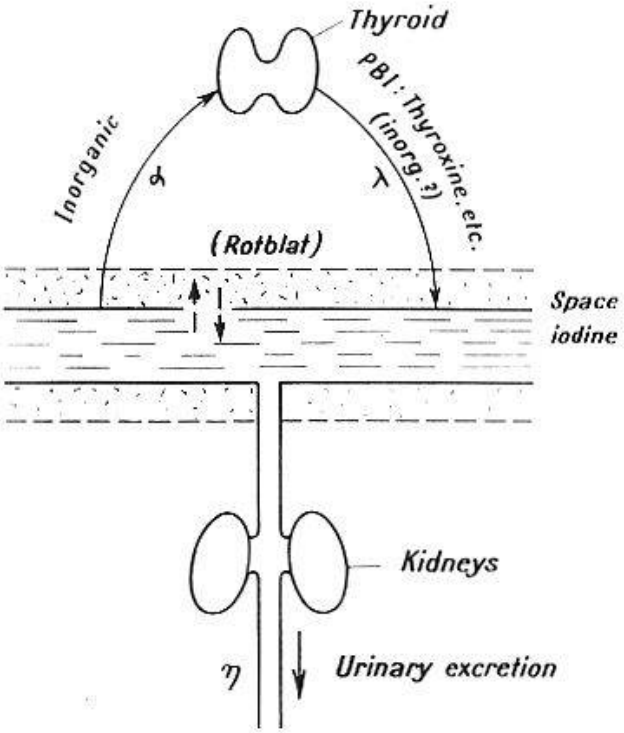

Fig. 3. Diagram of the three principal flows of iodine in the organism after injection into the blood (in the centre the two flows to and from the tissues were considered by *Rotblat* and *Marcus* [6]).

Flow of inorganic radioiodine from the plasma to the thyroid during dt $\quad aSdt$

Flow of inorganic radioiodine from the plasma through the kidneys during dt $\quad \eta Sdt$

Whole flow of *organic and inorganic radioiodine* from the thyroid to the plasma $\quad \lambda Tdt$

Hence we are considering these three movements only and we are disregarding the destruction of the thyroxine-like or protein-bound radioiodine of the third flow. We have seen that the destruction takes place much later than the first few days. We assume, too, that the organic phase of the third flow $\lambda T dt$ is negligible in regard to the first two inorganic movements and does not affect them. We will see later that these assumptions are correct for hypo- and normal functions during the first days, but only partially correct for hyperthyroidism.

It is possible then to write directly the following differential equations:

(1) $dT = \alpha S dt - \lambda T dt$ (Thyroid)

(2) $dS = -\alpha S dt + \lambda T dt - \eta S dt$ (Iodine space)

(3) $dU = \eta S dt$ (Urine)

and

(4) $S_0 = T + S + U = \text{Constant.}$

The radioiodine of the cellular extrathyroidal phase is disregarded in these equations. The first equation may be written*

(5) $$S = \frac{1}{\alpha}\left[\frac{dT}{dt} + \lambda T\right]$$

and after derivation

(6) $$\frac{dS}{dt} = \frac{1}{\alpha}\left[\frac{d^2T}{dt^2} + \lambda \frac{dT}{dt}\right]$$

If we introduce S and $\frac{dS}{dt}$ in the second equation, we obtain

$$\frac{1}{\alpha}\left[\frac{d^2T}{dt^2} + \lambda \frac{dT}{dt}\right] = -\frac{\alpha+\eta}{\alpha}\left[\frac{dT}{dt} + \lambda T\right] + \lambda T$$

or

$$\frac{d^2T}{dt^2} + (\alpha + \eta + \lambda)\frac{dT}{dt} + \eta\lambda T = 0$$

hence, a linear equation with constant coefficients:

$$T = C\left[e^{-(a-b)t} - e^{-(a+b)t}\right]$$

with

(7) $$\boxed{\begin{aligned} 2a &= \alpha + \eta + \lambda \\ b &= \sqrt{a^2 - \eta\lambda} \end{aligned}}$$

* Mrs. *C. Trümpy*, at the request of one of us (*G. J.*) found a first solution of these equations.

and the limit conditions

$$t = 0 \qquad T = 0,$$
$$t = 0 \qquad S = S_0$$

the second of which assumed an immediate equilibrium after injection in the extracellular phase. This assumption is thus only approximately realized with intravenous injection and not at all with oral administration.

For the blood, we obtain immediately through (5):

$$S = \frac{C}{a}\left|(a+b-\lambda)\,e^{-(a+b)t} - (a-b-\lambda)\,e^{-(a-b)t}\right|$$

and with the initial condition $S = S_0$,

$$C = \frac{a S_0}{2b}$$

By integration of equation (3) we obtain the urinary excretion

$$U = \eta \int_0^t S dt = \frac{\eta S_0}{2b}\left\{\frac{2b}{\eta} - \frac{a+b-\lambda}{a+b}e^{-(a+b)t} + \frac{a-b-\lambda}{a-b}e^{-(a-b)t}\right\}$$

U equals S_0 for $t = \infty$.

The three functions sought are thus exactly:

Activity of the thyroid:

(8) $$\boxed{T = \frac{a S_0}{2b}\left|e^{-(a-b)t} - e^{-(a+b)t}\right|}$$

Activity of the whole blood and extracellular liquid (iodine space):

(9) $$\boxed{S = \frac{S_0}{2b}\left|(a+b-\lambda)\,e^{-(a+b)t} - (a-b-\lambda)\,e^{-(a-b)t}\right.}$$

Activity of the total urinary excretion up to the time t:

(10) $$\boxed{U = \frac{\eta S_0}{2b}\left|\frac{2b}{\eta} - \frac{a+b-\lambda}{a+b}e^{-(a+b)t} + \frac{a-b-\lambda}{a-b}e^{-(a-b)t}\right|}$$

It can be verified that the relationship

(4) $$T + S + U = S_0$$

is always observed.

4. *Characteristics of the functions* T, S, and U. *Values of the parameters* α, η *and* λ

Thyroid function T

The *maximum* T_m of the function T has the expression

$$T_m = \frac{\alpha S_0}{\sqrt{\eta\lambda}} \left(\frac{a-b}{a+b}\right)^{\frac{\alpha}{2b}}$$

and is thus a complicated function of α, η and λ. *The maximum of the uptake curve depends on the three movements: uptake rate, urinary excretion rate and flow rate from the thyroid. Hence, it has no simple significance at all in the dynamics of radioiodine, and ought not to have any direct importance for the diagnosis of the biological function.*

But it is interesting to see that the *initial slope* of the uptake curve

$$\left|\frac{dT}{dt}\right|_0 = T_0'$$

is

$$\boxed{T_0' = \alpha S_0}$$

If we agree to take $S_0 = 1$ or $S_0 = 100\%$ (relative activity of the injection measured with the same geometry and diffusion as that of the thyroid), *the initial slope of the uptake curve is equal to the uptake rate* α *of the inorganic iodine of the plasma through the thyroid.* Hence, this initial slope has, physically, a clear significance. α may be expressed in % per hour of S_0.

Considering equation (7) we see that, in semi-logarithmic coordinates, the uptake curve T appears as the difference of two exponential functions, i.e. of two straight lines (fig. 4). This fact may be actually verified on nearly all uptake curves. The coefficient $(a—b)$ is determined by the slight slope of the curve after the maximum between the second and the following 4 to 7 days after the injection. The coefficient $(a+b)$ is determined by the second exponential, i.e. by the difference between the first exponential and the uptake curve. This second exponential corresponds to a short half-life of about one to five hours and is nearly the same as the exponential given by *Myant N. B.* (10), *Myant N. B.* and al. (11) in their clearance definition, if the first exponential is disregarded. $(a+b)$ and $(a—b)$ are independent of the calibrating of S_0; but $\frac{\alpha}{2b}$, which

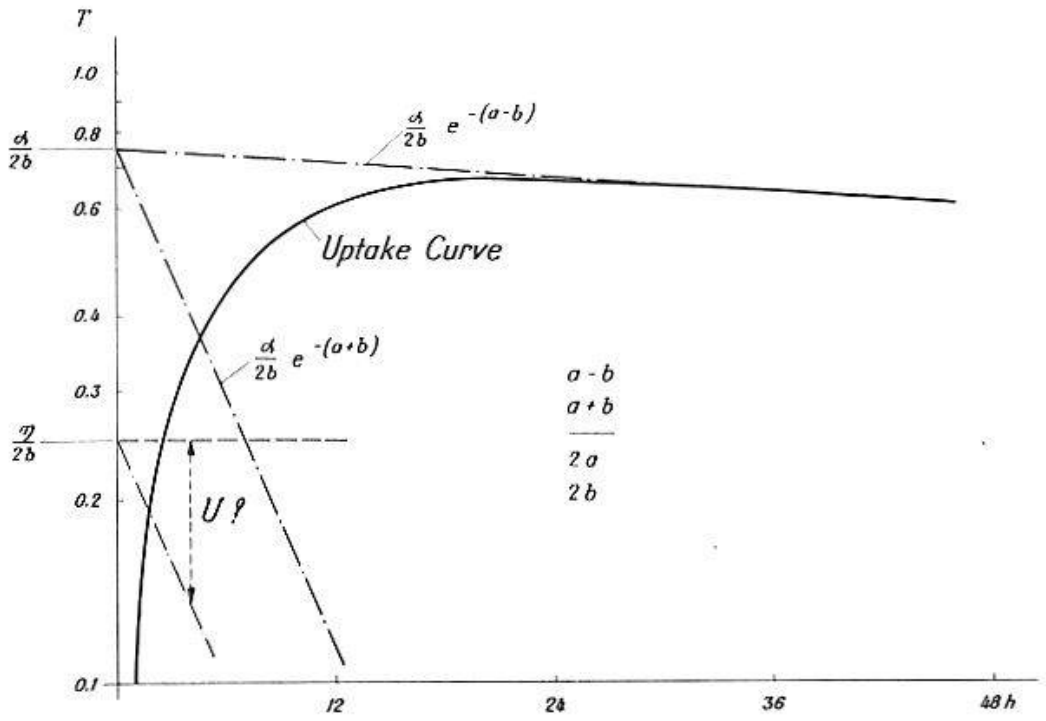

Fig. 4. According to this theory, the uptake curve in semi-logarithmic coordinates is the difference of two exponentials (straight lines) $\frac{a}{2b}e-(a-b)$ and $\frac{a}{2b}e-(a+b)$ the slope of which gives a and b.

is also determined by the uptake curve, depends on the calibrating. a, b and $\frac{a}{2b}$ are hence given by the uptake curve and a may be calculated immediately. The correspondence between a and the initial slope T_0' for 58 cases enables the correctness of the theory to be assessed to a certain extent. (See Table 1).

The third column of the Table gives in % the difference $\frac{T_0'-a}{a}$; the mean value of that difference in 58 cases amounts to 14.2%.

As the accuracy of the uptake curve's initial tangent, determined by the first experimental points, is no better than 10 to 15% on the one hand and as the initial condition $S = S_0$ for $t = 0$ is only approximately realised on the other hand, the correspondence between a and T_0' must be considered as satisfactory. a, which corresponds to the whole uptake curve, must be more accurate than T_0'. The very good correlation between T_0' and a (coefficient + 0.988) must be stressed.

From equations (3) and (9) we see that *the urinary excretion rate* η *is given by the initial slope* U_0' *of the tangent to the excretion curve* U, *when we agree to take* $S_0 = 1$.

$$\boxed{U_0' = \eta S_0}$$

Table 1

Comparison between theoretical and experimental parameters

Uptake rate parameters % S_0 per hour			Excretion rate parameters % S_0 per hour		
a by the whole uptake	T'_0 initial slope	$\frac{T'_0-a}{a}100$ Deviation	By the whole uptake curve	U'_0 by the excretion curve	$\frac{U'_0-\eta}{\eta}100$ Deviation
7.6	10.0	+24	9.8	5.5	− 45
3.3	2.8	−15.2	11.5	19	+ 65
3.7	3.5	− 5.4	19.7	10.0	− 49
32.5	29	−11	4.8	22	+358
46.2	50	+ 8.2	11.1	17	+ 53
12.5	11.0	−12.8	14.4	9.5	− 34
35.6	38	+ 6.7	10.0	18	+ 80
6.1	6.0	− 1.6	13.0	20.5	+ 58
11.2	12.3	+ 9.8	15.5	24	+ 55
16.7	15.5	−72	5.0	17.5	+250
10.2	13.0	+27	13.0	18	+ 38.5
12.4	14.0	+12.9	6.7	8.5	+ 27
39.5	32	−19	6.6	20	+230
8.7	6.4	−26	8.0	9.0	+ 12.5
68.0	90	+32	7.4	14	+ 88
18.4	18	− 2.2	4.9	4.5	− 8.2
14.4	13.5	− 6.3	97	19	− 80
54	43	−20	6.7	12.5	+ 86.6
68	67	− 1.2	15	10.0	− 33
320	260	−18.8	7.5	12.0	+ 60
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.
Mean value of the absolute deviation of 58 cases		±14.2%	Mean value of the absolute deviation of 29 cases		±69.7%
Correlation coefficient		+0.988	Correlation coefficient		+0.158

The only method of determining the initial slope U'_0 in practice accurately is probably by the introduction of catheters in the ureters and, as *Rotblat J.* and *Marcus R.* (6) did, by the taking of many samples of urine during the first two hours. As we could not apply this method, we contented ourselves with taking two samples, without catheter, from the patient at about 40 and 80 minutes which gave us two points U_1 and U_2. Through these two points and the origin we drew the urinary excretion curve and, approximately, the latter's initial tangent U'_0.

The corresponding theoretical value η of U'_0 was determined simultaneously with the rate of the thyroid flow λ by the uptake curve, as follows:

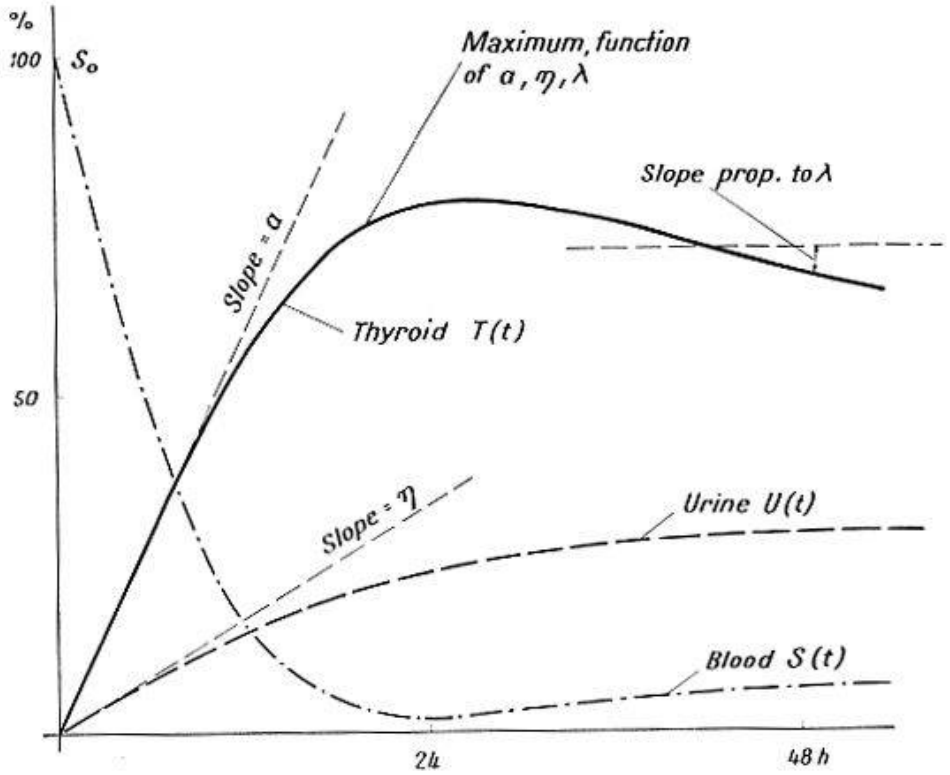

Fig. 5. Significance of the three parameters α, η, and λ. $-\alpha$ = initial slope of the uptake curve T (t) of the thyroid. η = initial slope of the urinary excretion curve U (t). λ, proportional to the slope of the uptake curve after the maximum. S (t), iodine space activity.

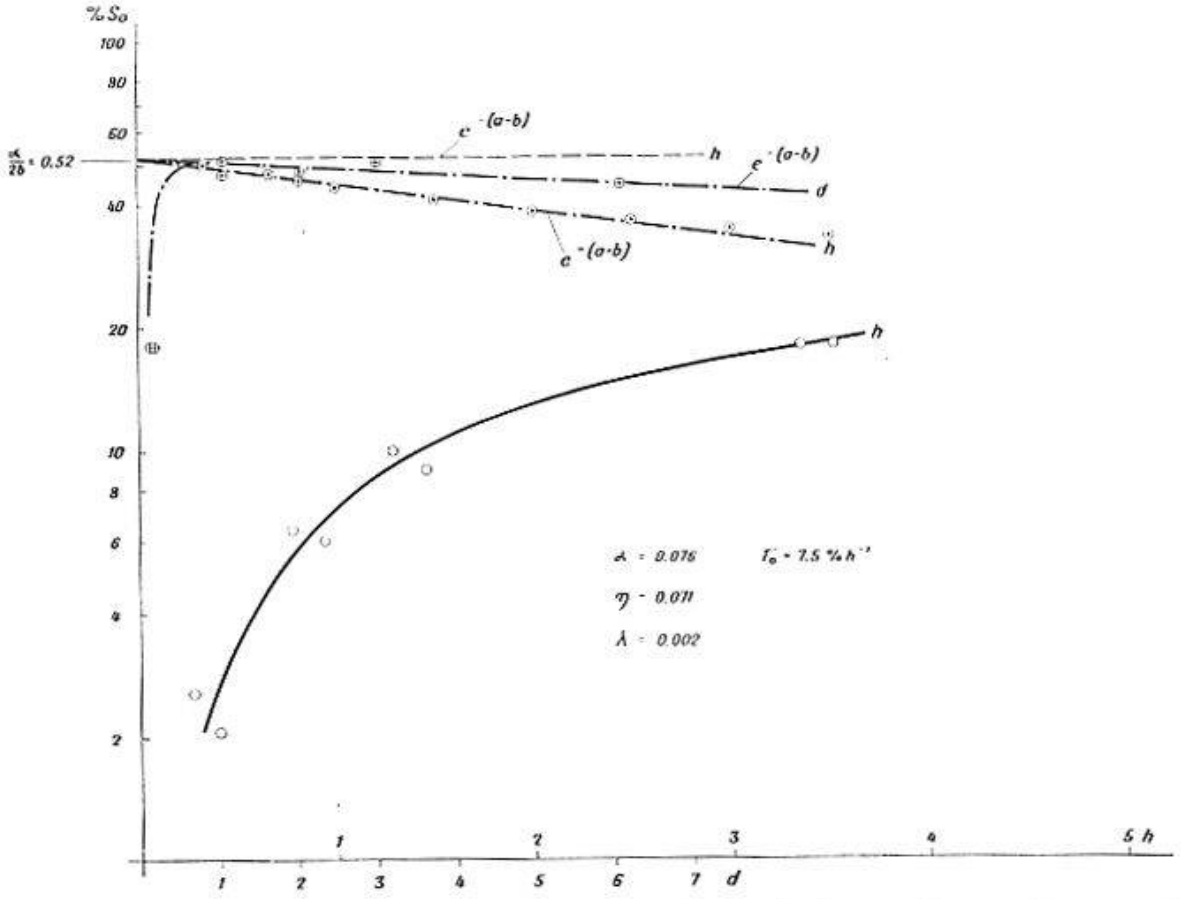

Fig. 6. Uptake curve of a normal function in semi-logarithmic coordinates. Decomposition into two straight lines and calculation of the coefficients (abscissæ in days [d] or hours [h]).

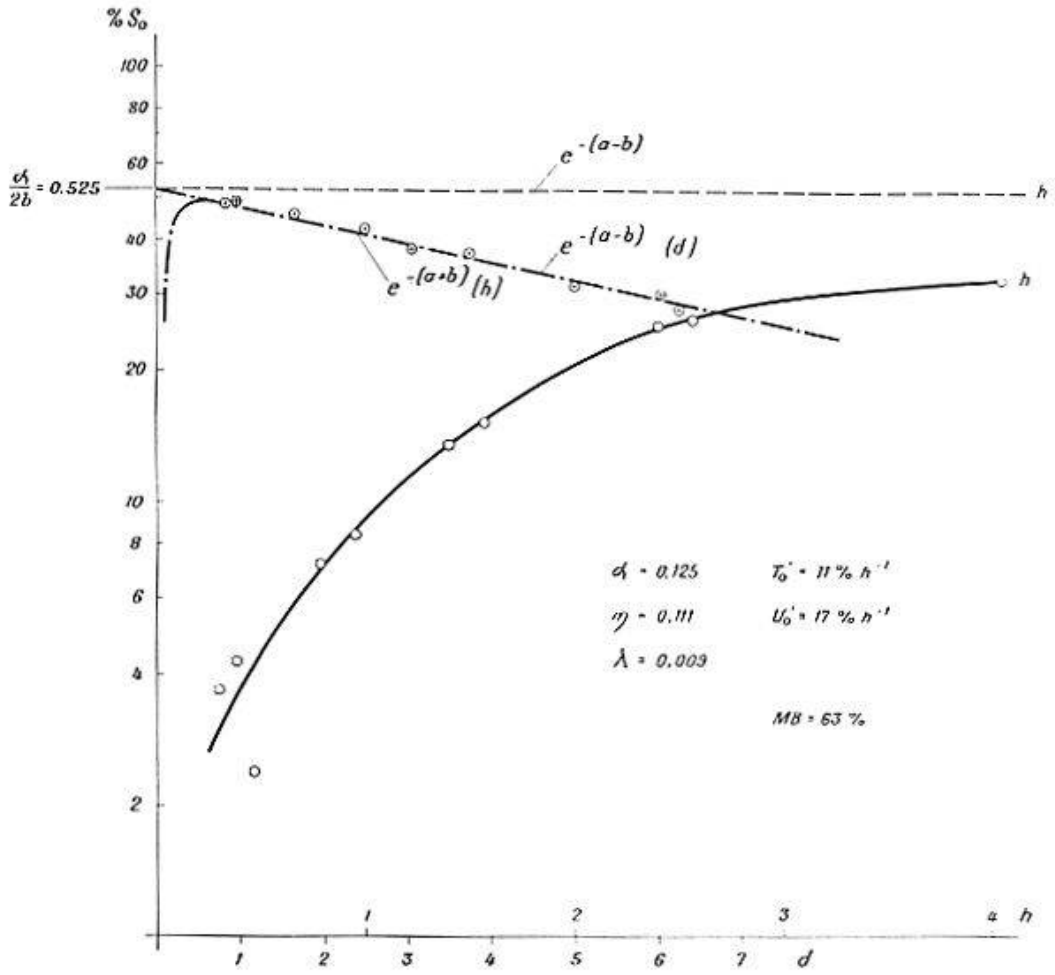

Fig. 7. Uptake curve of a normal function in semi-logarithmic coordinates. Decomposition into two straight lines and calculation of the coefficients (abscissæ in days [*d*] or hours [*h*]). The high basal metabolic rate is caused here by a cardiac insufficiency.

Having determined a, b, and α, as indicated above, we have from equation (7)

$$\lambda = \frac{(a+b)(a-b)}{\eta}$$

η and λ are determined simultaneously with this relationship and the condition $2a = \alpha+\eta+\lambda$.

By means of the uptake curve it is also possible to determine the three coefficients which describe, by means of three principal flows, the whole thyroid function. It must be said that in practice, the use of semi-logarithmic paper shows that the whole method is much simpler than it appears from the above mathematical explanations. Fig. 6 to 9 show the application of the method to four cases: two normal, one hypofunction and one hyperfunction.

It is now important to compare the experimental value U_0' of the initial urinary excretion and η as calculated by the uptake curve. The comparison is made in the table on page 95. We see that in some cases

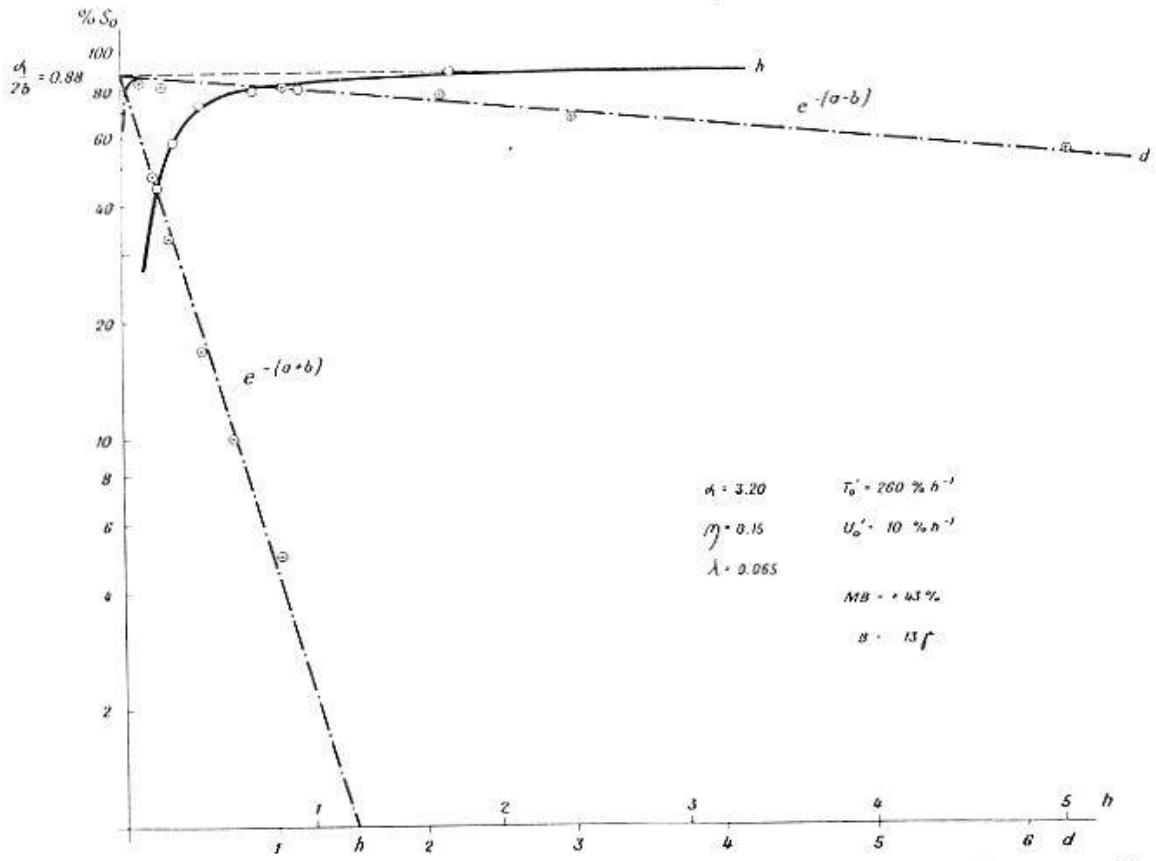

Fig. 8. Uptake curve of a hyperfunction in semi-logarithmic coordinates. Decomposition into two straight lines and calculation of the coefficients (abscissæ in days [d] or hours [h]).

U_0' and η are not very different, but that in others the differences are very great. The mean value of the absolute deviation amounts to $\pm 70\%$ and the correlation coefficient to $+ 0.16$. The correspondence is very poor. The uptake curve does not enable the initial urinary excretion rate to be foreseen. This discordance may have many explanations: on the one hand U_0' is badly defined, on the other hand the excretion rate is probably not constant for one individual and may be influenced by a great number of psychic and physiological factors. U_0' probably gives a momentary and η a mean value*.

But the best foundation for this three-parameter theory is that the uptake curve may be represented, according to equation (8) of T, as

* Assuming that λ (the thyroidal flow) may be disregarded during the first hour, the total urinary excretion (10) may be written

$$U \simeq \frac{\eta S_0}{2b}\left[1 - e^{-(a+b)t}\right].$$

In semi-logarithmic coordinates U, in the initial region, ought to appear as the difference between a horizontal line and the straight line $e^{-(a+b)t}$, the slope of which has been given above by the decomposition of the uptake curve (see fig. 4).

But it must be said—probably owing to imperfect taking of the urine samples—that only in some cases did the values U_1 and U_2 verify this analytical form.

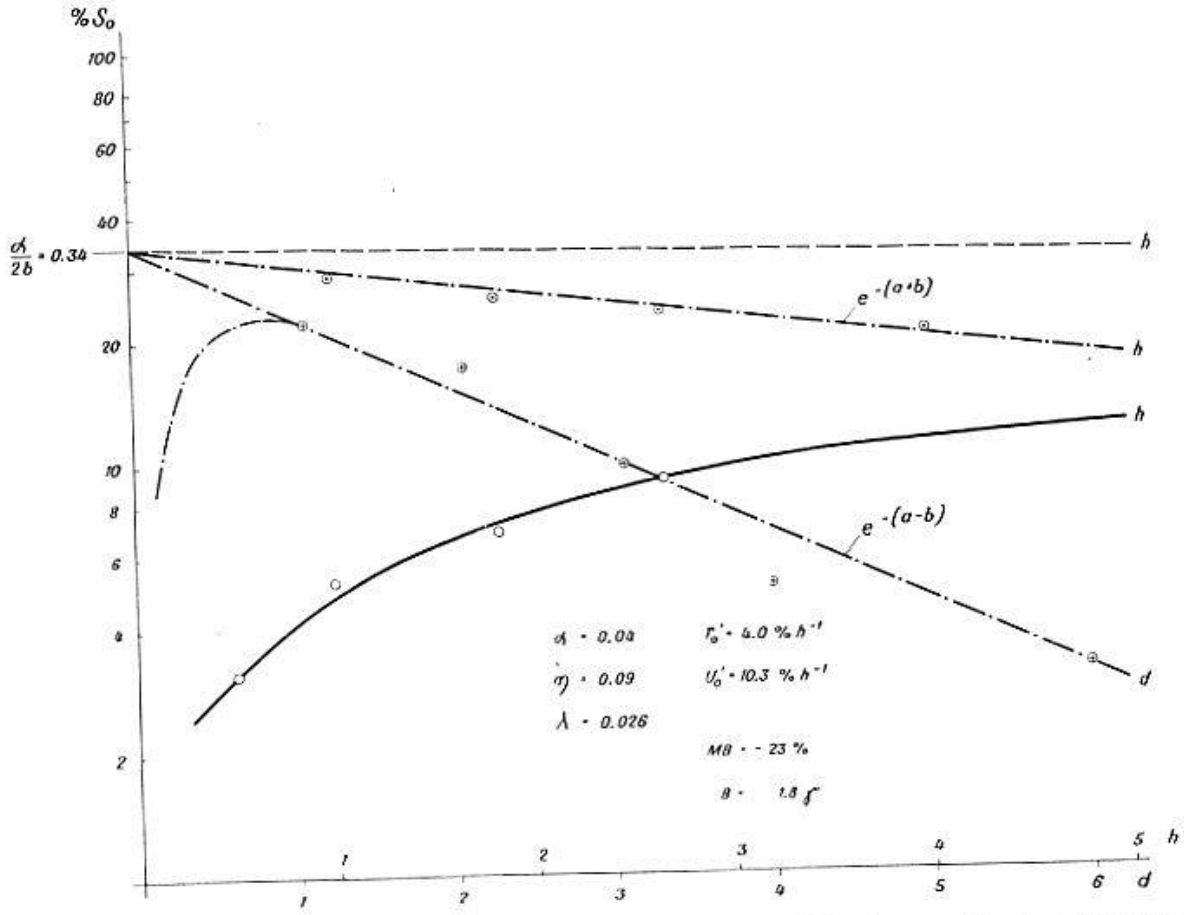

Fig. 9. Uptake curve of a hypofunction in semi-logarithmic coordinates. Decomposition into two straight lines and calculation of the coefficients (abscissae in days [d] or hours [h]).

the difference of two exponential functions. Out of 60 cases which were observed for 4 to 8 days, in 49 the representation was very good (differences less than 5%), in 7 it was fair (differences 5 to 10%) and only in 4 was it very bad. These 4 bad cases were two thyrotoxicoses treated with propylthiouracil or thiomidil, a very strong Morbus Basedow and a strong hypothyreosis. The 7 cases with differences of from 5 to 10% are all thyrotoxicoses. But the first group also contains 7 cases of hyperthyroidism in which the experimental points fit very well with the two exponentials. Hence it is surprising to see that the theory is practically as suitable for hyperfunction.

The other basis of the theory is the very good correspondence between a and the initial slope of the uptake curve.

5. *The biological and pathological significance of the three parameters*

After intravenous injection of ^{131}I this theory was applied to 85 cases of normal and pathological thyroid functions.

T_0'	was determined in all cases, i.e.	85
U_0'	was determined in	35 cases
T_{max}	was determined in	60 cases
λ	was determined in	57 cases.

The patients came from the Medical Clinic (Prof. *Loeffler*), the Neumünster Hospital (Prof. *F. Koller*), and the Radiotherapeutic Clinic (Prof. *H. R. Schinz*). In every case the physician* had to determine the *intensity of the function* from the clinical point of view only, at the moment when the tracer was made. This determination was made with general medical observations, pulse, basal metabolic rate, etc., and in some cases with the analysis of the total organic iodine (Barker) of the plasma. For the following statistics the patients were therefore divided into seven classes according to the clinical intensity of their function:

Table 2

Intensity of the function		Class
Hypofunction	very strong	−3
	medium	−2
	weak	−1
Euthyroid (normal)		0
Thyrotoxicosis (hyperfunction)	weak	+1
	medium	+2
	very strong	+3

This careful evaluation was done in the clinics and separately from the laboratory determinations. In some cases, when the clinician hesitated between two classes, he wrote 2 to 3 (2.5) or −2 to −1 (−1.5). In every case special attention was paid to finding out if the basal metabolic rate was determinant for the thyroid function or if it could be explained by other medical reasons.

a) The biological significance of the maximum uptake T_{max}.

Out of the total of 85 cases, the maximum of the uptake curve was determined on 60 patients who were observed for 4 to 8 days. 3 cases are excluded from the statistics: 2 received "Iodobil" or "Ioduron" as X-rays contrast medium and one was an alcoholic with cirrhotic liver. The results are given in fig. 10. It will be seen that it is a *general tendency for the maximum uptake to increase with the intensity of the function.* In particular, the few cases of hypofunctions are nearly always lower than the normal and hyperfunction cases. But the normal range is very ex-

* Grateful acknowledgement is made to Prof. *F. Koller*, Dr. *L. Morandi*, Dr. *Oppikofer*, Dr. *Goehre*, Dr. *Siegenthaler*, and many others who applied the clinical methods to determine the intensity of the function of their patients.

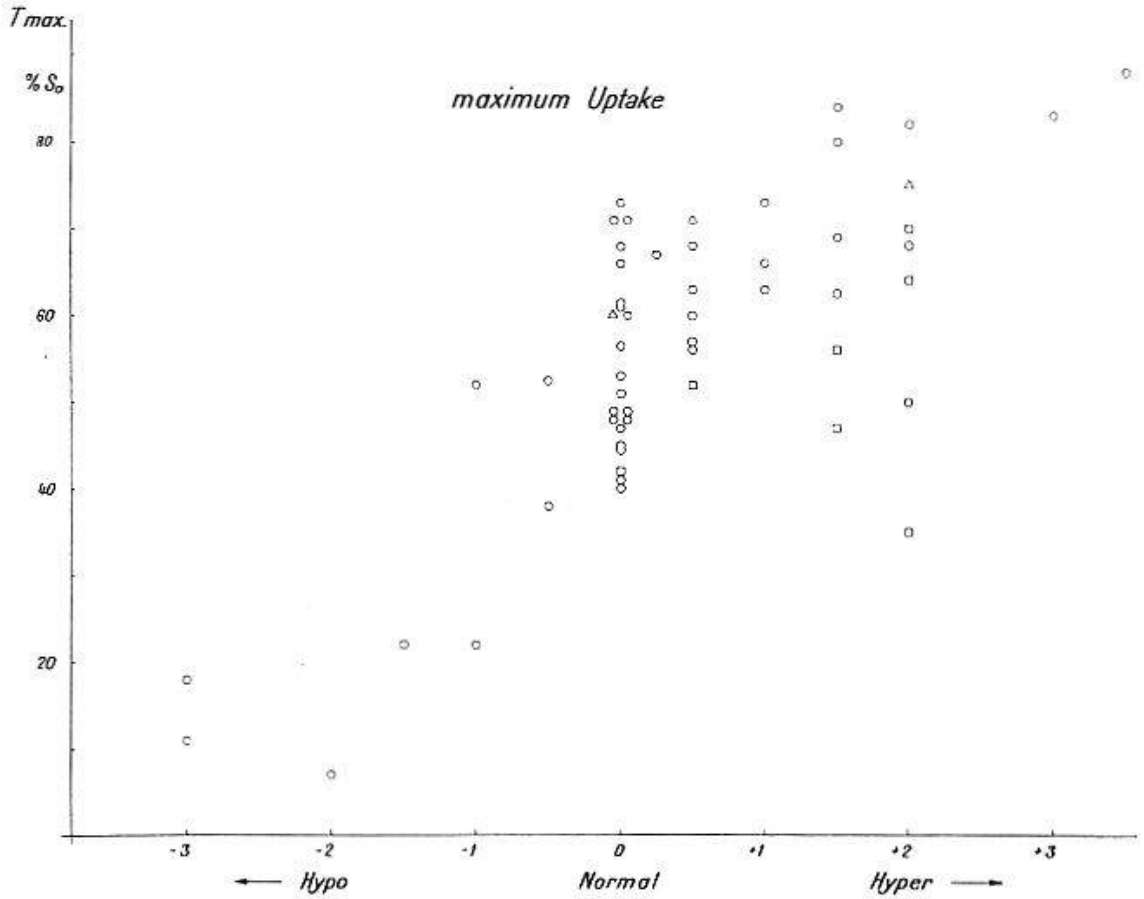

Fig. 10. Distribution diagram of the maximum uptake T_{max} in 57 patients. Abscissa: class of the function.

tensive and stretches from 40 to 75%; many (about two thirds) of the hyperfunction cases are situated within these limits. It is thus not possible with the maximum uptake to make the distinction between normal function and hyperfunction. Hence, our results confirm those obtained by *Oddie T. H.* and *Scott R. K.* (5), *Berson* et al. (2) and many other authors.

b) The biological significance of the initial urinary excretion rate U_0'.

Out of the total of 85 cases, the initial urinary excretion rate U_0' was determined with two samples of urine taken about 40 and 80 minutes after injection on 38 patients. One patient who had received "Iodobil" earlier is excluded from the statistics. In four cases the intravenous injection did not succeed and was effected partially or totally outside the vein. Fig. 11 gives the statistical results. It is immediately clear that the initial rate—in the conditions of our measurements—has no biological significance at all. The range of the normal function is much extended and contains all the other values. It was thus not necessary to pursue the investigation in that direction. *Hence, the initial urinary excretion rate is independent of the intensity of the thyroid function.*

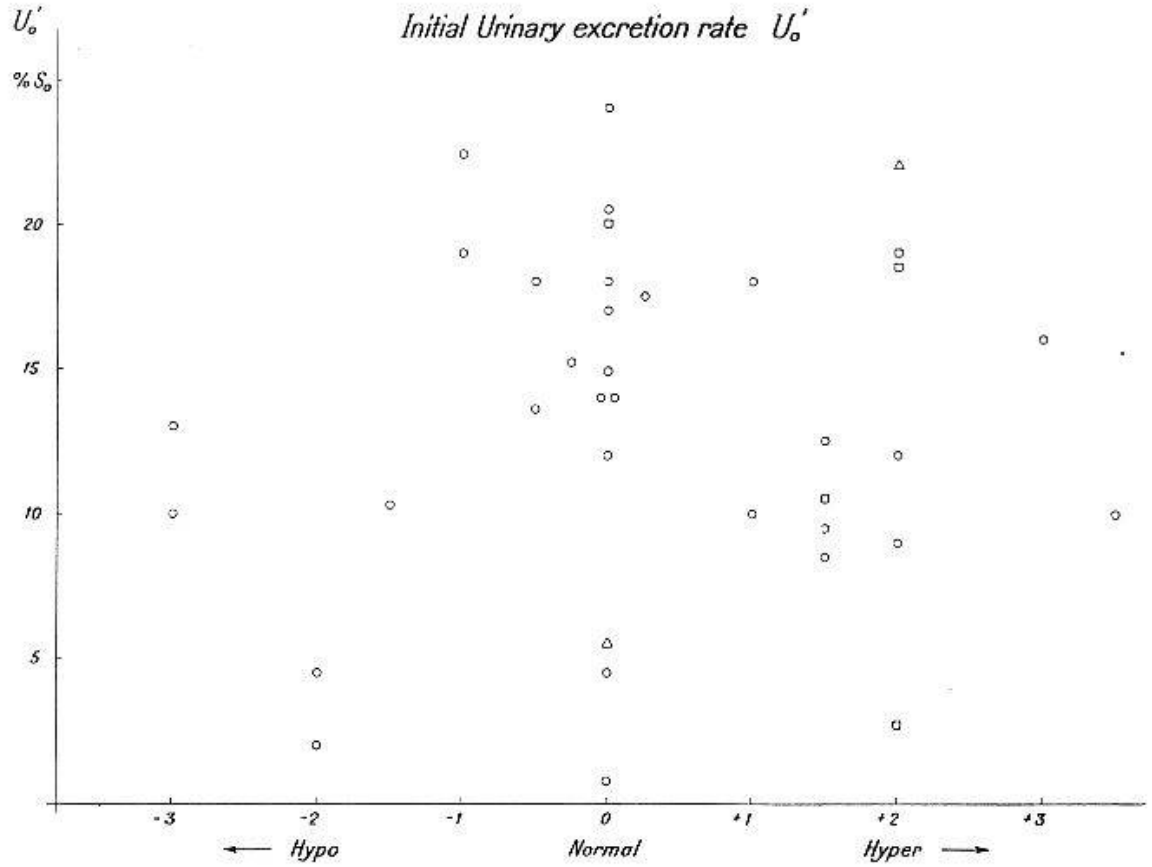

Fig. 11. Distribution diagram of the initial urinary rate U_0' in 37 patients. Abscissa: class of the function.

If we consider the *total urinary excretion* which is nearly completed after 3 or 4 days, we must remember that its value is about equal to $(100—T_{max})$. This total excretion might have a slight significance, the same as T_{max} for the hypofunction, but it could not be applied for the diagnosis of hyperfunction.

Confirming these results, *Berson S. A.*, *Jalow R. S.*, *Sorrentino J.*, and *Roswit B.* (2) have shown that the *initial renal clearance* measured during the first 35 minutes after intravenous injection is without significance for the diagnosis of the function.

c) The biological significance of the uptake rate α or the initial slope T_0'.

As we have already shown that there is no appreciable difference between the theoretical value α and the experimental one T_0', we are only considering here the statistical results of the initial uptake rate T_0'.

T_0' was determined after intravenous injection by the whole thyroid uptake curve or that curve recorded during the first 2 or 3 hours only, for all the 85 patients examined. In 7 cases the injection was partially or totally subcutaneous. 5 cases are excluded from the statistics and will be considered separately below. The results of the 80 cases are given graphically in fig. 12.

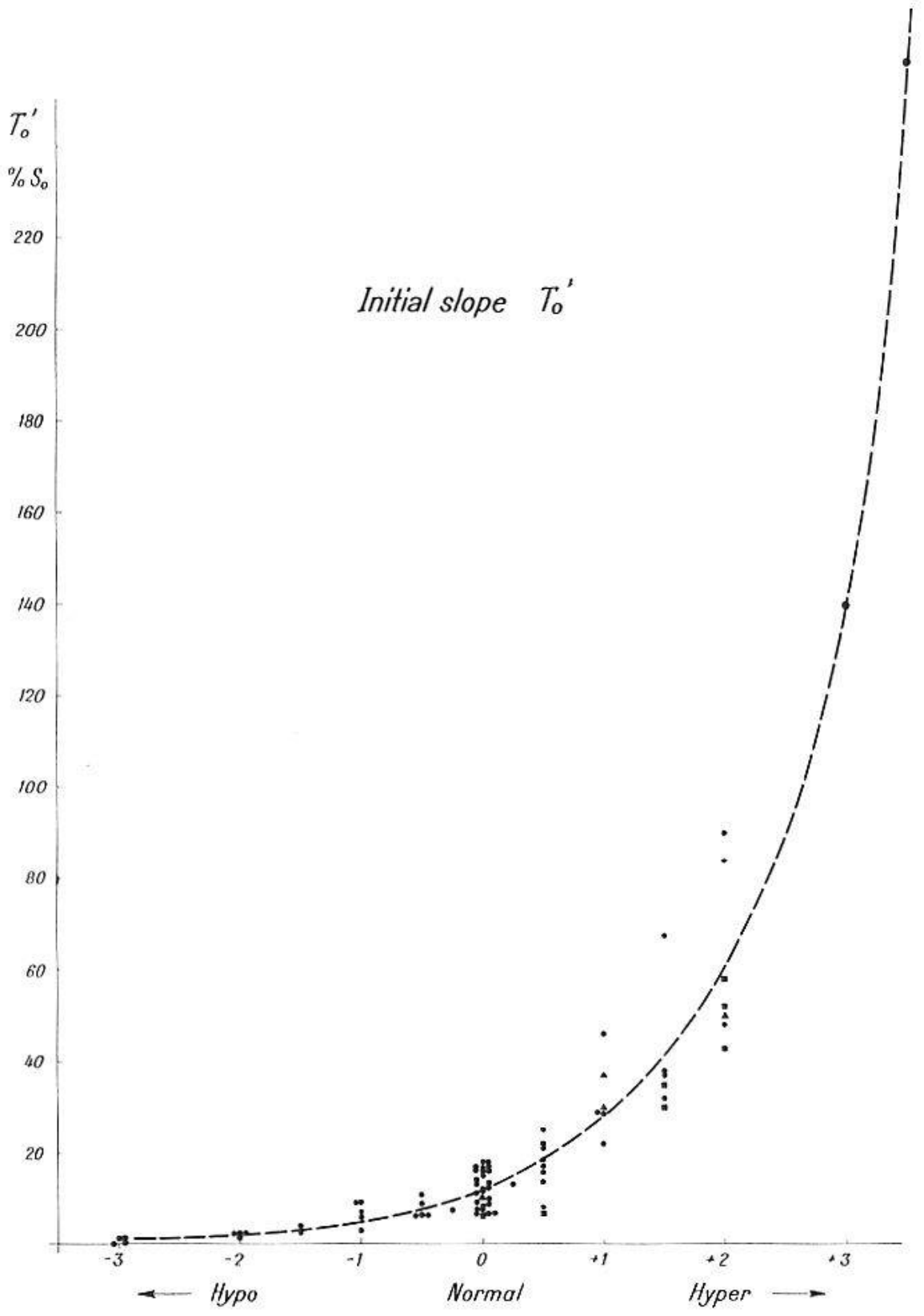

Fig. 12. Distribution diagram of the initial slope T_0' of the uptake curve in 80 patients. Abscissa: class of the function. ■ treated with antithyroidal drugs, ▲ treated with pituitary extracts.

The most striking result is first *the considerable variation of the initial uptake rate* T_0' in the normal and pathological range. From the very strong hypofunction (myxœdema) to the very strong thyrotoxicosis, the initial rate varies from a few $^0/_{00}$ to more than 200% S_0 per hour. We have here a variable which is much more sensitive and extended than the other parameters considered hitherto. The second very important observation is that T_0' permits a complete separation of the normal and pathological cases on the one hand and, on the other, is able to give the *intensity* of the pathological deviation. It is surprising how well the experimental points are placed on the same mean curve, the deviation being no more than $\pm$ half an intensity class.

If we admit that the normal functions correspond to the classes —0.5 to +0.5, the *normal* range for T_0' goes from 7 to 18% S_0 per hour. The *hyperfunction* (classes 1 to 3) is characterized by a T_0' ranging from 23 to more than 200% S_0 per hour (there is one case with $T_0' = 260\%$ h^{-1}). The *hypofunction* (classes —1 to —3) is characterized by a T_0' ranging from 5% S_0 per hour to a few $^0/_{00}$. 5 to 7 and 18 to 23% h^{-1} are intermediary and uncertain functions at the confines of the normal range.

11 cases of patients who were treated with extracts of pituitary or antithyroidal drugs are included in these statistics. For these cases, too, T_0' gives correctly the intensity of the thyroid function during the treatment.

In conclusion, the initial tangent T_0' *of the uptake curve or the uptake rate* a *is perfectly able to give a clear distinction of the normal and pathological functions and the actual intensity of the thyroidal function.*

Table 3

Intensity of the function		Class	Uptake rate T_0' % S_0 per hour
Hypofunction	very strong	—3	0 to 1
	medium	—2	1 to 3
	weak	—1	3 to 5
Normal		0	7 to 18
Thyrotoxicosis (hyperfunction)	weak	1	23 to 40
	medium	2	40 to 90
	very strong	3	90 and over

The values of λ_T of *Rotblat J.* and *Marcus R.* (6), which we have already noted and the definition of which coincides with that of a, tally very well with ours for the normal and pathological functions.

The aberrant cases which are not included in the statistics are the following:

Table 4

Clinical diagnosis	Medical class	T_0' in % $S_0 h^{-1}$	Reason for aberration
Liver cirrhotic, alcoholic, gastritis, metabolism +3%	0	3.0	Intoxicated?
Thyrotoxicosis, metabolism +51%	+2	4.1	Received "Ioduron" as contrast medium 8 days before
Psychopathic, inactive tuberculosis, metabolism −7 to −1%	0	4.6	Received "Iodobil" for cholocystography 20 days before
Strong thyrotoxicosis, metabolism 70 to 98%, Barker 7.7 γ%	+3	3.5	Received "Iodobil" as contrast medium one month before
Diabetes mellitus, thyrotoxicosis, metabolism +23 to +38%, cardiac insufficiency, Barker 4.3 γ%	0 to +1	3.0	Very ill, not explained

In 2 cases therefore the aberration is not explained, but in the 3 others the administration of iodine preparation for radiography is the explanation for the reduction of T_0'.

As $\alpha \cong T_0'$ it is now possible to understand why T_{max} is far from being a good variable for the diagnosis but has only the general tendency to increase with the class of the function. We gave on page 93 the mathematical expression of T_{max}. If λ is small, one may write:

$$T_{max} \sim \frac{\alpha}{\alpha + \eta}.$$

In this simplified expression, α is preponderant in the fraction because it is alone in the numerator, but the denominator is equal to $\alpha+\eta$ where η is very variable and, as we have seen, totally independent of the function. This expression has the same mathematical form as *Keating*'s formula for the maximum uptake using the clearance values given on page 85.

d) The biological significance of the flow rate parameter λ

λ was determined in those cases where the uptake curve could be recorded for 4 to 8 days on the patient, i.e. in 57 cases. 3 cases which had received an iodine preparation and another case (alcoholic with cirrhotic liver) are excluded from the statistics. The latter are given in fig. 13.

The results are somewhat surprising. In the normal range λ varies from a few ‰ to about 1.5% per hour. All the hypofunctions are included in the normal range. For the hyperfunctions there is a general

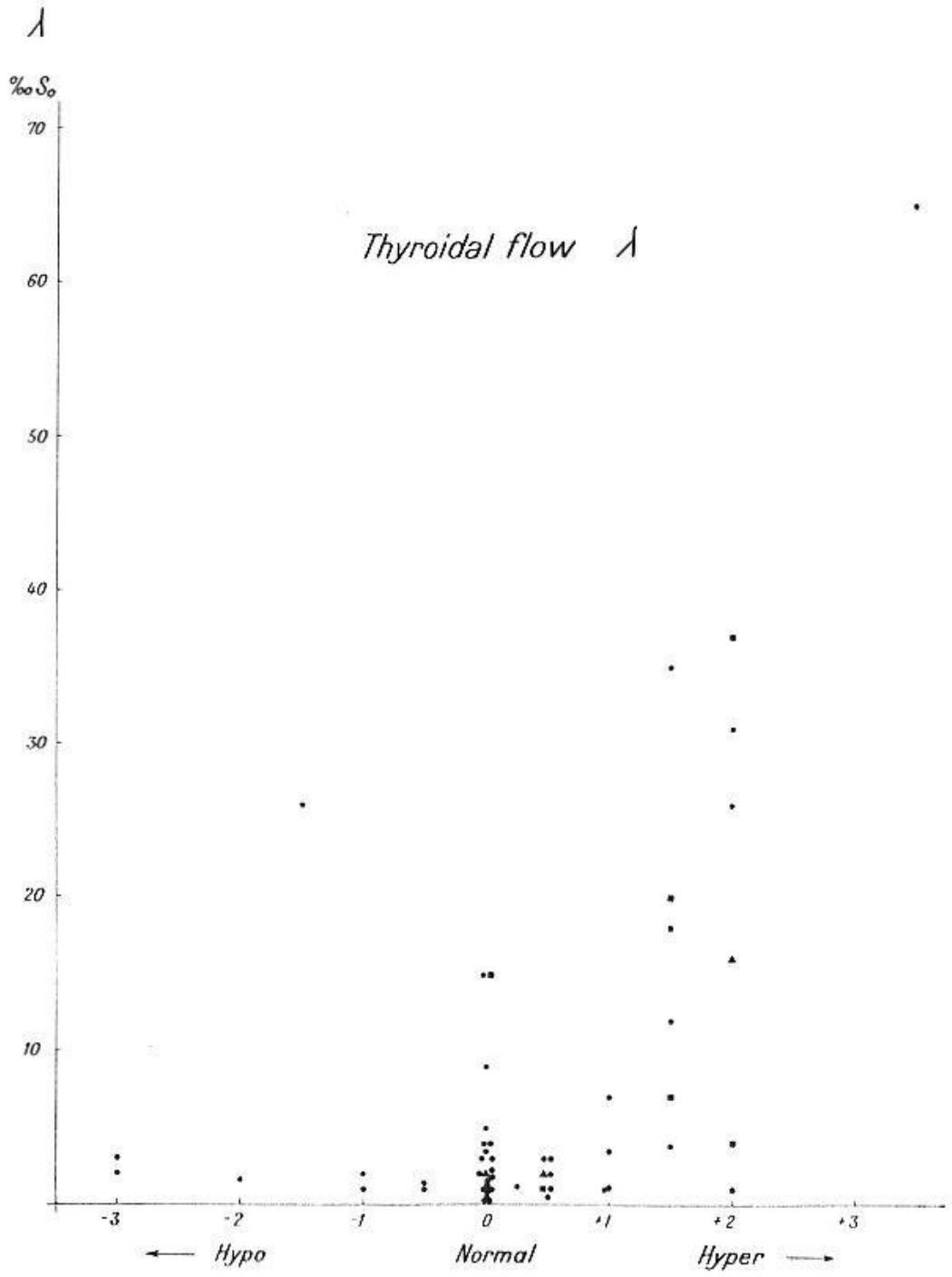

Fig. 13. Distribution diagram of the thyroidal flow rate parameter λ. Abscissa: class of the function. ■ treated with antithyroidal drugs, ▲ treated with pituitary extracts.

tendency to increase strongly to 6.5%, but more than half are included in the normal range. *The flow rate parameter λ is thus far from being a suitable parameter for the diagnosis of the function.*

As the protein-bound iodine of the plasma is usually considered a good parameter for the diagnosis, the flow of radioactive iodine from the thyroid to the plasma ought also to have some significance if it could be expressed in mg of tracered iodine per hour. But for

that determination we ought to know the thyroid's total iodine content J in mg. The radioactive flow would thus be

$$J\,\lambda \quad \text{in mg per hour.}$$

It is because J is probably very variable from one subject to another that λ alone has almost no significance for the determination of the intensity of the function.

6. *The experimental method*

The relative activity of the thyroid is measured with the collimator and Geiger-Müller counter shown in fig. 14. The measurement is taken 40 cm from the neck with a lead collimator which encloses the thyroid in a large field of 13×15 cm, covering the whole of the neck and stretching to below the clavicle. Lead shielding at least 3 cm thick protects the counter against radiation coming from outside this field. The geometry of the collimator enables every point in the field to irradiate the counter with the same sensitivity. The figure shows at the bottom a cylindrical geometry which, although frequently employed, is bad (point C irradiates only a fraction of the counter). The counter is fitted with a lead filter 0.5 mm thick (maximum sensitivity to γ-rays of ^{131}I).

In the field of measurement the thyroid is enclosed in a mass of strongly vascularized tissues of which the activity of the blood and extracellular liquid is not negligible. The measurement must hence be corrected. The *correction for the extrathyroidal activity* in the field of the collimator is performed as follows:

We make the plausible assumption that a few minutes after the endovenous injection the relative activity of the extrathyroidal tissues, measured on the surface of the neck in the field of the collimator, and the relative activity measured at a point on the surface of the thigh are

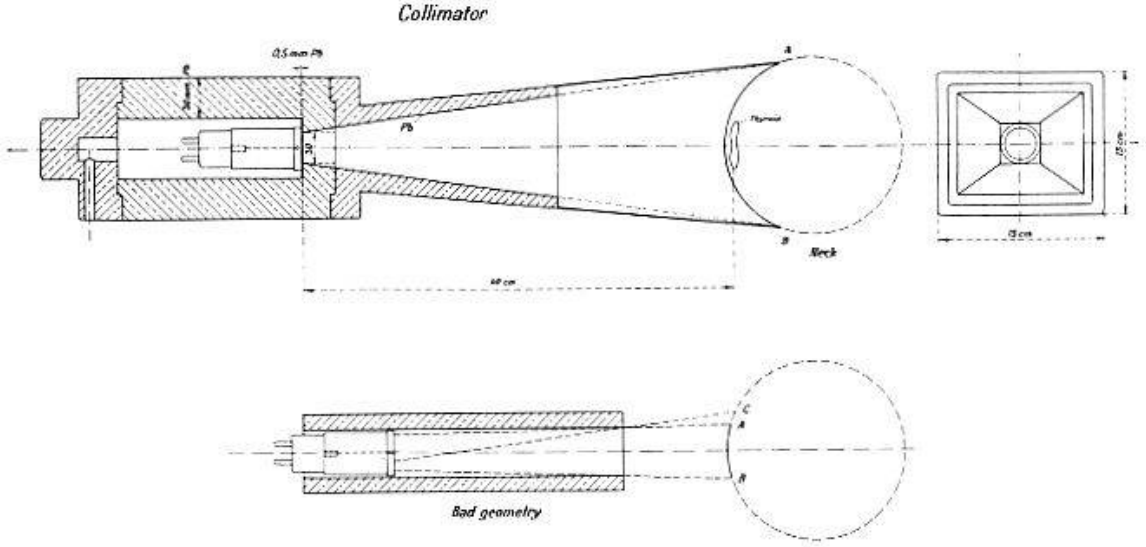

Fig. 14. Section of the collimator for the measurement of thyroidal activity.

in a constant ratio k which is independent of time. This *ratio* k is measured between 4 to 7 minutes after the injection with a *second counter* equipped with a little cylindrical lead collimator. With the aid of the latter a certain number of measurements are taken on the neck outside the thyroidal space. The mean value of these measurements is then related to the activity on the thigh at the same time. This second counter records, throughout the measurements of the thyroid, the relative activity on the thigh (curves shown in fig. 2).

As the two counters have different geometries it is necessary for the calculation of the correction to determine the ratio k' of their efficiency. This is done with a plexiglas cylinder (15 cm in diameter) containing a solution of ^{131}I. The ratio of the relative activities measured in the geometries of each of the two counters equals k' (0.04 in our experiments). The correction which must be made on each thyroid measurement is then:

$$\text{(Relative activity on the thigh)} \times kk'$$

This value is subtracted.

Fig. 15 and 16 show the influence of the correction in four cases: two normal, one hypo- and one hyperfunction. It will be seen that the correction modifies the initial tangent T_0' by between 30 and 100%. It is thus very important.

The photograph in fig. 17 shows the arrangement of the two counters on the patient. The second counter on the thigh is protected from the radiation of the radioiodine of the bladder by a 5 cm lead shielding.

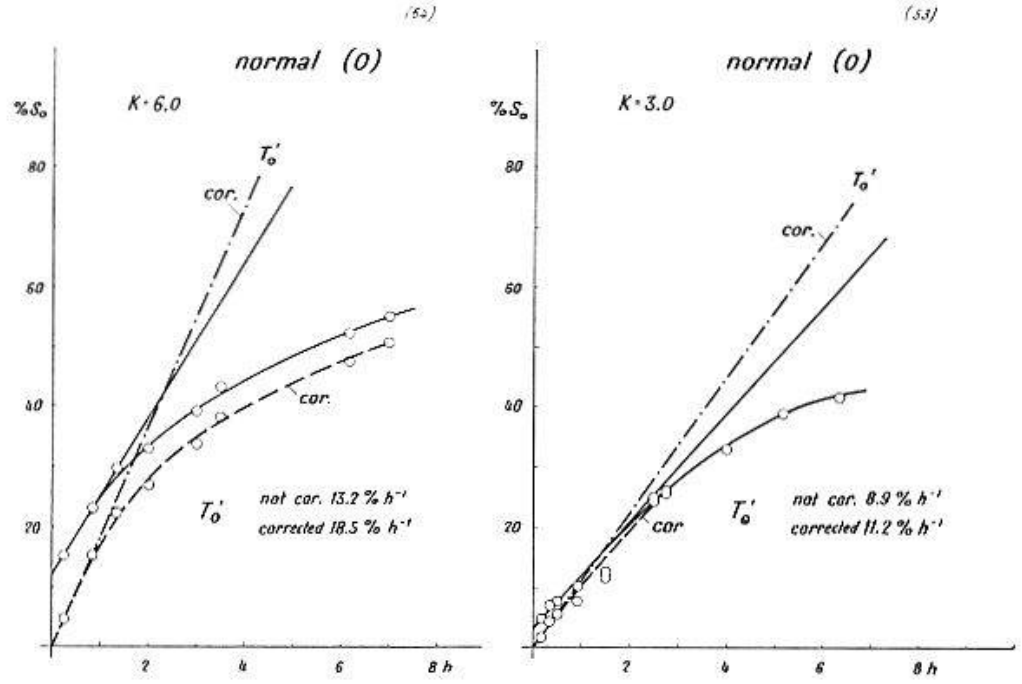

Fig. 15. Initial region of the uptake curve with and without correction of the extrathyroidal activity (2 normal cases).

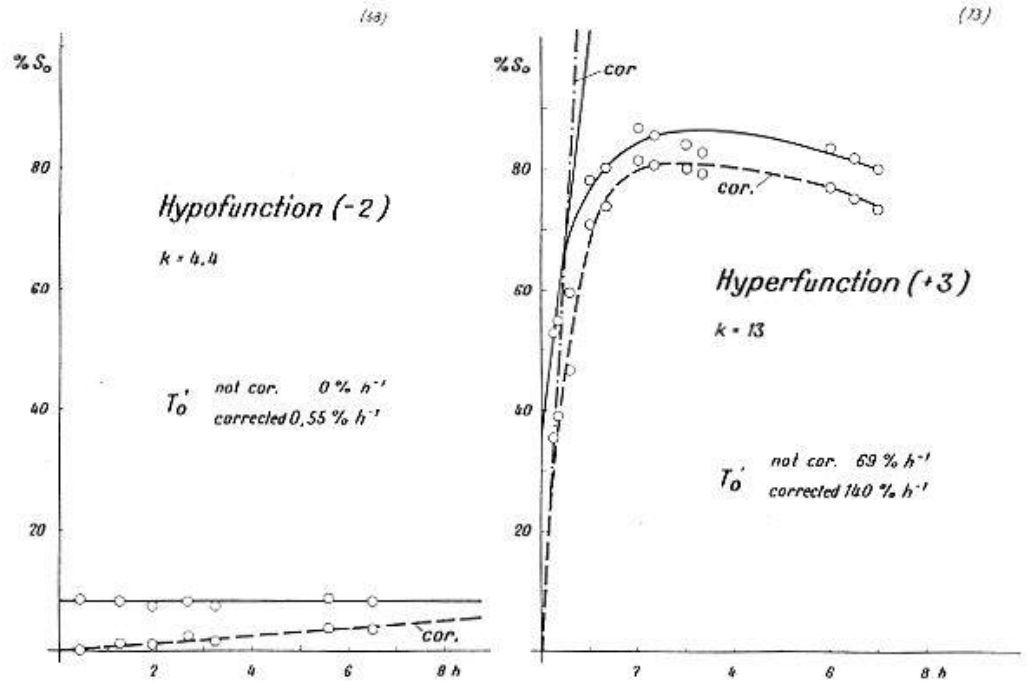

Fig. 16. Initial region of the uptake curve with and without correction of the extrathyroidal activity (one hypo- and one hyperfunction).

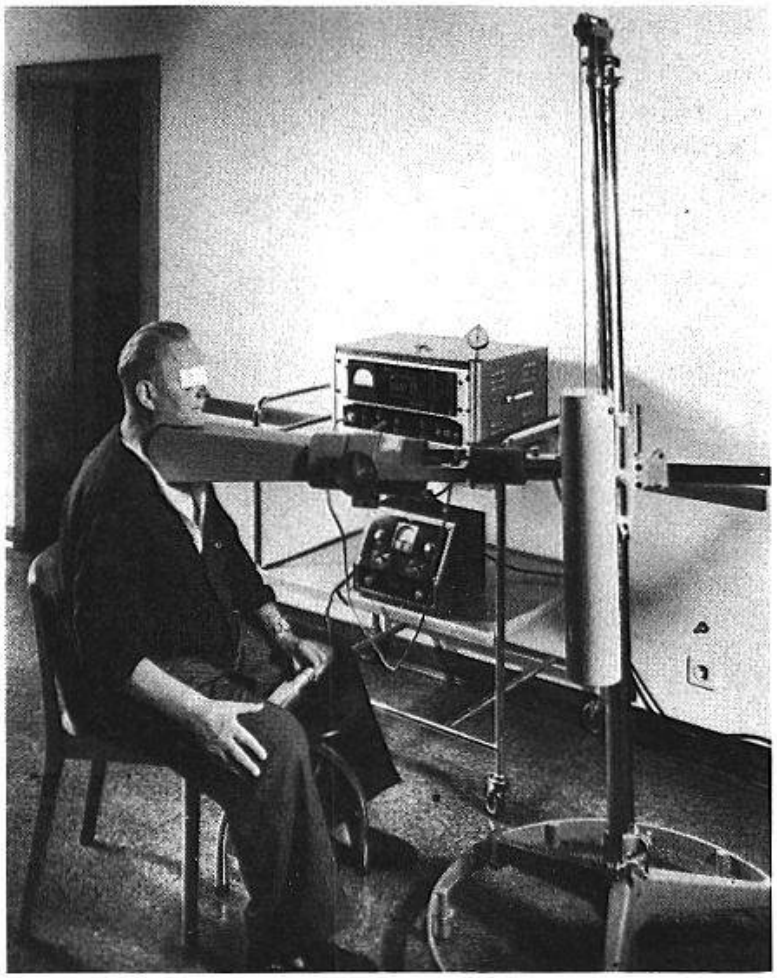

Fig. 17. Arrangement of the two counters on the patient for recording simultaneously the relative activity of the thyroid and the activity of the iodine space.

The *calibrating* of the injected solution in the geometry of the thyroid's counter is carried out in a 50 ml glass container having roughly the form of the thyroid, which is arranged in a cylindrical plexiglas container filled with water. This cylindrical container is 12 cm in external diameter, 3 mm thick and 14 cm high; it serves as a phantom for the simulated thyroid.

The active solution is withdrawn in a syringe which is weighed before and after the injection so that the weight of solution is known exactly. The quantity of solution for the calibrating is determined in the same way and diluted in 50 ml of water.

For the calibrating of the solution it is important to employ a container which has the shape of the thyroid. We give below the comparative measurements of this container and of a cylindrical, 100 ml bottle (Jena) half filled:

Table 5

Arrangement	50 ml container in shape of thyroid c.p.m.	100 ml Jena bottle half filled c.p.m.
Thyroidal container in air (not immersed)	205	177
Immersed in a beaker (diameter 15 cm) filled with water	201	179
Immersed in a plexiglas container (diameter 14 cm, wall thickness 4.5 mm) .	195	–

We now employ an external cylindrical plexiglas container 3 mm thick. Four successive calibrations of the same solution at one week intervals have shown differences of 0.2 to 1.7%.

The photograph in fig. 18 shows the arrangement for the calibrating.

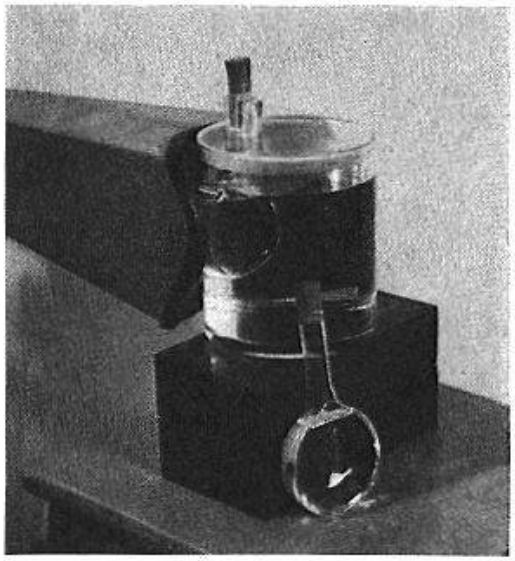

Fig. 18. Arrangement for the calibrating of the ^{131}I solution enclosed in a container having the shape of the thyroid, placed in a cylindrical plexiglas container filled with water.

7. Discussion of the experimental results and comparison with other methods

The uptake rate a of the inorganic radioiodine by the thyroid, measured by the initial slope T_0' of the uptake curve which is corrected from the extrathyroidal activity, thus appears to be a very sensitive parameter for indicating the intensity of the function. Considering the whole normal and pathological domain in man, we see that his factor may vary in a ratio of about one to several thousands. The pathological deviations may be as much as ten times higher or lower than the normal values.

From the parameter a in % per hour it is possible to calculate the thyroidal clearance g in ml per minute if the iodine space V in litres is known. We have

$$g = \frac{1000\, a\, V}{60 \times 100}\,.$$

Assuming a mean weight of 65 kg (most of our cases were women) and an iodine space of 26%, then the mean value of V is 17 litres. In the following table our values for the uptake rate are converted into thyroidal clearances according to the above assumptions. These values must be compared with those of authors (*Berson S. A., Yalow R. S., Sorrentino J.*, and *Roswit B.* [2]) who determined the thyroidal clearance during the first half hour after intravenous injection and corrected the measurement for the activity of the extrathyroidal space:

Function	$a = T_0'$ % per hour	Thyroidal clearance g in ml/ min.	
		Authors, Zurich (calculated from a)	*Berson* et al. New York
Hypofunction	0 to 5	0 to 14	0 to 4.2
Normal	7 to 18	20 to 51	3.7 to 41
Hyperfunction	23 to 260	65 to 485*	74.5 to 512

* Calculated with the right weight of 43 kg

As the accuracy of our calculation with a mean weight is no better than about 10%, it is surprising to see how well the calculated clearances from Zurich tally with the experimental clearances from New York. Only the limits between "normal" and "hypofunction" seem not to be the same, the normal range in New York appearing to be much lower than in Zurich. Probably the "normal range" needs a clearer definition, as the patients of a hospital are not very good material for the definition of a normal range. On the other hand, *Berson* et al. considered 5 hypofunctions only and we have considered 15. Moreover, in hypofunction or

low normal function the increase of activity during the first half hour is very reduced and is not very different from that of the extrathyroidal space. The measurement may involve a greater error. In these cases, we have thought it necessary to determine the initial slope by measurements effected over a period of two to three hours. Moreover, we measure the ratio k (extrathyroidal activity) 4 to 7 minutes after the injection and not 1 to 2 minutes after, as *Berson* (2) et al. did.

Yet, the cases of thyrotoxicosis are defined by about the same values with both methods in both towns.

If we remember again the results obtained in London by *Rotblat* and *Marcus* (6) which agree with ours, we can say that there are no great differences between London, New York and Zurich for the normal and pathological range of the uptake rate of inorganic iodine by the thyroid.

In conclusion, it must be stressed that the uptake rate of the inorganic iodine expressed in % per hour is a very significant notion, which is perhaps more intuitive than the clearance expressed in ml per minute. The flow of inorganic iodine going up to the thyroid may be directly calculated from a. If, for a man weighing 70 kg and having 26% iodine space (thus $V = 18$ litres), we take a mean concentration of 0.5 μg inorganic iodine per 100 ml (*Klein E.* [28]) with $a = 12\%\ h^{-1}$ (normal case), the flow of inorganic iodine amounts to 0.26 mg per day. If this total flow were transformed into thyroxine—which is not at all sure—we should find a daily production of thyroxine of 0.40 mg in the normal man with variation of $\pm 50\%$. This production would be about ten times higher in cases of hyperfunction and ten times lower in cases of hypofunction.

It is known that the quantity of thyroxine produced by a normal man in one day is evaluated at about 0.5 mg.

Grateful acknowledgement is made to, Mr. Jan Bigland M. A., of the English Institute, Zurich, for correcting this text.

Summary

The authors develop a three-parameter theory for the radioiodine investigation of the thyroid, taking into account the uptake rate of inorganic iodine by the gland, the urinary inorganic excretion rate and the flow rate of total iodine from the thyroid to the plasma. The uptake curve appears with great accuracy as the difference of two exponentials from which the 3 rates may be calculated. The urinary excretion rate is without significance for the diagnosis of normal and pathological cases. The maximum uptake and the flow rate of radioiodine from the thyroid to the blood are also of little significance. But the uptake rate a of the

inorganic iodine which is shown to be equal to the initial slope of the uptake curve, corrected from the extrathyroidal activity, appears to be a very valuable parameter for the purpose of discriminating between normal and pathological function. We found for α:

Hypofunction	0 to 5% h^{-1}
Normal	7 to 18% h^{-1}
Hyperfunction	23 to 260% h^{-1}

From an evaluation of the iodine space (26% of the total weight) it is possible to convert these values into thyroidal clearance values. The converted values coincide with those of other authors for hyperthyroidism and the upper region of the normal ranges, but the inferior limits of the latter are noticeably different. This difference may be caused by the methods of measurement.

Zusammenfassung

Mit Hilfe der Absorptionsrate des anorganischen Radiojods in der Schilddrüse, der Nierenausscheidungsrate und der Schilddrüsenabflußrate wird eine Dreiparametertheorie der Radiojod-Traceruntersuchung der Schilddrüsenfunktion entwickelt. Der zeitliche Verlauf der Radiojodaufnahme durch die Schilddrüse nach einer intravenösen Injektion läßt sich sehr genau mathematisch formulieren. Die zeitliche Aktivitätskurve der Schilddrüse erscheint als Differenz zweier Exponentialfunktionen, welche die Berechnung der drei Parameter erlauben. Die Nierenausscheidungsrate ist für die Diagnostik von normalen und pathologischen Fällen absolut bedeutungslos. Die maximale Speicherung der Schilddrüse und die Schilddrüsenabflußrate sind ebenfalls von geringer Bedeutung. Dagegen ist die Absorptionsrate α der Schilddrüse wichtig. Sie ist, wie man beweisen kann, gleichwertig mit dem Steigungsmaß der Anfangstangente an der Anstiegskurve der Schilddrüsenaktivität. Sie hat sich als ein hervorragendes Parameter erwiesen, um die normalen und pathologischen Funktionen zu unterscheiden. Die Anfangstangente der Anstiegskurve gibt, nach Abzug der Aktivität außerhalb der Schilddrüse, auch die Größe der Abweichungen von der normalen Schilddrüsenfunktion. Wir haben für α gefunden:

Hypofunktion	0 bis 5% h^{-1}
Normale Funktion	7 bis 18% h^{-1}
Hyperfunktion	23 bis 260% h^{-1}

Durch eine Schätzung des gesamten extracellulären Flüssigkeitsraumes (26% des Körpergewichtes) ist es möglich, die Werte der Absorptionsrate in Werte der Schilddrüsenclearance umzuwandeln. Die konvertierten Werte entsprechen den Clearancewerten anderer Autoren

für Hyperthyreose und das obere Gebiet der normalen Funktion. Es gibt aber eine merkliche Differenz für die untere Grenze des normalen Gebietes. Sie kann durch die Methodik hervorgerufen sein.

Résumé

A l'aide du taux de fixation thyroïdien, du taux d'élimination rénale et du taux d'écoulement thyroïdien, on peut développer une théorie à 3 paramètres pour l'investigation de la fonction thyroïdienne par l'iode radioactif. La courbe d'ascension à la thyroïde apparaît avec une précision remarquable, comme la différence de deux fonctions exponentielles à l'aide desquelles les 3 paramètres fondamentaux peuvent être calculés. Le taux d'élimination urinaire est complètement dépourvu de signification pour le diagnostic différentiel des fonctions normales ou pathologiques. L'ascension maximum dans la thyroïde et le taux d'écoulement thyroïdien donnent également des résultats contradictoires. En revanche, le taux de fixation thyroïdien α de l'iode inorganique, dont on peut montrer qu'il est égal à la pente initiale de la courbe d'ascension corrigée de l'activité du territoire péri-thyroïdien, apparaît comme une variable remarquablement sensible pour le diagnostic de l'intensité de la fonction thyroïdienne. On a trouvé pour α:

Hypofonction	0 à 5% h^{-1}
Fonction normale	7 à 18% h^{-1}
Hyperfonction	23 à 260% h^{-1}

Par une évaluation de "l'espace iode" (26% du poids total), il est possible de convertir ces valeurs en valeurs de "clearance thyroïdienne". Les valeurs transformées coïncident avec celles d'autres auteurs pour l'hyperthyréose et la région supérieure du domaine normal; mais la limite inférieure de ce domaine est sensiblement différente. Cette différence peut être attribuée aux méthodes.

Riassunto

Basandosi sulla quantità di iodio radioattivo fissato nella tiroide, sul decorso di questa fissazione e sull'eliminazione renale, si può sviluppare una teoria a 3 parametri per lo studio della funzione tiroidea. La curva ascendente nella tiroide appare, con notevole precisione, come la differenza tra due funzioni esponenziali, mediante le quali si possono calcolare i 3 parametri fondamentali. La quantità eliminata con l'urina non ha alcuna importanza per la diagnosi differenziale delle funzioni normali e patologiche.

L'ascesa massima nella tiroide e la quantità di iodio di nuovo liberato da questa ghiandola danno pure risultati contradditori. Il valore tiroideo

di fissazione a dello iodio inorganico, che si può dimostrare essere uguale alla pendenza iniziale della curva ascendente, corretta causa l'attività della regione peritiroidea, appare invece come una variabile notevolmente sensibile per la diagnosi della funzione tiroidea. Si è trovato per a:

ipofunzione	da 0 a 5%	h^{-1}
funzione normale	da 7 a 18%	h^{-1}
iperfunzione	da 23 a 260%	h^{-1}

Calcolando lo "spazio iodio" (26% del peso totale), è possibile mutare questi valori in valori di "clearance" tiroidea. I valori trasformati coincidono con quelli di altri autori per l'ipertireosi e la regione superiore della zona normale, mentre il limite inferiore della normalità differisce notevolmente.

1. *Ansell G., MacGregor A. G., Miller H.*, and *Wayne E. J.:* Radioisotope Techniques, Vol. I, London 1953, p. 52. – 2. *Berson S. A., Yalow R. S., Sorrentino J.*, and *Roswit B.:* J. clin. Invest. **31,** 141 (1952). – 3. *Goodwin J. F., MacGregor A. G., Miller H.*, and *Wayne E. J.:* Quart. J. Med. **20,** 353 (1951). – 4. *Oddie, T. H.:* Brit. J. Radiol. **22,** 261 (1949). – 5. *Oddie T. H.*, and *Scott R. K.:* Brit. J. Radiol. **23,** 348 (1950). – 6. *Rotblat J.*, and *Marcus, R.:* Radioisotope Techniques, Vol. I, London 1953, p. 33. – 7. *Haigh C. P.*, and *Reiss M.:* Brit. J. Radiol. **23,** 534 (1950). – 8. *Reiss, M., Haigh C. P., Hemphill R. E., Maggs R., Reiss J. M.*, and *Smith S.:* J. Endocrin. **8,** 1 (1952). – 9. *Haigh C. P., Reiss C.*, and *Reiss J. M.:* J. Endocr. **10,** 273 (1954). – 10. *Myant N. B.:* Brit. Med. Bull. **8,** 141 (1952). – 11. *Myant N. B., Corbett B. D., Honour A. J.*, and *Pochin E. E.:* Clin. Sci. **9,** 405 (1950). – 12. *Morel F. F.:* Helv. physiol. pharmacol. Acta **8,** 52 (1950). – 13. *Morel F. F.:* Helv. physiol. pharmacol. Acta **8,** 146 (1950). – 14. *Hahn L.*, and *Hevesy G.:* Acta physiol. scand. **1,** 347 (1941). – 15. *Hevesy G.:* Radioactive Indicators, New York/London 1948, p. 191. – 16. *Kaltreider N. L., Meneely G. R., Allen J. R.*, and *Bale W. F.:* J. exp. Med. **74,** 569 (1941). – 17. *Myant N. B., Pochin E. E.*, and *Goldie, E.:* Clin. Sci. **8,** 109 (1949). – 18. *Trunnel J. B., Duffy B. J., Goodwin J. I., Peacock W., Kirschner L.*, and *Hill R.:* J. clin. Endocr. **10,** 1007 (1950). – 19. *Tubiana M.*, and *Sung S. S.:* Sem. Hôp. Paris **27,** No. 82, 1 (1951). – 20. *Harsha, W. N.:* J. clin. Endocr. **11,** 1524 (1952). – 21. *Horst W.*, and *Rösler H.:* Klin. Wschr. **31,** 13 (1953). – 22. *Rall J. E.:* J. clin. Endocr. **10,** 996 (1950). – 23. *Benua R. S., Albert A.*, and *Keating F. R.:* J. clin. Endocr. **12,** 1461 (1952). – 24. *Taurog A., Chaikoff I.*, and *Tong, N.:* J. biol. Chem. **184,** 99 (1950). – 25. *Myant N. B., Pochin, E. E.*, and *Goldie E. A.:* Clin. Sci. **8,** 109 (1949). – 26. *Gross J., Bogoroch R., Nadler N. J.*, and *Leblond C. P.:* Amer. J. Roentgenol. **65,** 420 (1951). – 27. *Taurog A.*, and *Chaikoff I.:* J. biol. Chem. **169,** 49 (1947). – 28. *Klein, E.:* Schweiz. med. Wschr. **84,** 146 (1954). – 29. *Joyet G.:* Schweiz. med. Wschr. **84,** 491 (1954).