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The initial tangent of the uptake curve as a test for diagnosis of the thyroid function with radioiodine [1] [2]

By **G. Joyet, F. Koller,** and **L. Morandi**
with the technical assistance of
Miss **M. Miller** and Mrs. **G. Joyet**

1. Introduction

In a first, theoretical, methodical and experimental paper (*G. Joyet* and Mrs. *R. Gautier* [1]), the following points were put forward and demonstrated:

a) In more than 90% of the cases, the *uptake curve of radioiodine* in the thyroid appears with great accuracy as the *difference of two exponentials* from which it is possible to deduce the values of three coefficients,

the uptake rate α of inorganic iodine by the gland,
the urinary inorganic excretion rate η through the kidneys,
the flow rate λ of total iodine from the thyroid to the plasma.

The three principal flows of radioiodine after administration into the blood—uptake by the thyroid, urinary excretion and flow from the thyroid to the blood— appear to obey a very exact mathematical law of continuity from which it is possible to deduce the mathematical functions of the blood, the thyroid and the urinary excretion.

b) The urinary excretion rate is without significance for the diagnosis of normal and pathological cases.

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[1] Lecture delivered at Lausanne to the Swiss Academy of Medical Sciences, November 6^{th}, 1954.

[2] Before the intravenous administration, which is always employed here, we essayed oral administration on 53 patients. The results of these cases are not reported, but this first experiment showed us the necessity of an intravenous injection. A certain number of these patients were kindly placed at our disposal by Dr. *W. Siegenthaler* of the Medical Service (Prof. *W. Löffler*) and Dr. *Kind* of the Psychiatric Clinic (Prof. *M. Bleuler*).

c) The maximum of the uptake curve is also devoid of general significance and permits the differentiation of the hypofunction only.

d) The flow rate of radioiodine from the thyroid to the blood is without significance either for the diagnosis, although the Basedow generally shows a high flow rate.

e) *The uptake rate α of the inorganic iodine of the plasma is shown to be equal to the initial slope T_0' of the uptake curve and appears to be a very valuable parameter for the discrimination between normal and pathological functions.* The parameter is a very sensitive one. From the very strong hypofunction (myxœdema) to the very strong thyrotoxicosis the initial tangent varies from a few $^0/_{00}$ to more than 200% per hour. The initial tangent 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.

We found, for the different clinical classes of the function:

Class of the function	Biological intensity of the function		T'_0 % S_0 per hour
−3	Hypofunction	very strong	0 to 1
−2		medium	1 to 3
−1		slight	3 to 5
0	Normal		5* to 20
+1	Hyperfunction (Thyrotoxicosis)	slight	23 to 40
+2		medium	40 to 90
+3		very strong	90 and over

* The more complete statistics of normal cases given later compelled us to enlarge the limits of the normal range from 7 to 18 to 5 to 20% h^{-1}.

S_0 being the relative activity of the radioiodine injected, measured in the same geometry and backscattering conditions as the activity of the thyroid. At the confines of the normal range the values 5 to 6 and 20 to 23% h^{-1} relate to uncertain functions for which it is not yet known if they are normal or slightly pathological.

f) It must be stressed that the initial tangent T_0' has a clear biological significance and measures the uptake rate of the inorganic iodine of the plasma which appears, for a given subject, as a constant biological activity of the thyroid. On the other hand, the measurements of the activity of the thyroid which are frequently made 6, 12, 24 or 48 hours after administration of the radioiodine as a routine test have no biological significance. They are the resultant of the three principal flows of iodine in the organism, that is to say the renal excretion, the flow of organic iodine from the thyroid to the plasma and the uptake rate of the inorganic iodine of the plasma by the thyroid. As only one of the rates of these three flows has a biological significance and the others little or none, the resultant may merely mask the true intensity of the function.

g) It must be remembered that nearly the same values of T_0' for the normal and pathological ranges were found with quite different methods in London and New York.

Rotblat and *Marcus* (2) in London, with their four parameters theory are able, with the two exponentials form of the urinary excretion curve, to determine the uptake rate of the thyroid which is equal to our initial tangent T_0'. They found for the mean value of the normal range 10% per hour $\pm 5\%$ (double the standard deviation), which nearly agrees with our limits for the normal range.

Berson, *Yalow*, *Sorrentino*, and *Roswit* (3) in New York measure the initial clearance which, as we have seen (*Joyet* et al. [1]) may be converted into uptake rate values after evaluation of the iodine space at 26% of the weight. The calculated values of the uptake rate in New York tally well with our experiments in Zurich for the "hyperfunction" and the upper limit of the "normal" range. Only the limit between "normal" and "hypofunction" seems to be much lower in New York than in Zurich. Probably the discrepancy is not objective but provoked by differences in the measurement of the extrathyroidal activity. *Berson* et al. (3) measure the extrathyroidal activity as early as one or two minutes after the intravenous injection, and we measure the activity ratio between the extrathyroidal space and the thigh four to seven minutes afterwards, knowing radioiodine takes five to ten minutes to diffuse in the iodine space. Moreover, our corrections are made each time we measure the activity of the thyroid, taking into account the simultaneous measurement of the relative activity of the iodine space on the thigh. For these reasons, our corrections for the extrathyroidal activity appear relatively to be much higher—especially for the hypofunction. The result is that the uptake rate for hypofunction in our system of measurement must be higher than with the system of *Berson* et al. This difference, however, is negligible for hyperfunctions and normal functions in the upper range.

h) As the initial uptake rate of radioiodine by the thyroid is directly proportional to the concentration of radioiodine in the plasma, *the only acceptable administration is the intravenous one.* Oral administration can cause great variations in the value of the initial tangent by reducing T_0' by about 1.5 to 3 times. The two groups of authors mentioned above also used intravenous injection.

As in the previous papers (1, 8), the clinical classification of the cases was made in the seven classes -3, -2, -1, 0, $+1$, $+2$, $+3$. The cases were classified according to the general impression, the presence, and severity of the symptoms and—last, not least—the course of the disease, known by prolonged observation.

Hyperthyroidism and thyrotoxicosis

In the *slight cases* (class $+1$) the thyroid gland was slightly enlarged. Palpitations, a slight tachycardia and a light tremor of the fingers contributed to the probable diagnosis. In the *medium cases* (class $+2$) there were those with definite struma occasionally slightly pulsating. Besides a clear tremor and distinct tachycardia, these cases also exhibited nervousness, subfebrile temperature and sweating. In the *serious cases* (class $+3$) the symptoms were: pulsating struma, even more increased tachycardia and tremor, and definite eye-symptoms (exophthalmus, etc.).

Hypothyroidism

The probable diagnosis in the *slight cases* (class -1) was indicated by a certain slowing down of mental processes and associations, shivering, increased fatigue, paresthesia and constipation. In the *medium cases* (class -2) the above symptoms were more definite and also included slight myxœdema, a rough skin and brittle hair. The *class -3 cases* showed the *complete picture* with fully developed myxœdema.

It must be said that the classification was made clinically and independently of the tracer. For the classes ± 2 and ± 3, this was usually possible without too much difficulty. Doubtful cases were ranged in class ± 1 (slight dysfunctions) or 0 (normal). The final decision in what group such a case had to be classified was necessarily somewhat arbitrary. The following statistics are given with this reservation in mind.

Fig. 1 and 2 show on an enlarged scale the distribution diagrams of 222 cases of hypo-, normal and hyperfunctions. The medical class of the function is plotted in abscissa and T_0' in ordinate. One can see again, as in the preceding papers (1, 8), the enormous variation of T_0' in the whole pathological and normal range. 22 cases, in which a clear contact of the patient with some form of iodine could be proved, are excluded from Fig. 1 and 2.

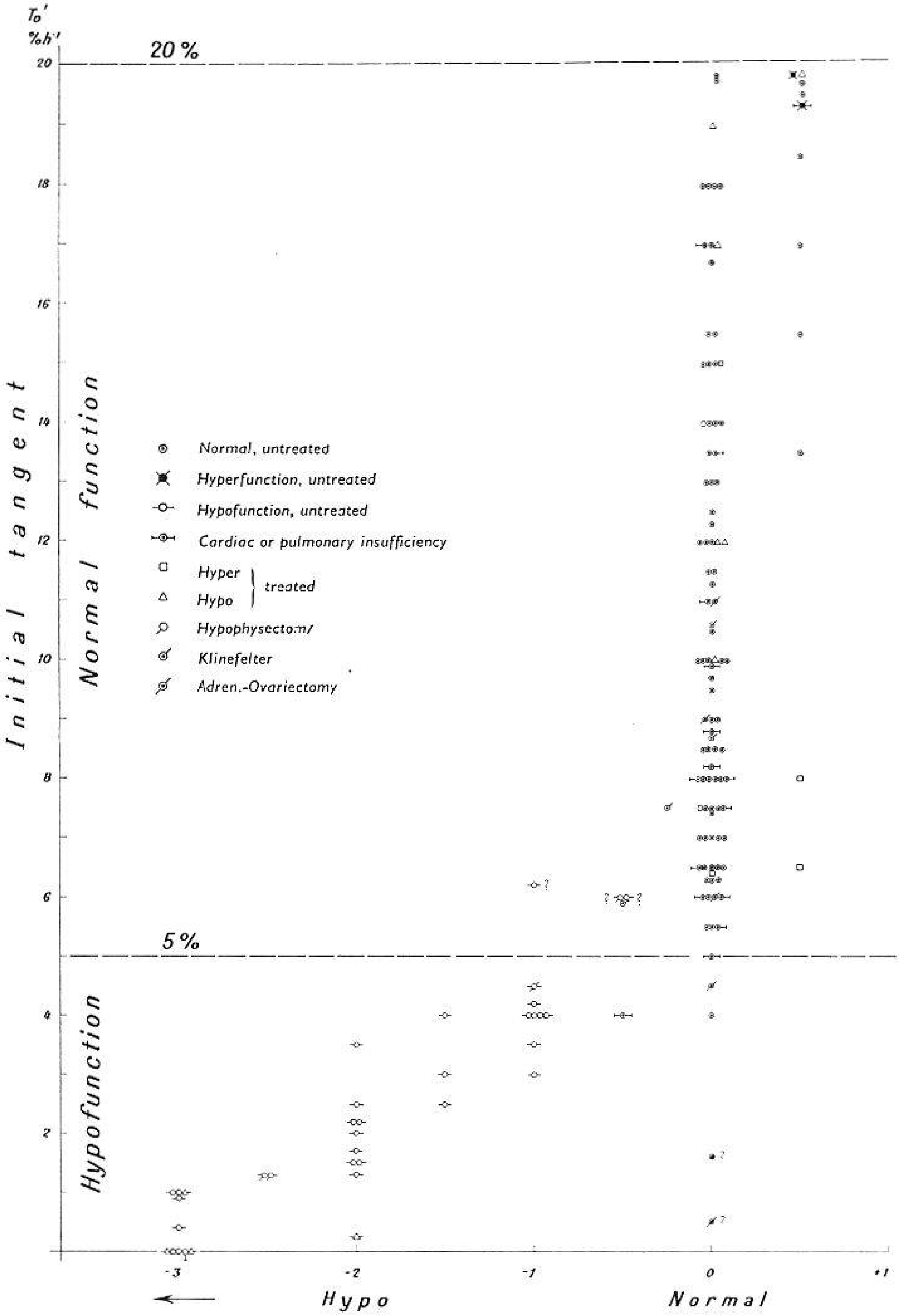

Fig. 1. Distribution diagram of 222 tests of thyroid function: *Normal* and *Hypofunctions.* Abscissa: Clinical classification. Ordinate: T'_0. The different circles, triangles, etc., provide further clinical information: they indicate if the cases with clinical hypo-, normal or hyperfunction were treated or untreated, complicated by cardiac or pulmonary insufficiency, etc. (see legend).

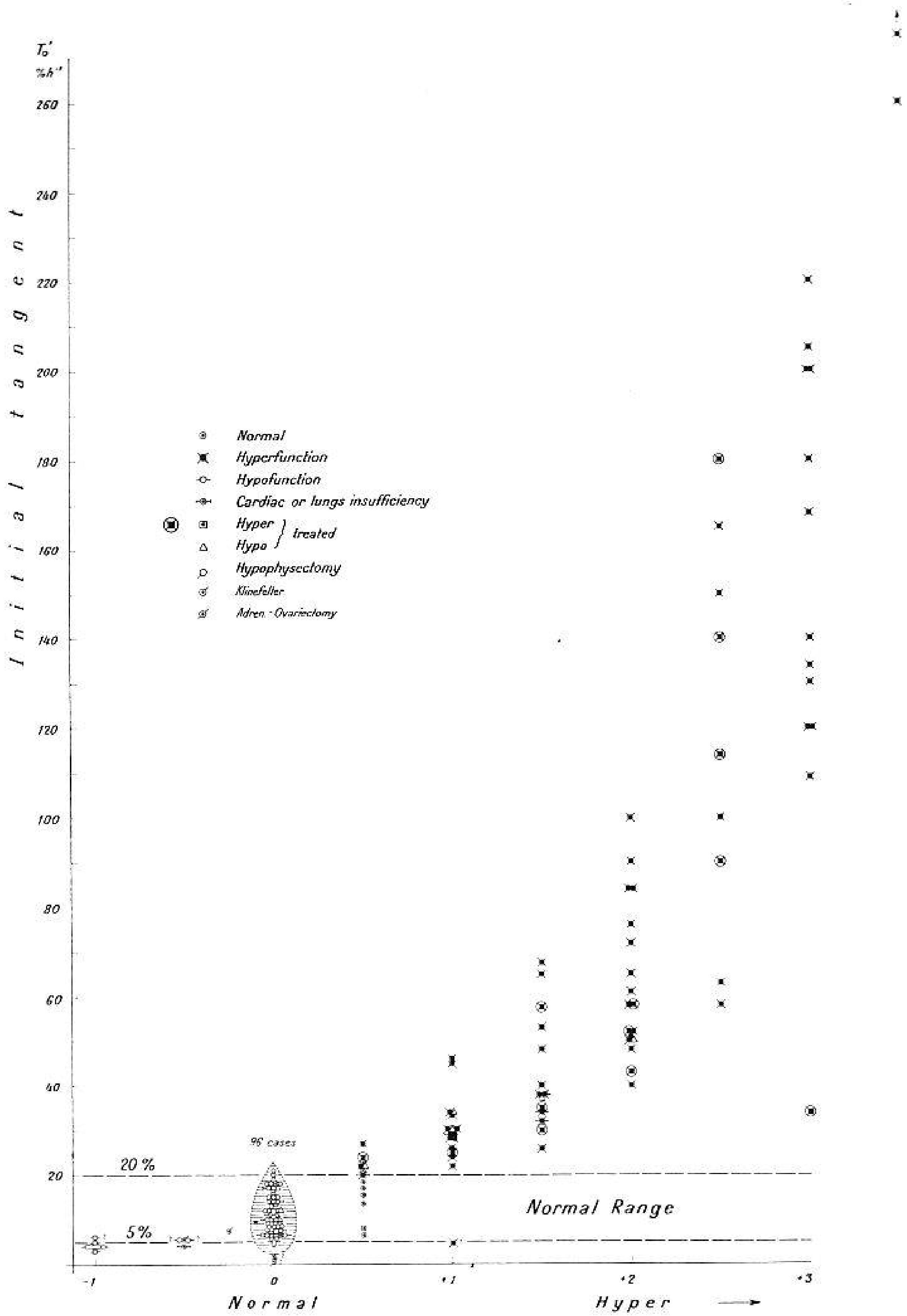

Fig. 2. Distribution diagram of 222 tests of the thyroid function: *Normal* and *Hyperfunctions*. Abscissa: Clinical class. Ordinate: T'_0 (see also legend of Fig. 1).

Fig. 3 gives the frequency distribution of 83 cases of normal functions (class 0). T_0' on the abscissa is plotted in logarithmic scale in order to obtain nearly a symmetrical curve which we would not have with a linear abscissa. The mean value amounts to 10% per hour with a standard deviation equal to $\begin{smallmatrix}+5.1\\-3.4\end{smallmatrix}$ %. 95% of the cases (2σ) fall between the limits of 4.7 and 20.7%. If we take 5 and 20% per hour as the limits of the normal range we exclude 4% only of the total cases.

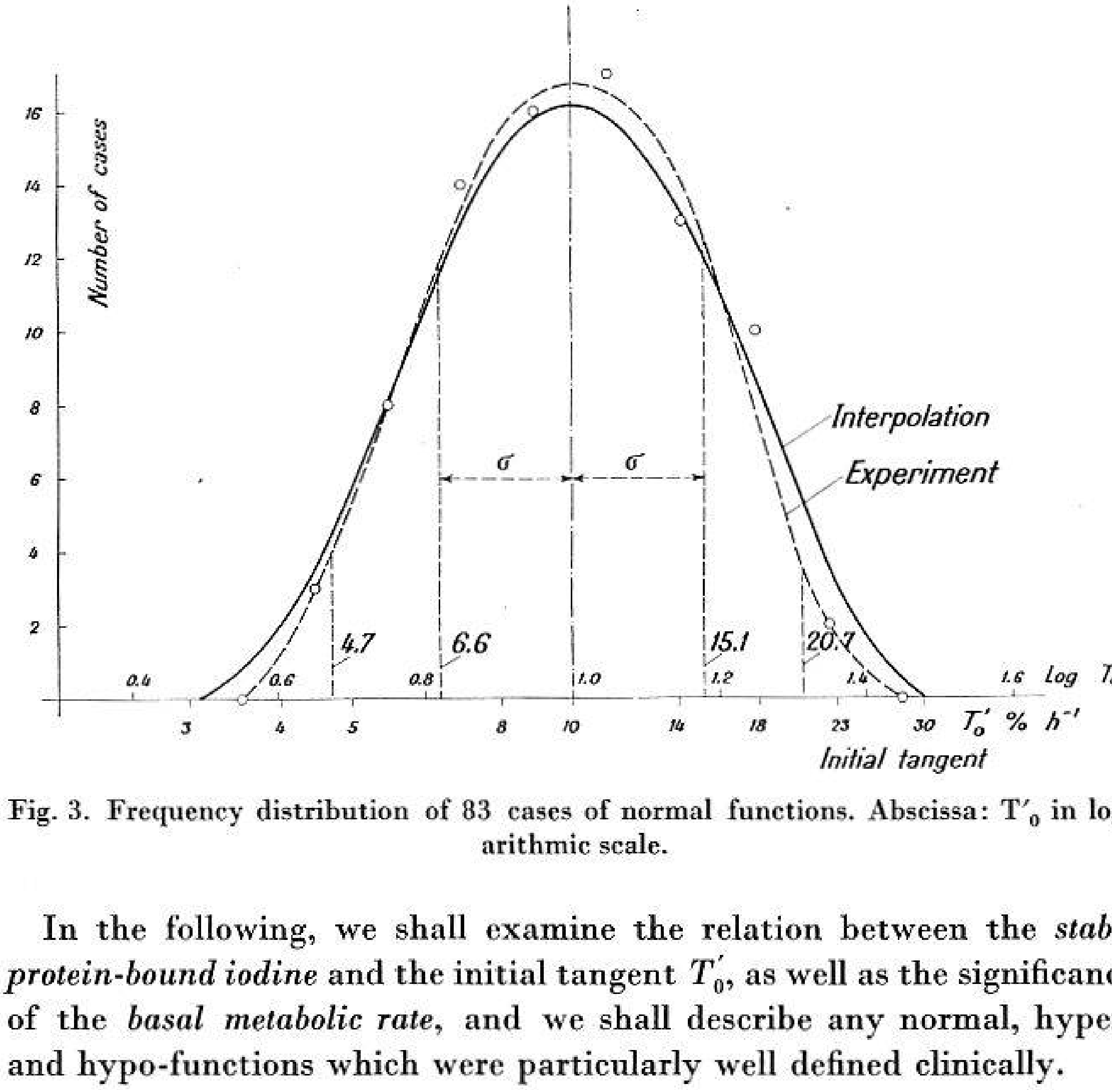

Fig. 3. Frequency distribution of 83 cases of normal functions. Abscissa: T'_0 in logarithmic scale.

In the following, we shall examine the relation between the *stable protein-bound iodine* and the initial tangent T_0', as well as the significance of the *basal metabolic rate*, and we shall describe any normal, hyper- and hypo-functions which were particularly well defined clinically.

We shall show the effect of *pituitary extracts*, *antithyroidal drugs* and *hypophysectomy* on the initial tangent T_0'.

2. *The initial tangent T_0' and the basal metabolic rate*

In nearly all cases the basal metabolic rate was determined two or three times some days before and after the iodine tracer; only in a few cases was the determination made but once. The mean values are plotted in the abscissa on the distribution diagram of Fig. 4. In order to simplify the drawing, the initial tangent T_0' is shown as a logarithmic ordinate, but the enormous variation of the test in the normal and pathological range must be borne in mind. The significance of the different symbols is explained at the bottom of the figure.

Most of the measurements of the BMR were made with the apparatus of *Sanburn:* closed circuit, atmosphere of nearly pure oxygen, nose nipped, tube in the mouth, duration of the measurement 10 minutes. The patient is in exact basal conditions. The apparatus is a modification of that of *Harris* and *Benedict*[3].

In the following, we consider as abnormal only those BMR which are greater than +12% or lower than −12%.

a) Basal metabolic rate greater than +12%

Out of 104 cases suspected to have a hyperfunction in 69 only was the diagnosis of hyperthyroidism confirmed. In 60 of these cases of hyperfunction T_0' was higher than 20%; in 8 cases only which received an X-ray contrast preparation T_0' was clearly lower than 20%; one case is unexplained ($T_0' = 4.5\%\ h^{-1}$, BMR +29%).

The 35 cases in which the metabolism was high (>12%), but the thyroidal function normal were made up as follows:

13 cardiac insufficiency,
3 cancer of the lungs,
2 vegetative dystonia or sympathicotonia,
1 paranoid schizophrenia,
1 chronic alcoholism,
2 hyperfunction treated, now clinically normal,
4 contact with iodine,
1 hypothyroidism treated,
8 unexplained.

In all the 61 cases, except one in which, simultaneously, the BMR was higher than +12 and T_0' higher than 20% h^{-1}, the diagnosis of thyrotoxicosis was plainly confirmed. The only exception was a neurovegetative dystonia with $T_0' = 21\%$.

Thus, when simultaneously T_0' is greater than 20% h^{-1} and the BMR greater than +12%, there is a more than 98% probability that the case is one of hyperfunction.

[3] According to Dr. *P. Galletti* of the Medical Polyclinic (Prof. *P. H. Rossier*), the apparatus of Sanburn gives values which are a few per cent too low and differences in the reproducibility of about 4 to 8%. For the normal man $2\sigma = \pm 10$–12% (P = 0.05). A fraction only of all the cases were measured with the apparatus of *Knipping*.

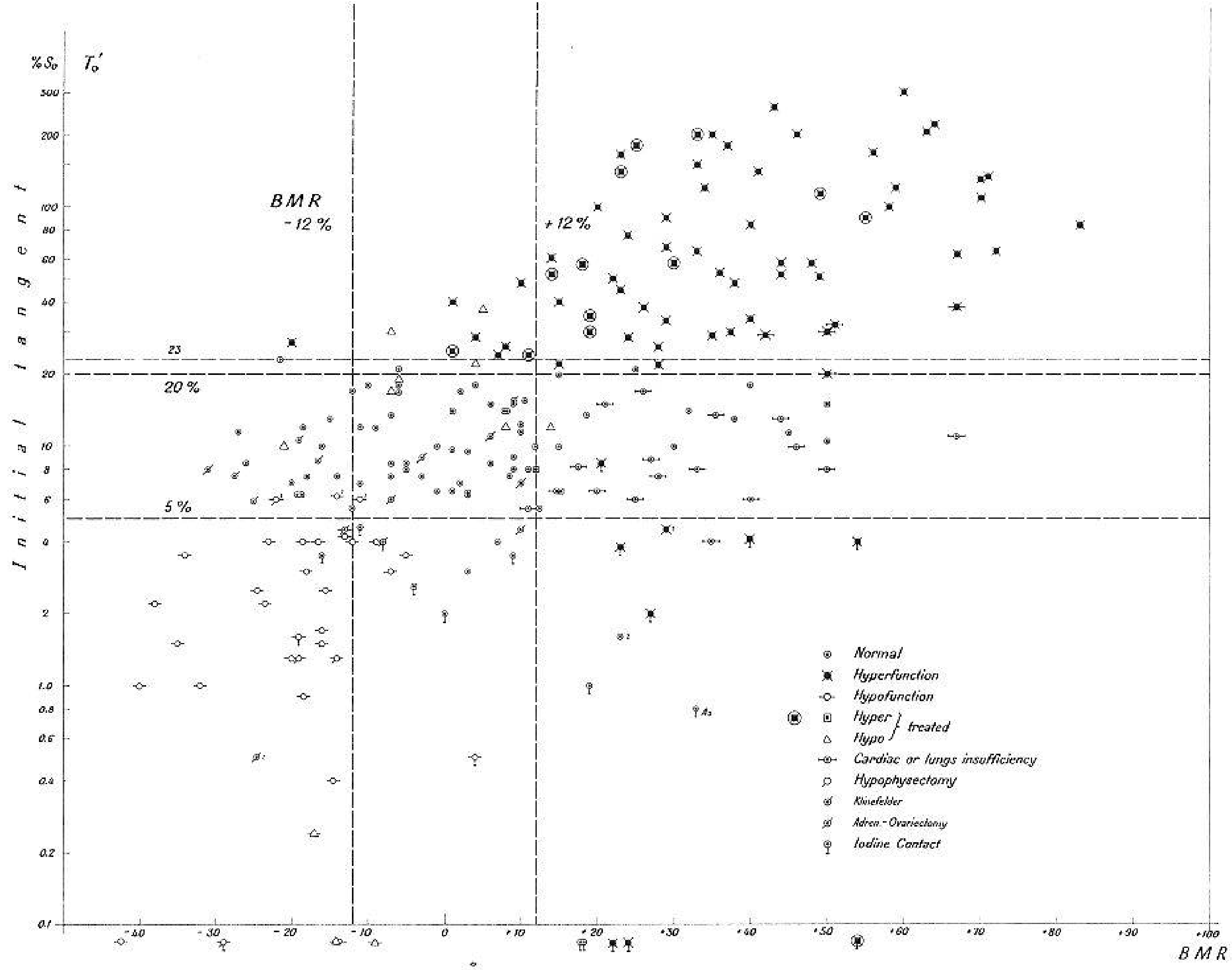

Fig. 4. Distribution diagram of 222 cases of normal and abnormal thyroid function. Abscissa: BMR. Ordinate: T'_0.

b) Basal metabolic rate lower than —12%

In this class, which includes 50 cases suspected of thyroidal hypofunction, the diagnosis of hypofunction was confirmed as often as 28 times. All those 28 cases of hypofunction have an initial tangent T_0' which is lower than 5% per hour.

However, two cases, for which $5 < T_0' < 7\%\ h^{-1}$, were suspected, too, of hypofunction for the following reasons: Barker 1.7 γ, dry skin and BMR —14%; cancer of the breast, Barker 2.1–3.6 γ, hypothermia, BMR —22%, but these two cases remain uncertain.

The cases where the metabolism was low (<—12%), but the thyroidal function measured by T_0' normal were as follows:

1 Diabetes mellitus,
1 hypofunction treated with pituitary extracts (Ambinon),
1 hyperfunction treated with antithyroidal drugs,
1 slight hyperfunction clinically doubtful,
2 anorexia nervosa,
8 cases of normal function where the depression of the metabolism is not explained,
4 Klinefelter Syndrome on which *Koller* and *Siegenthaler* (4) have reported in a separate paper.

In all the 30 cases, with two exceptions in which simultaneously the BMR was lower than —12% and the initial tangent lower than $5\%\ h^{-1}$, the diagnosis of a hypofunction was confirmed. The two exceptions were a case of adrenalectomy and ovariectomy and one with normal function which was in contact with iodine owing to a cholecystogram 2 weeks previously.

It must be said that hypofunction is much more difficult and uncertain to diagnose than hyperthyroidism, and that the frontier for T_0' in the lower region must be confirmed by the measurement of normal men who are not in-patients of a hospital.

In conclusion, we would state that out of all the 154 cases in which the basal metabolic rate was highly abnormal, i.e. higher than +12% or lower than —12%, in 97 only was a hyper- or a hypofunction clinically confirmed. *Thus the thyroid function is actually disturbed in 63% only of the patients in whom an abnormality of the basal metabolic rate is found.*

But if basal metabolic rate and initial tangent are both simultaneously abnormal ($+12\% < BMR < -12\%$ *and* $23\% < T_0' < 5\%\ h^{-1}$) *the clinical function is nearly always abnormal (85 cases and 2 exceptions).*

c) Initial tangent T_0' higher than 23% h^{-1}

Fig. 4 shows that 67 determinations are included in this range, of which 65 were really cases of hyperfunction. The two other cases are hypofunctions treated with pituitary extracts. These cases will be studied at greater length later.

It is important to see that 10 cases of this group—i.e. about a sixth—have a normal or lower metabolism.

The *intermediate range* $20 \leq T_0' \leq 23\%$ h^{-1} comprises 8 cases of whom 4 had hyperfunctions or were treated with Ambinon, one had a neuro-vegetative dystonia and three had clinically normal functions (Barker = 5.6, 3.8 and 3.6 γ).

d) Initial tangent T_0' lower than 5% h^{-1}

This class includes 57 cases of which 33 had really hypofunction. In 17 other cases the initial tangent was greatly reduced by earlier application of X-ray contrast medium (in one case with arsenical drugs). We will discuss these cases later. In 7 instances, then, the reduction of the initial tangent was explained neither by a hypofunction nor by a contact with iodine. These 7 exceptions were:

1 cancer of the breast with adrenalectomy (Barker 6.1 γ, BMR +10%). $T_0' = 4.5\%$ h^{-1}.

1 cirrhotic liver, alcoholism, gastritis (BMR +3%). $T_0' = 3.0\%$ h^{-1}.

1 vegetative dystonia, no hypofunction (BMR +23%). $T_0' = 1.6\%$ h^{-1}. Contact with iodine not excluded.

1 diabetes with insulin resistance (BMR +35%), cardiac insufficiency, $T_0' = 4\%$ h^{-1}.

1 tuberculosis with lobectomy, tachycardia, slight tremor (BMR +29%). $T_0' = 4.5\%$ h^{-1}.

1 cancer of the stomach with metastases (BMR +7%). $T_0' = 4\%$ h^{-1}.

1 cancer of the breast, ovariectomy and adrenalectomy (Barker 3.3 γ, BMR −24%). $T_0' = 0.5\%$ h^{-1}.

All these cases are therefore very exceptional ones.

The *intermediate range* $5 \leq T_0' \leq 6\%$ h^{-1} comprises 9 cases most of whom had normal functions. 2 hypofunctions only are included in this range, the diagnosis of which is somewhat uncertain (Barker 3.6 γ). Among the 7 normal functions are 3 cases of cardiac insufficiency, 1 of cancer of the breast after adrenalectomy and ovariectomy, 1 Klinefelter Syndrome.

In conclusion, if the initial tangent T_0' alone is measured and is greater than 23% or lower than 5%, and no contact with iodine is detected, the

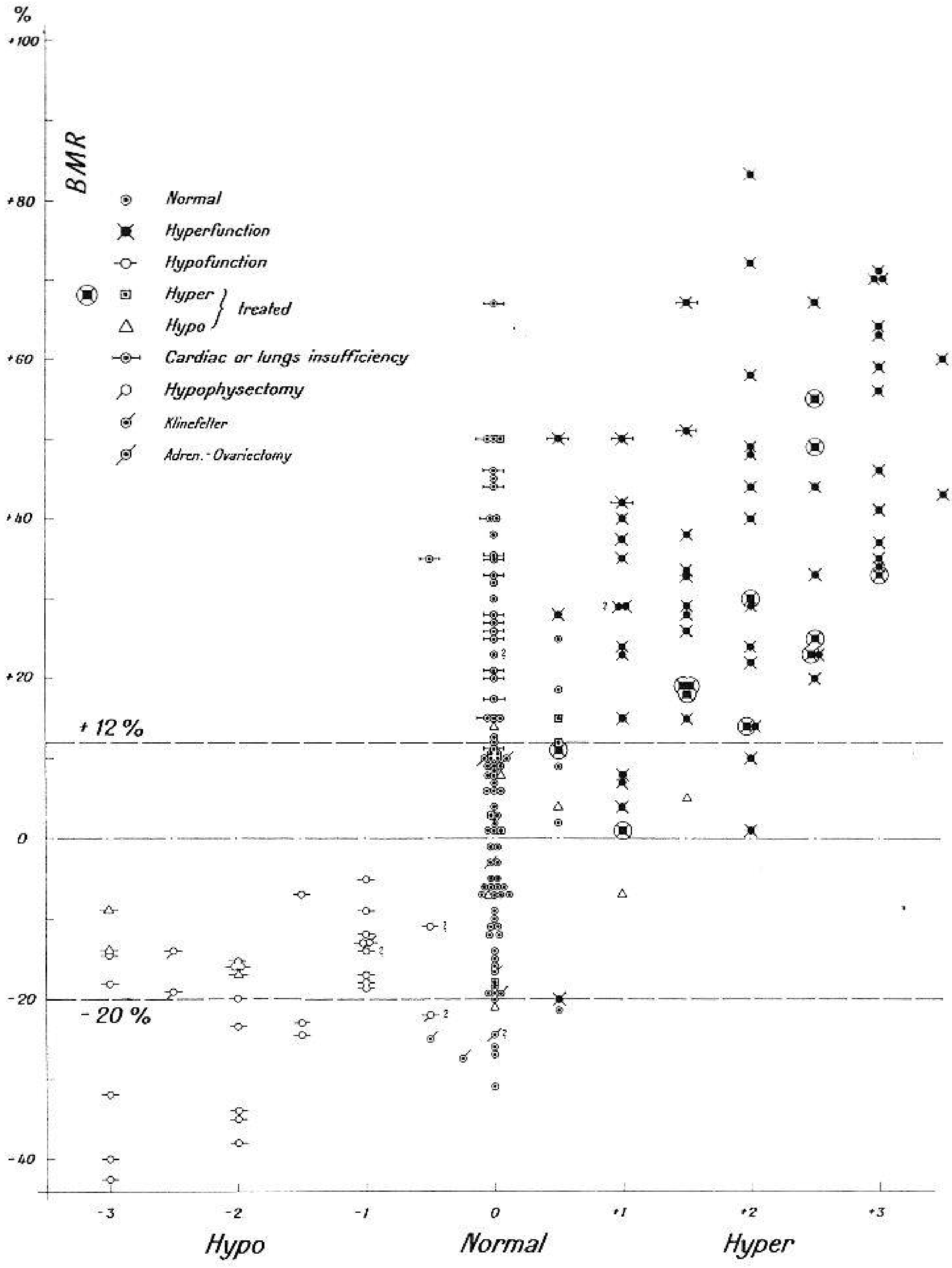

Fig. 5. Distribution diagram of 205 cases of normal and abnormal thyroid function. Abscissa: Clinical class. Ordinate: BMR (see also legend of Fig. 1).

thyroidal function is abnormal in 92% of the cases. The function is normal with the same condition in 96% of the cases if T_0' is in the range of 5 to 20% h^{-1}.

This conclusion emphasizes the diagnostic value of T_0' compared with that of the BMR.

3. The basal metabolic rate and the clinical intensity of the function

Fig. 5 gives the distribution diagram for the basal metabolic rate of 205 cases in terms of the clinical intensity of the function. We observe here the well-known general tendency for the BMR to increase with the intensity of the function. But the normal range is very extensive and stretches from about −20 to about +50%. About three quarters of the hyperfunction cases and two thirds of the hypofunction ones are situated within these limits. The indications of the BMR appear to be somewhat better if we exclude the cases of cardiac and pulmonary insufficiency (cancer of the lungs, hypertension, dyspnœa). The upper limit of the normal range is thus situated at +12% (11 cases excluded). But the inferior limit is not symmetrical to the upper one and is situated at about −20%. Having settled these limits, we see that out of a total of 69 cases of thyrotoxicosis, 7, i.e. 10%, are situated in the normal range of the BMR. Considering the 29 cases of hypofunction which are not doubtful, 20 cases, i.e. two thirds, are in the normal range. The difficulty of discriminating between the hypo and the normal functions with the BMR is again encountered here.

The fact that the basal metabolic rate is unable alone to determine the intensity of the thyroid function is confirmed by the distribution diagram of Fig. 5. Cardiac or respiratory insufficiency, vegetative dystonia, tumours of the lungs, dyspnœa are the principal causes of an abnormal BMR, apart from disturbances of thyroid function.

4. The clinical intensity of the function and the PBI (Barker)

The protein-bound iodine of the plasma was determined in 91 cases with the *Barker* (5) method. Some of the chemical determinations were made in the Medical Polyclinic of the University (Prof. *P. H. Rossier*) under the direction of Dr. *A. Labhardt*, and the others in the Chemical Laboratory of the Department of Medicine, under the direction of PD. Dr. *H. Rosenmund.* The distribution diagram is given in Fig. 6 in terms of the clinically determined medical class of the patients. It must be stressed that the number of thyrotoxicosis cases in which the PBI was determined is not very high because the diagnosis of these dysfunctions is

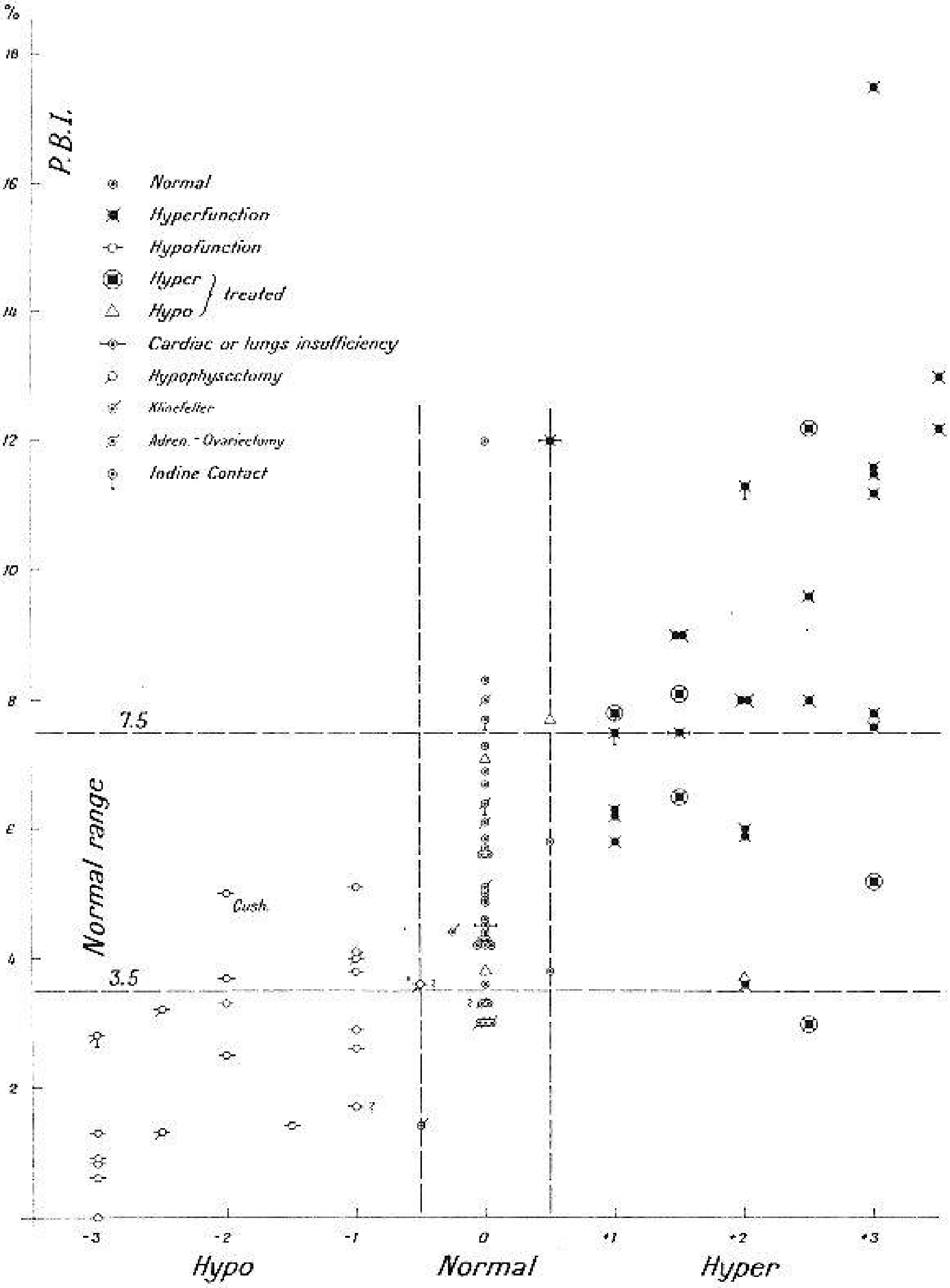

Fig. 6. Distribution digram of 91 cases of normal and abnormal function. Abscissa: Clinical class. Ordinate: PBI (see also legend of Fig. 1).

generally easier for the clinician. It was principally in doubtful cases, in order to discriminate between normal and hypofunctions, that the PBI was determined in about half our cases.

Barker et al. (6) consider in their first statistics 3.5 $\gamma\%$ as the lower value for the normal range and hesitated between 7.0 and 8.0 $\gamma\%$ for the upper limit. Considering 3.5 up to 7.5 $\gamma\%$ as the normal range, we see that 3 clinically normal cases only are outside this range. 6 others all have something abnormal: One case (7.7 $\gamma\%$) has a normal function, having received "Joduron" for a pyelogram; four cases with 3.0, 3.0, 3.3 and 8.0 $\gamma\%$ were observed after adrenalectomy and ovariectomy and one with 3.0 $\gamma\%$, too, has a Klinefelter syndrome. Among the 18 hypofunctions considered clinically as well established, 4 are situated in the normal range. These exceptions are an anorexia mentalis which was difficult to characterize, two weak hypofunctions, one adrenalectomy.

The results are less good for thyrotoxicosis. 10 cases of hyperfunction are situated in the normal range. In one normal case, which, however was treated for 3 days with pituitary extracts (500 mg Ambinon) and showed clinical signs of hyperthyroidism, the Barker is only 3.7 $\gamma\%$. The duration of treatment was too short to cause the PBI to rise[4].

In conclusion, out of a total of 91 cases shown in fig. 6, in 24, i.e. somewhat more than a quarter, the measurement of the PBI did not agree with the clinical evaluation of the function. The Barker test appears to be better for the discrimination of hypofunction than for the distinction of hyperthyroidism.

5. The PBI (Barker) and the initial tangent T_0'

In the distribution diagram of Fig. 7, the initial tangent T_0' is shown logarithmically as a function of the PBI. The distribution shows that T_0' has a general tendency to rise with the PBI. The latter varies from about 0.5 to about 18 $\gamma\%$, i.e. nearly 40 fold. But the corresponding variation of T_0' goes from less than 1% to more than 200% per hour, i.e. a factor greater than 200. The range of the initial tangent is thus 5 to 10 times more extensive than that of the PBI.

In 13 cases of slight, medium and strong hyperfunction, T_0' is greater than 23% h^{-1} but the PBI is in or below the normal range. Among the 8 cases which appear as normal for the PBI, but lower than 5% h^{-1} for T_0', 5 were clinically confirmed as hypofunctions. Of the 3 remaining normal cases 2 were measured after adrenalectomy and 1 was in contact with iodine. In 10 cases which appear outside the normal range for the PBI, but are normal for T_0', 8 cases have clinically normal functions (3 with adrenalectomy and 2 Klinefelters), 1 case has a clinically uncertain hypofunction and 1 a hyperfunction after iodine contact. It must be pointed out here that the error in the determination of the PBI probably amounts to $\pm 1\ \gamma$, so that the normal range is not so exactly limited.

In conclusion, the results of T_0' agree with those of the Barker determination in 63% only of the cases. Where they disagree, T_0' more often

[4] The action of pituitary extracts is discussed later.

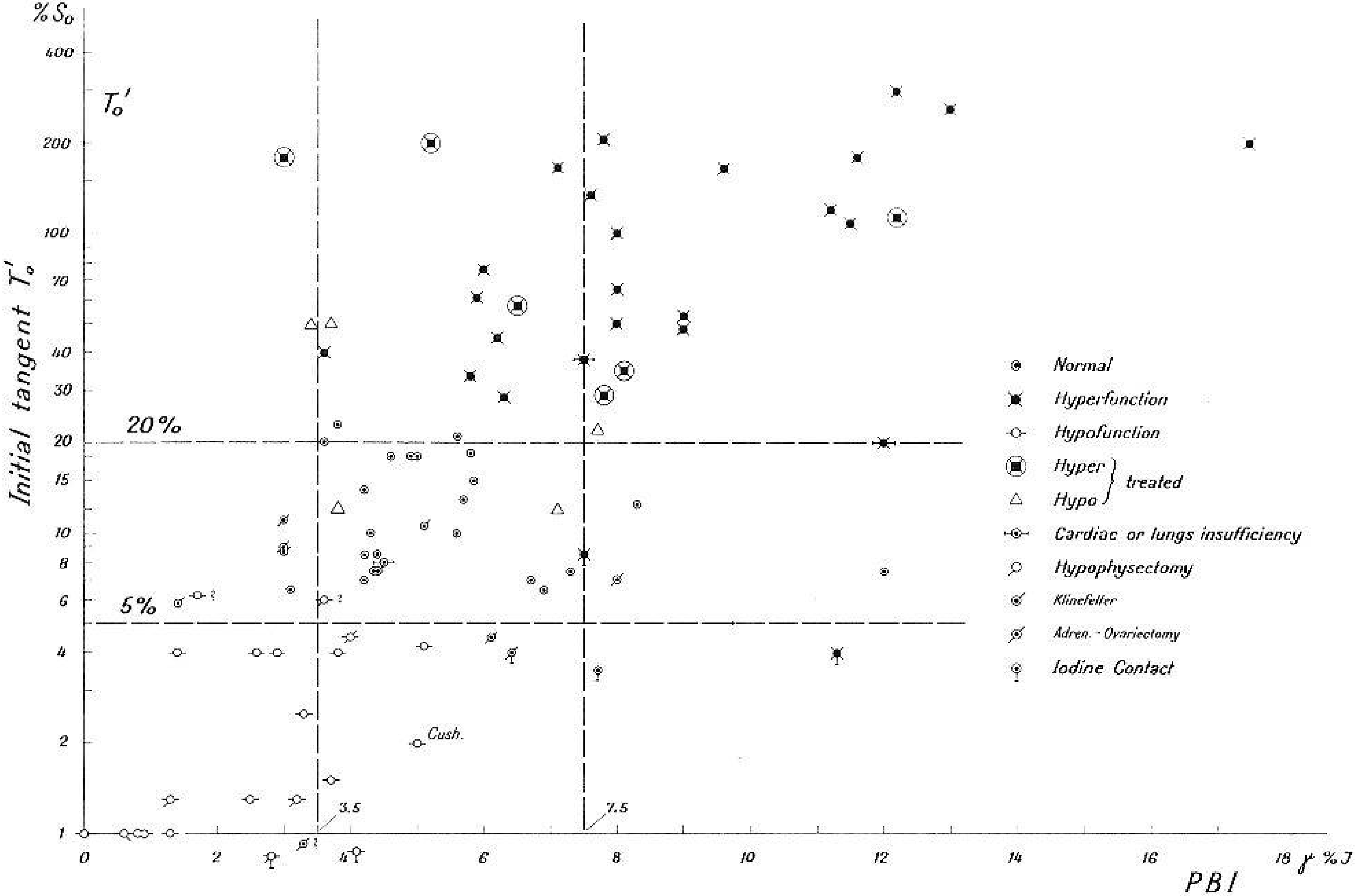

Fig. 7. Distribution diagram of normal and abnormal functions. Abscissa: PBI. Ordinate: Initial tangent T'_0 (logarithmic scale).

gives the right diagnosis in our cases than PBI, especially for hyperfunctions. For hyperfunctions, when T_0' is lower than 5% h^{-1}, the only exception is when the patients have been subjected to adrenalectomy.

6. *Examples of some normal functions, thyrotoxicosis and hypofunctions*

We give in the following some typical examples of normal and abnormal functions, illustrated in every case with the uptake curve during the first few hours and the sketch of the initial tangent. In some cases the curve was recorded for 4 to 8 days and the three coefficients (α = uptake rate, η = urinary excretion rate, λ = thyroidal flow rate) were determined with the graphical method published in the previous paper (1).

Amersham's isotonic and sterile radioiodine was intravenously injected in each case in the morning, after a usual breakfast, between 8.30 and 10.30. No soporific or medication influencing the thyroid was given on the preceding days (except where such an influence was recognized and allowed for).

In each case the patient was carefully interrogated to see if an important quantity of iodine had been absorbed as a medicament, contrast medium or ointment, or in connection with a gynecological investigation or dental treatment during the previous 6 months.

a) Examples of cases with normal functions

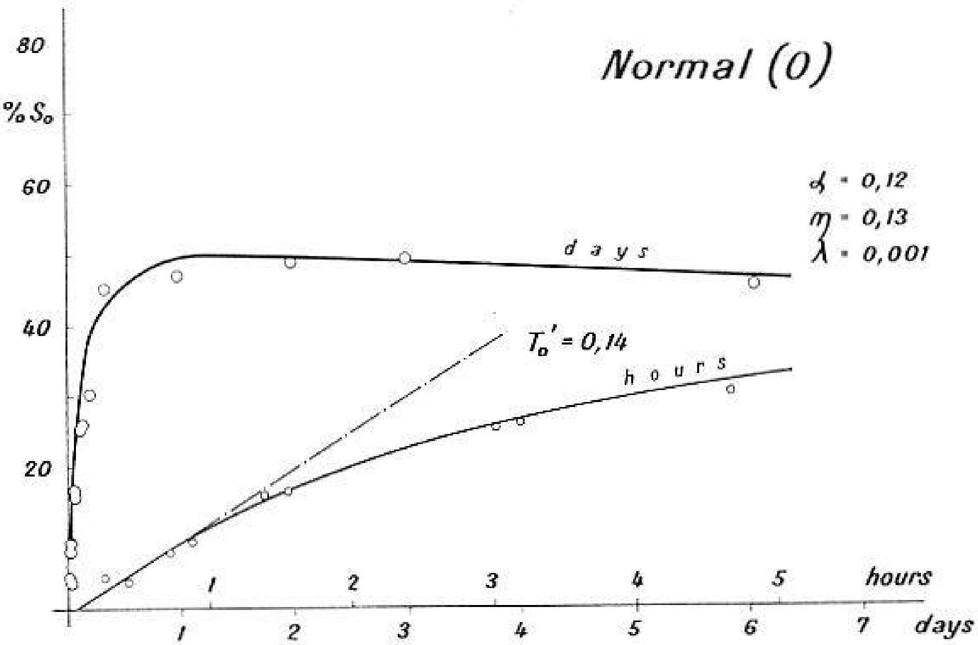

Fig. 8. Hyperthyroidism suspected? Woman 52 years old, 81 kg, enlarged thyroid, sporadic tachycardia, BMR +8%, Barker 4.2 γ%, no contact with iodine. Initial tangent T'_0 = **14%** h^{-1}, *normal function.*

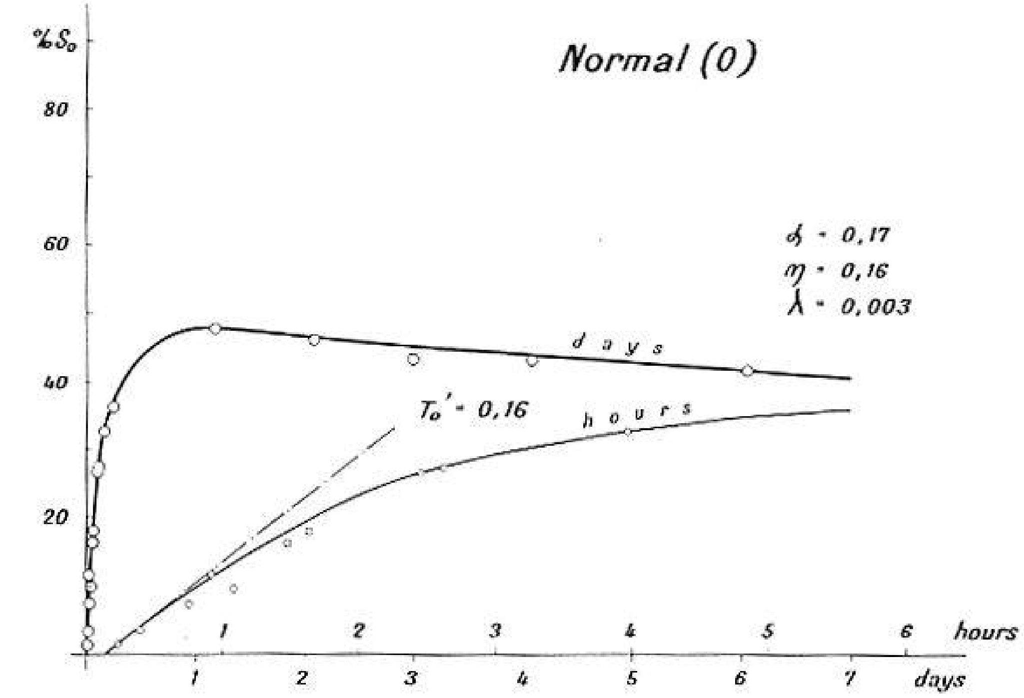

Fig. 9. Vegetative dystonia, hypertension, hyperthyroidism? Woman 39 years old, 61 kg, enlarged thyroid, BMR +15, +6%. No contact with iodine. Initial tangent T'_0 = **15.5% h^{-1}**, *normal function.*

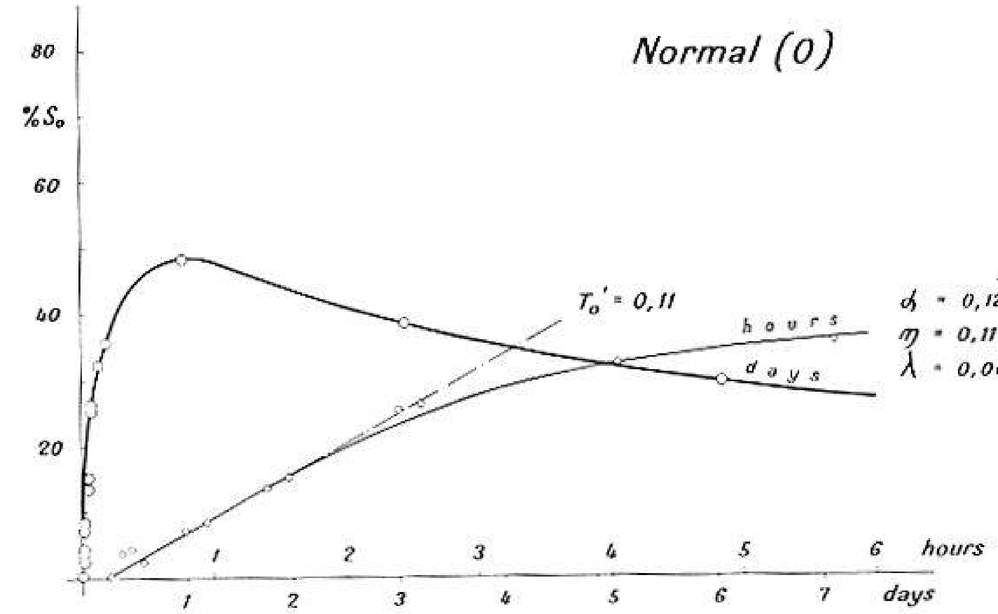

Fig. 10. Cardiac insufficiency, hyperthyroidism? Woman 58 years old, 63 kg, normal thyroid, BMR +67%, tachycardia, no contact with iodine. Initial tangent T'_0 = **11% h^{-1}**, *normal function.*

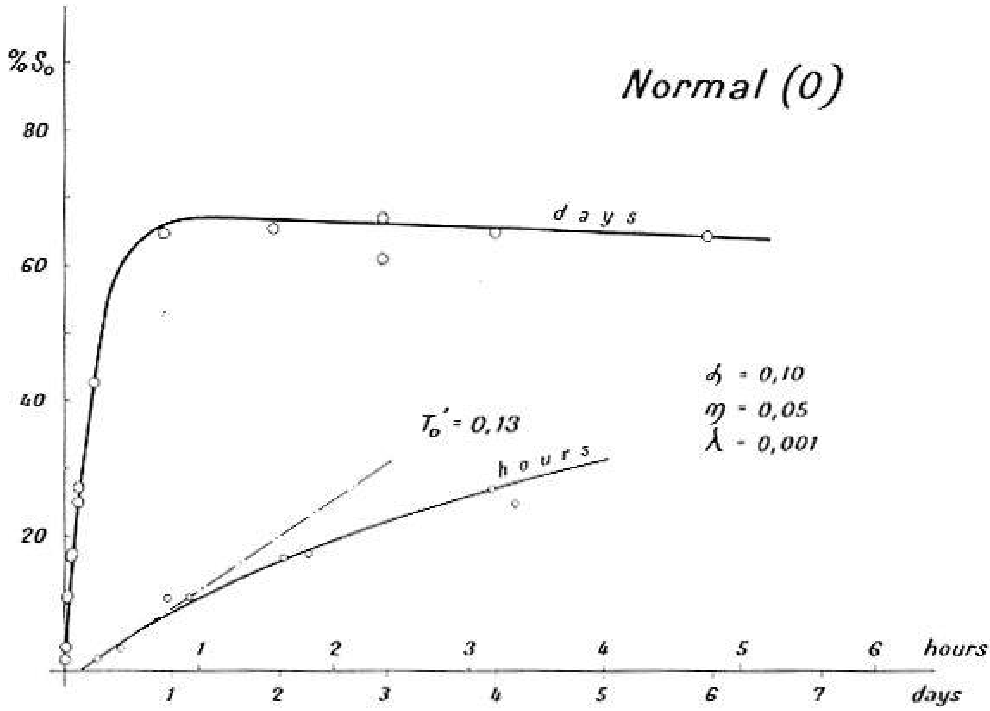

Fig. 11. Slight hyperthyroidism? Man 26 years old, 56 kg, tachycardia, nervousness, enlarged thyroid, BMR -15%, Barker 5.7 $\gamma\%$, no contact with iodine. Initial tangent $T'_0 = \mathbf{13\%}\ \mathrm{h}^{-1}$, *normal function.*

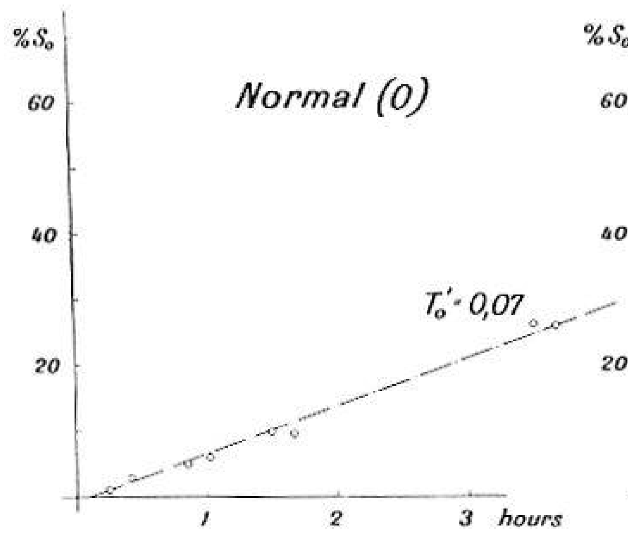

Fig. 12.

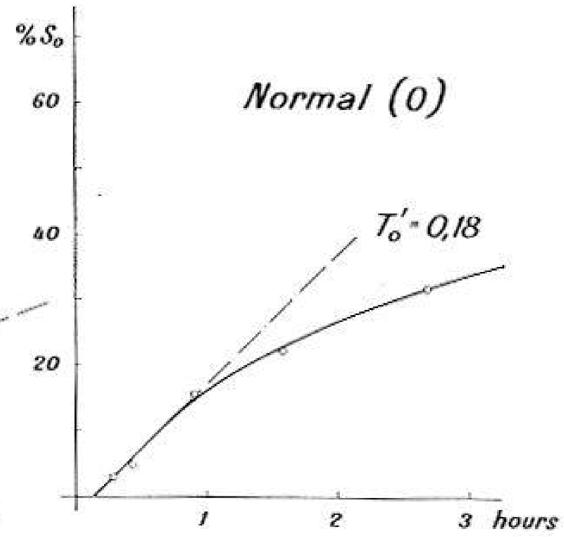

Fig. 13.

Fig. 12. Anorexia mentalis, hypometabolism? Woman 45 years old, 50 kg, enlarged thyroid, BMR -19, -18, -22%, Barker 6.7 $\gamma\%$. No contact with iodine. Initial tangent $T'_0 = \mathbf{7.0\%}\ \mathrm{h}^{-1}$, *normal function* (hypometabolism due to malnutrition).

Fig. 13. Alcoholismus chronicus, tremor, hyperthyroidism? Man 58 years old, 58 kg, tremor, tachycardia, BMR $+36$, $+43$, $+40\%$, Barker 5.0 $\gamma\%$, no contact with iodine. Initial tangent $T'_0 = \mathbf{18\%}\ \mathrm{h}^{-1}$, *normal function.*

All the cases in which the BMR is not significant for the thyroid function must be stressed.

b) Examples of cases with hyperthyroidism (Fig. 14–21)

In Fig. 18 and 20, the Barker is at the limit of the normal range, but the initial tangent and the rapid fall of the uptake curve after the maximum permit a clear discrimination of hyperthyroidism. In Fig. 21, the tracer indicates a slight hyperfunction and stresses the importance of cardiac insufficiency for the BMR.

We must emphasize that in *all hyperfunctions* the rapid fall of the uptake curve after the maximum is characteristic. But it must be said that this rapid fall is not determinant, because it may appear sometimes in cases of normal function (see Fig. 10) and, as we will see later, in hypofunction, too (see Fig. 24).

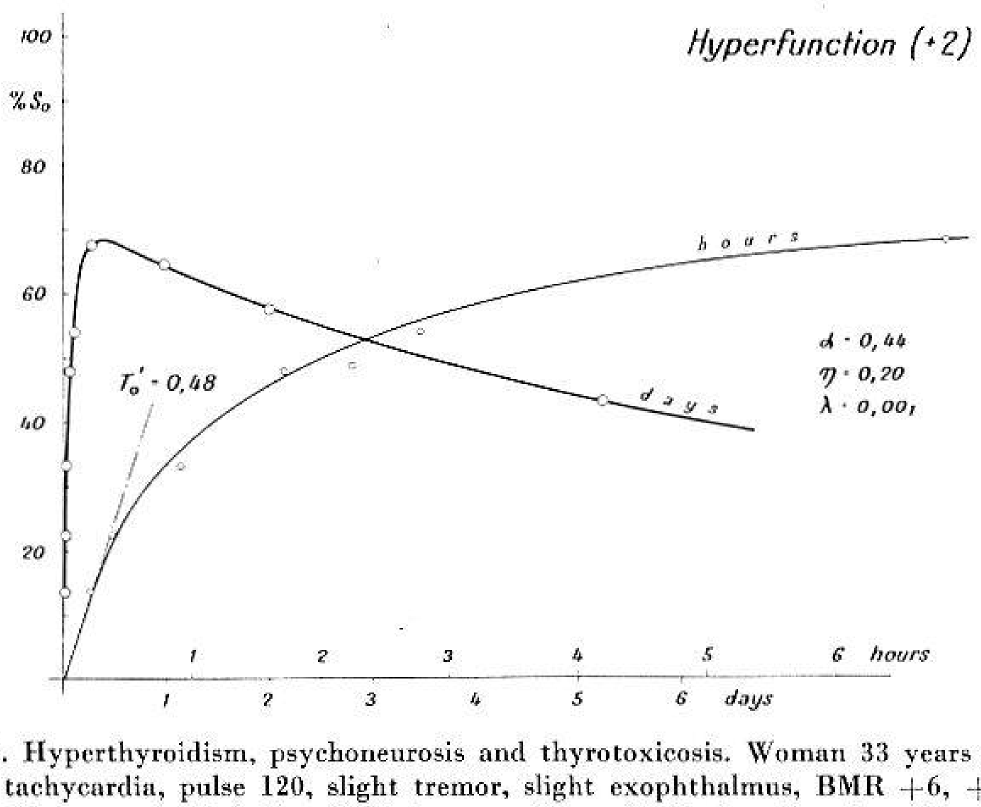

Fig. 14. Hyperthyroidism, psychoneurosis and thyrotoxicosis. Woman 33 years old, 60 kg, tachycardia, pulse 120, slight tremor, slight exophthalmus, BMR +6, +10, +15%. No contact with iodine. Initial tangent T'_0 = **48%** h^{-1}, *medium hyperfunction*, class +2.

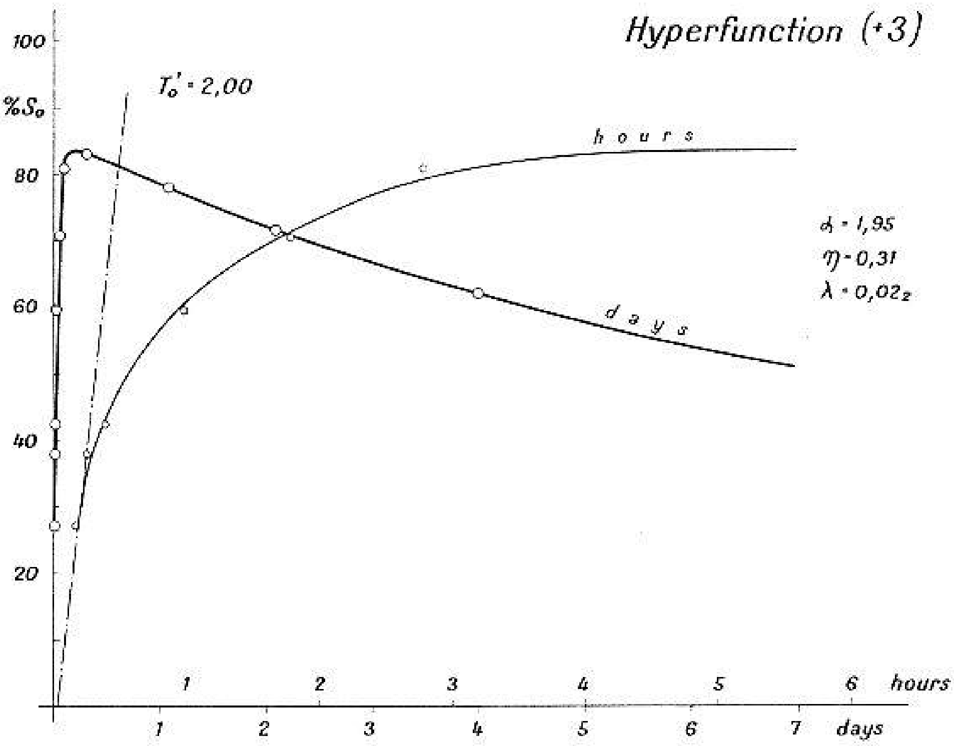

Fig. 15. Classic thyrotoxicosis. Girl 14 years old, 33 kg, exophthalmus, tachycardia, BMR +59, +51%, Barker 17.5 γ%, no contact with iodine. Initial tangent $T'_0 =$ **200%** h^{-1}, *very strong hyperfunction*, class +3. (By courtesy of Dr. *Spaar*, Kinderspital Zurich, Prof. *G. Fanconi*.)

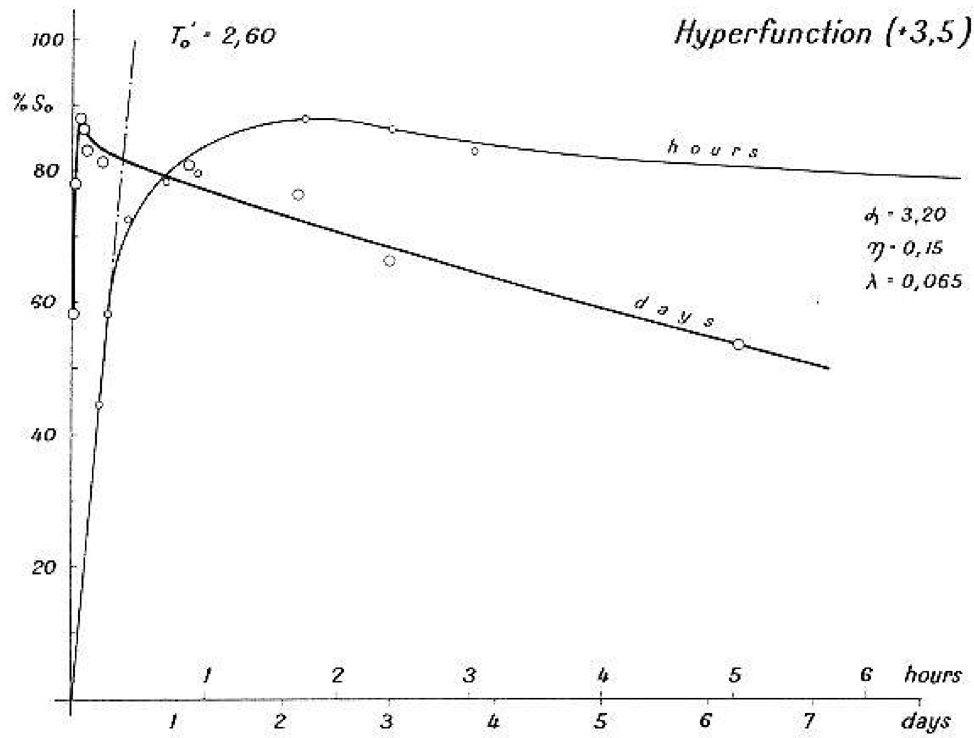

Fig. 16. Thyrotoxicosis. Boy 16 years old, 43 kg, infantilism, enlarged thyroid, tachycardia, pulse 135, tremor, BMR +43, +43%, Barker 13 γ%. Initial tangent $T'_0 =$ **260%** h^{-1}, *very strong hyperfunction*, class +3.5. (By courtesy of Dr. *Tobler*, Kinderspital Zurich, Prof. *G. Fanconi*.)

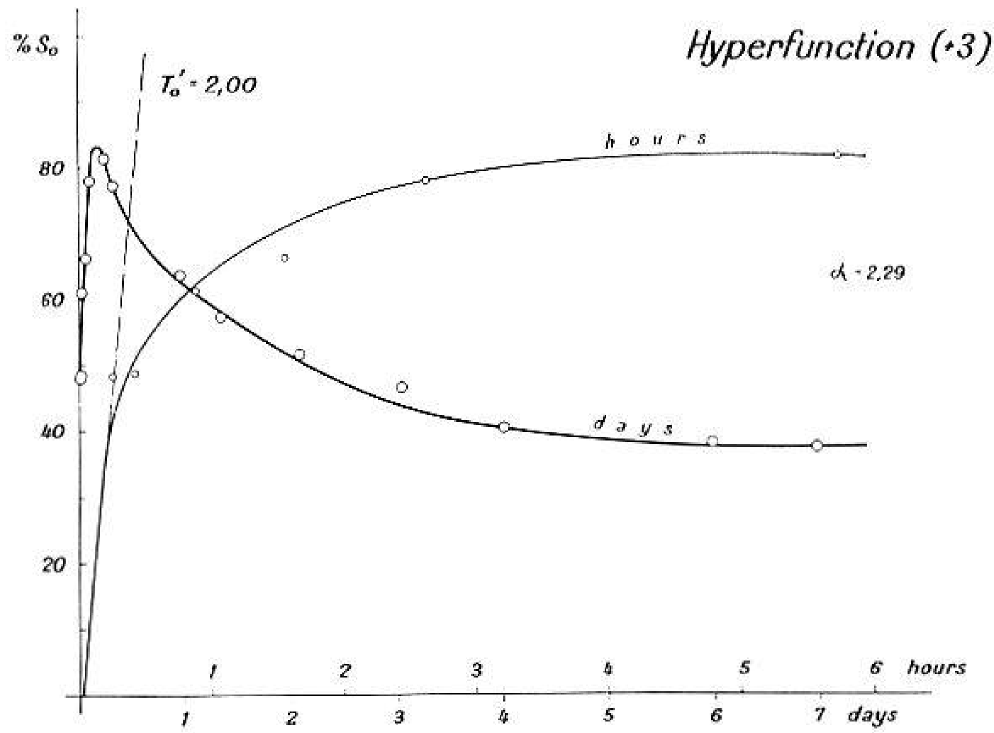

Fig. 17. Classic thyrotoxicosis. Woman 57 years old, 52 kg, exophthalmus, tachycardia, pulse 120, BMR +35%, no contact with iodine. Initial tangent $T'_0 = \mathbf{200\%}\ \mathbf{h^{-1}}$, *very strong hyperfunction*, class +3.

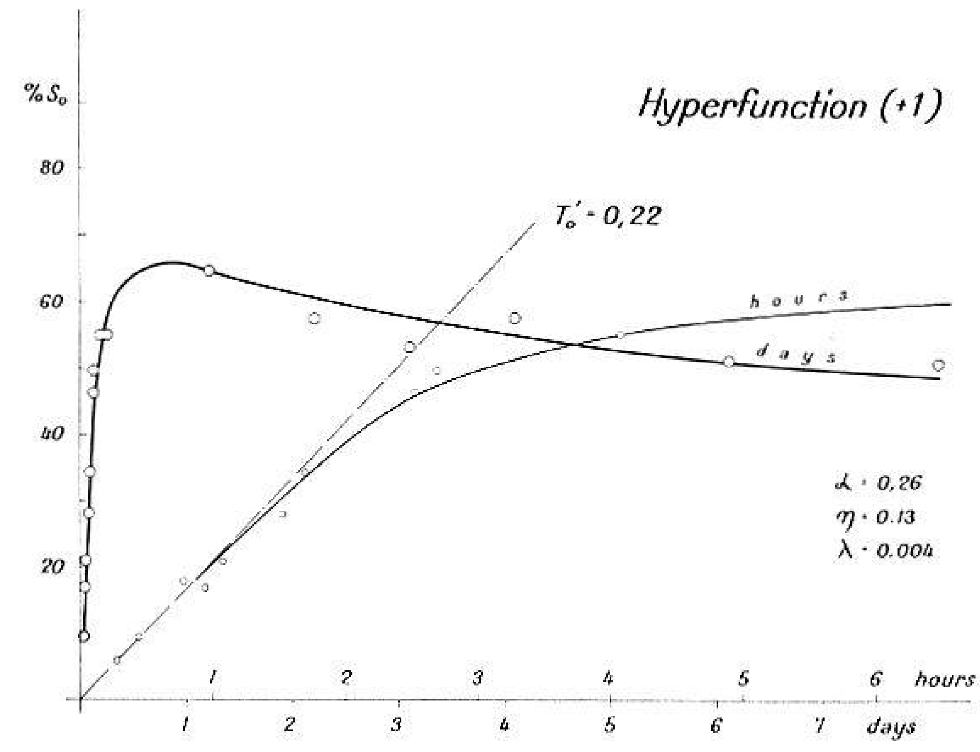

Fig. 18. Thyrotoxicosis. Woman 64 years old, 72 kg, exophthalmus, slight tremor, pulse 90, BMR +30, +40%, Barker 7.8 γ%, no contact with iodine. Initial tangent $T'_0 = \mathbf{22\%}\ \mathbf{h^{-1}}$, *slight hyperfunction*, class +1.

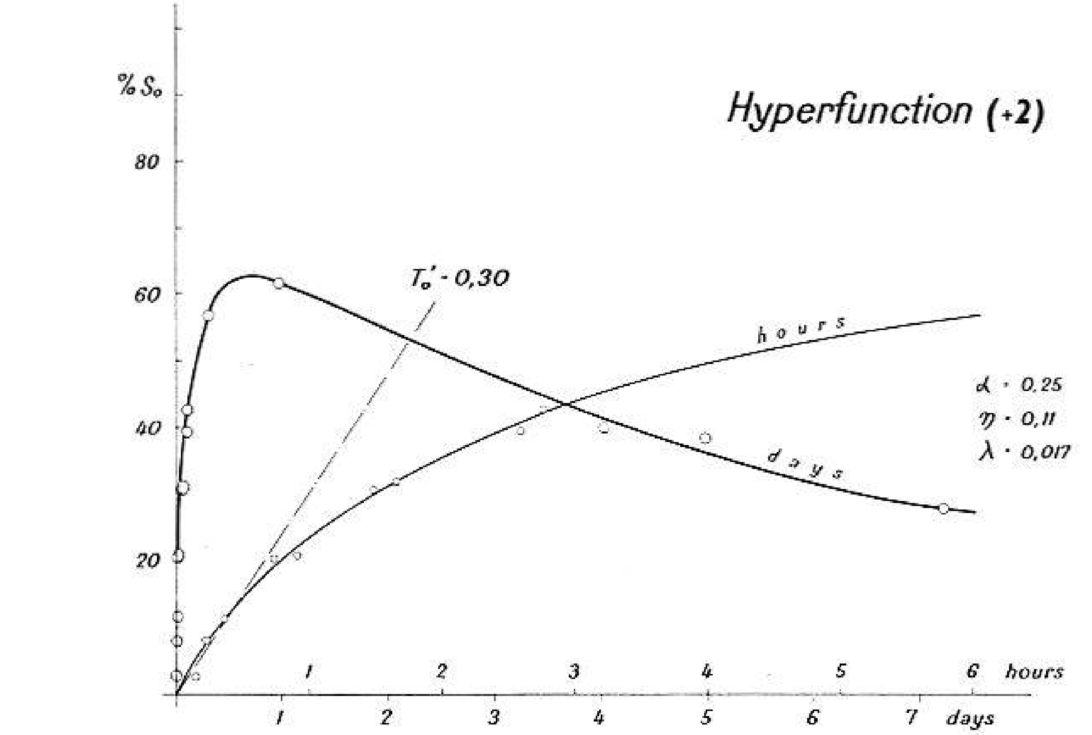

Fig. 19. Thyrotoxicosis. Woman 41 years old, 49 kg, enlarged thyroid with struma nodosa, tachycardia, BMR +48, +27%, no contact with iodine. Initial tangent T'_0 = **30% h^{-1}**, *medium hyperfunction*, class +2.

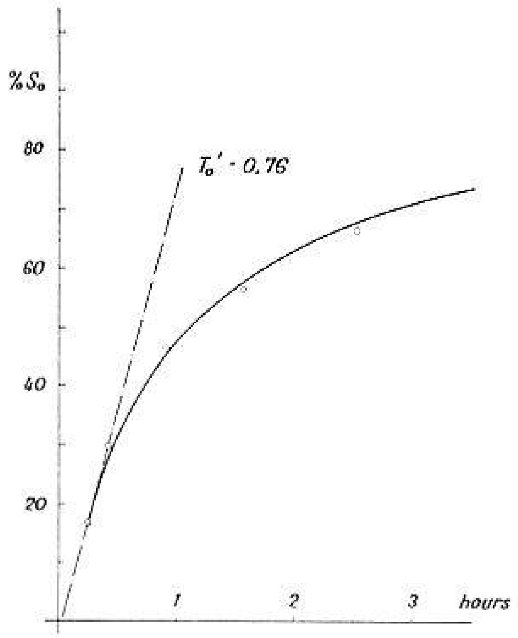

Fig. 20.

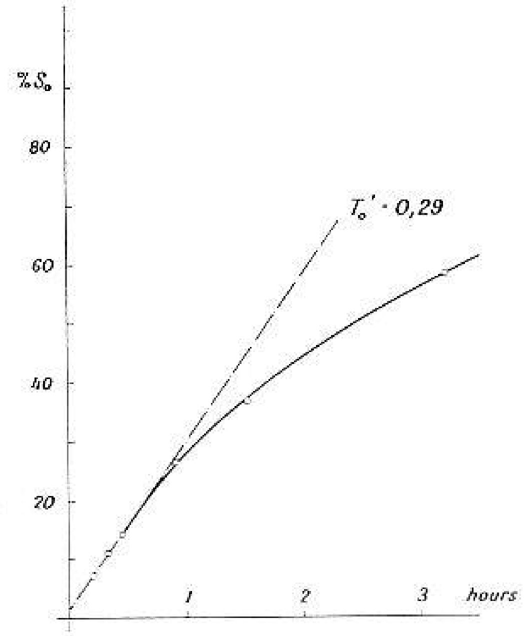

Fig. 21.

Fig. 20. Thyrotoxicosis. Man 52 years old, 53 kg, enlarged thyroid, tachycardia, BMR +26, +22, +23%, Barker 6.0 γ%, no contact with iodine. Initial tangent T'_0 = **76% h^{-1}**, *medium hyperfunction*, class +2.

Fig. 21. Thyrotoxicosis, slight hypertonia, cardiac insufficiency. Man 82 years old, 44 kg, slight exophthalmus, enlarged thyroid, no tremor, no tachycardia, BMR +40%, no contact with iodine. Initial tangent T'_0 = **29% h^{-1}**, *slight hyperfunction*, class + 1.

c) Examples of cases with hypofunctions

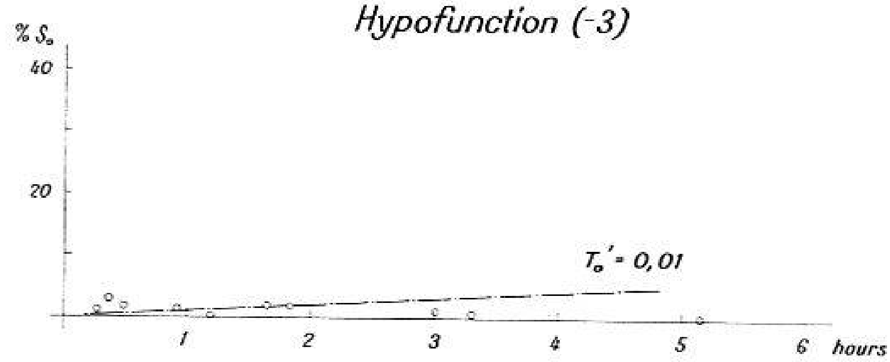

Fig. 22. Strong myxœdema. Woman 41 years old, 65 kg, obese, thyroid reduced, cholesterol 290 mg%, BMR -32%, Barker 0.8 $\gamma\%$, slight contact with iodine. Initial tangent $T'_0 = \mathbf{1\%}\ \mathrm{h}^{-1}$. *Strong hypofunction*, class -3.

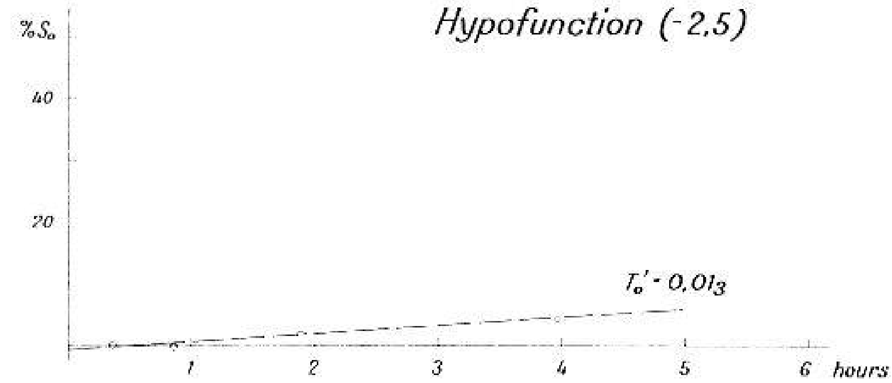

Fig. 23. Anterior pituitary insufficiency, myxœdema habitus. Male adult, 78 kg, cholesterol 286 mg%, BMR -20%, Barker 2.5 $\gamma\%$, no contact with iodine. Initial tangent $T'_0 = \mathbf{1.3\%}\ \mathrm{h}^{-1}$. *Medium hypofunction*, class -2. (By courtesy of Dr. *C. K. Huber*.)

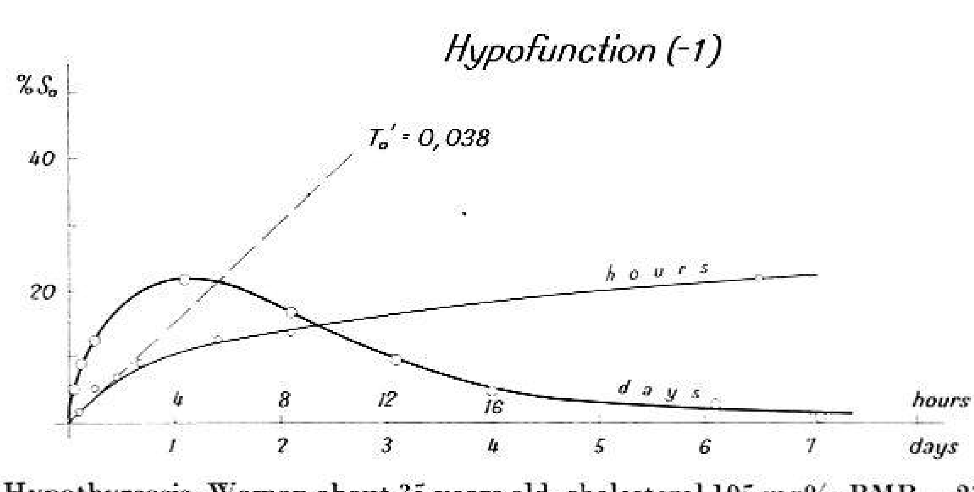

Fig. 24. Hypothyreosis. Woman about 35 years old, cholesterol 195 mg%, BMR -23%, Barker 1.4 $\gamma\%$. Seven days' treatment with thyroxin one week before, no other contact with iodine. Initial tangent $T'_0 = \mathbf{4.0\%}\ \mathrm{h}^{-1}$. *Slight hypofunction*, class -1. The rapid fall of the uptake curve after the maximum should be stressed.

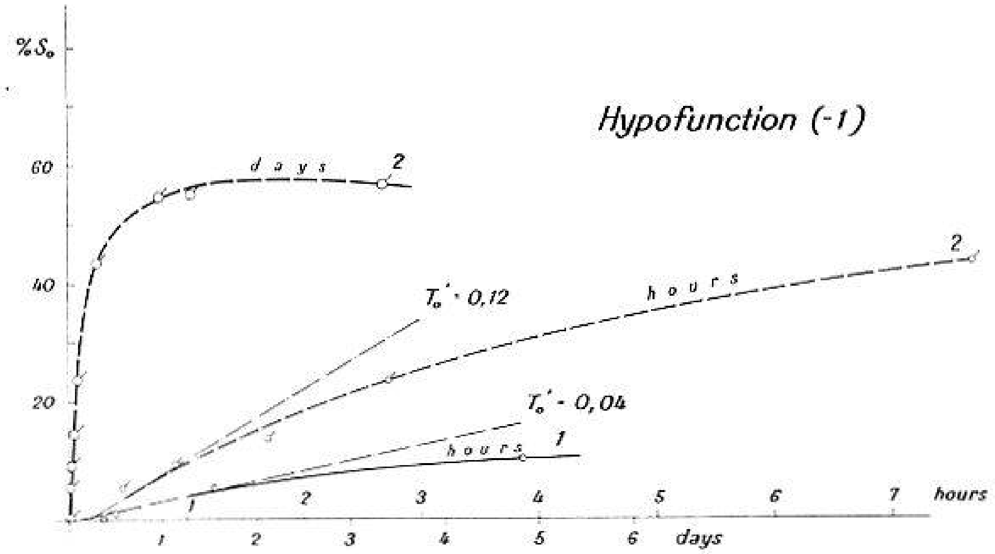

Fig. 25. Slight hypofunction, hypergonadotrophism, hypogonadism, diabetes mellitus, adiposity. Cholesterol 200 mg%, BMR −9%, Barker 2.9 γ%, no contact with iodine. Initial tangent $T'_0 = 4\%\ h^{-1}$ (curve 1). *Slight hypofunction*, class −1. Treatment with pituitary extracts (Thyrotropar Armour, 200 U.S.P.U.). After: BMR +8%, Barker 7.2 γ%. Initial tangent $T'_0 =$ **12%** h^{-1} (curve 2). (By courtesy of Dr. *A. Labhardt*, University Medical Polyclinic (Prof. *P. H. Rossier*.)

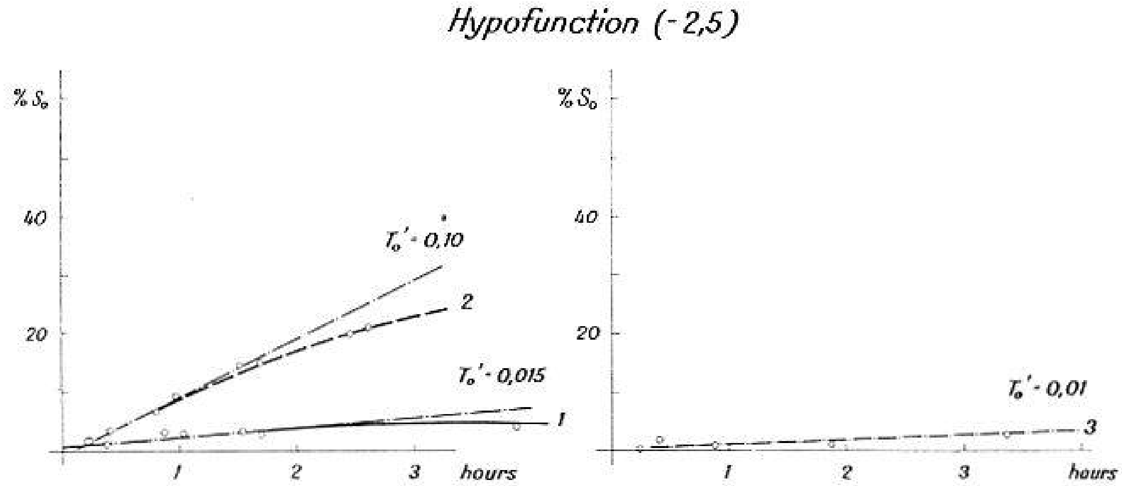

Fig. 26. Morbus Sheehan, panhypopituitarism. Woman 52 years old, 64 kg, myxoœdema, pituitary insufficiency. Atrophy of the thyroid. Cholesterol 150–175 mg%, BMR −38, −21, −40%, Barker 0.0, 0.6, 1.3, 0.9 γ%. No contact with iodine. Initial tangent (first, curve 1) $T'_0 =$ **1.5%** h^{-1} (third, 6 months later, curve 3), $T'_0 =$ **1.0%** h^{-1}. *Strong hypofunction*, class −2 to −3. Treatment with pituitary extracts (2000 H.L.U. Ambinon in 10 days followed by second tracer). Initial tangent $T'_0 =$ **10%** h^{-1} (curve 2). Hence a hypofunction of the pituitary.

7. *The influence of pituitary extracts or hypophysectomy on the initial tangent T'_0*

The following table shows the influence of pituitary extracts or TSH on the initial tangent in 11 cases. The clinical intensity of the function is given by the class number in the second column. The second "tracer" was always made the day after the end of the treatment.

Action of pituitary extracts on T'_0.

Case	Class	Before treatment T'_0 % h^{-1}	Before treatment Barker γ%	After treatment T'_0 % h^{-1}	After treatment Barker γ%	Treatment
♀ Hypothyreosis	−2	**1.5**	3.7	**12**	3.8	Ambinon (Organon) 4×100 H.L.U.[1]
♂ Hypofunction of pituitary	−1.5	**2.5**	–	**17**	–	id. 10×200 H.L.U.[1]
♀ Normal	0	**7**	–	**30**	–	id. 6×100 H.L.U.[1]
♀ Normal	0	**6.5**	3.7	**50**	–	id. 4×100 H.L.U.[1]
♀ Hypothyreosis, myxœdema	−2	**0**	–	**0**	–	id. 3×100 H.L.U.[1]
♀ Hypothyreosis	−2	**2.2**	–	**37**	–	id. 5×200 H.L.U.[1]
♀ Myxœdema, Morbus Sheehan	−2.5	**1.5**	–	**10**	–	id. 10×200 H.L.U.[1]
♂ Hypofunction	−1	**4**	2.9	**12**	7.2	T.S.H. Armour 10 U.S.P.U.[2]
♀ Pituitary insufficiency	−1.5	**0.5**	6.8 (thyroidea)	**34**	6.0	T.S.H. Armour 3×10 U.S.P.U.[2]
				1 (3 weeks later)	5.3	
		one month without thyroidea:				
		3	4.5	**19**	7.6	T.S.H. Armour 1×10 U.S.P.U.[2]
♂ Hypofunction suspected	−1?	**0.2** (one year thyroidea)	5.3			
		9 months without thyroidea:				
		2.7	3.2	**10.5**	5.5	T.S.H. Armour 2×10 U.S.P.U.[2]
♀ Normal function after adrenalectomy and ovariectomy and partial hypophysectomy	0	**0.5**	3.3	**49**	3.4	T.S.H. Armour 3×10 U.S.P.U.[2]

[1] Heyl-Laqueur Units.
[2] United States Pharmacopœia Units.

The great influence of the short hormonal treatment on T'_0—that is, on the uptake rate of the inorganic iodine of the plasma by the thyroid—is most impressive. The hypofunction is shifted into the normal range, and the normal function into the hyperfunction range. In one case only, of primary hypofunction of the thyroid and a classic case of myxœdema, there is no modification of T_0'; the other endocrine functions are relatively normal. The number of PBI (Barker) measurements is too few in these statistics to show a systematic influence on this test[5]. Probably the hormonal treatment ought to be pursued for many weeks until the quantity of thyroxine secreted by the thyroid is able to raise the level of PBI in the blood. If we take account of the evaluation of *Triantaphyllidis*, *Ambrosino*, *Tubiana* and *Cukier* (7) for the pool of thyroxine in the normal man (1500 γ in 46% of the weight[6]), it would take about 2 weeks to raise the Barker by about 3 γ%.

This method enables us then to show in a short time if the hypofunction is primary or secondary.

Hypophysectomy was performed on the following 6 patients, all women with cancer of the breast and metastases (Neurosurgical Clinic, Prof. *Krayenbühl*). In all the 4 cases in which the operation was considered clinically as complete, T_0' was greatly reduced below the normal range (the values in parenthesis indicate the number of days after the operation that the second test was performed). The same result seems to appear for the Barker, which is always reduced after total hypophysectomy. In the partial hypophysectomy of the second case, the low T_0', 18 days after the operation, is probably explained by a contact with iodine; 7 months later T_0' was normal.

Action of hypophysectomy on T'_0.

Before Hypophysectomy					Hypophysectomy	After Hypophysectomy			
Case	Class	T'_0	Barker	BMR		Class	T'_0	Barker	BMR
1	0	**7.5**	7.3	−14	Total	−3	**0** (55)	2.8 (45)	−34
2	0	**10**	4.3	+30	Partial	−0.5	**0.6** (18)	4.8 (26)	− 3
						0	**7.0** (210)		+ 2
3	0	**7.0**	6.9	–	Total	−1	**4** (70)	2.5 (60)	−25
						−2.5	**1.3** (120)	3.2*(120)	−14
4	0	**10**	–	+15	Total	0	**1.0** (26)	3.9 (18)	− 8
						−3		1.3 (140)	
5	0	–	–		Total	−2	**1.3** (43)	4.2 (38)	−19
								3.4 (90)	
6	0	–	6.0	+ 2	Partial	−0.5	**6** (55)	3.6 (60)	−21

* Hypofunction treated with thyroidea.

[5] A special study of the influence of pituitary extracts on hypofunctions has been made with the assistance of Dr. *Goerre* and Dr. *Amstein* and will be published in extenso later.

[6] *Berson* et al. (9) in five euthyroid cases found 1200 to 9200 γ for this pool.

Despite the small number of cases investigated, it is to be hoped that T_0' will be a valuable test for the control of the extent of a hypophysectomy.

8. *The influence of various treatments of hyperfunctions on the initial tangent T_0'*

As will be shown below, the initial tangent is also able to show the actual effect of the treatment of thyrotoxicosis with antithyroidal drugs or radioactive iodine. When the treatment is effective, it reduces the values of T_0' to the normal range. In an ineffective or incomplete treatment, T_0' maintains abnormally high values.

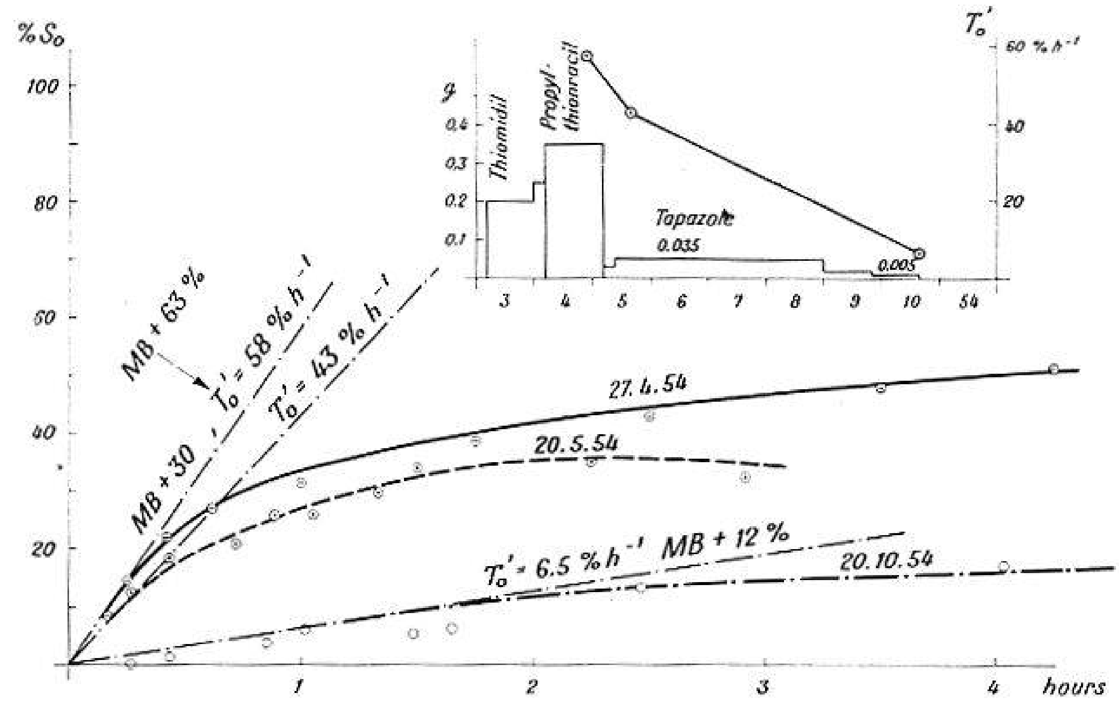

Fig. 27. Treatment of a Basedow case with various antithyroidal drugs. Fall of T'_0 with the success of the treatment.

Fig. 27 shows the influence of *various antithyroidal drugs* on a woman 42 years of age, with Basedow (class +2) from the 3rd to the 10th month of 1954. "Thiomidil" with the given dose had almost no effect, "Propylthiouracil" only a slight one. "Tapazol" on the other hand was able to reduce the function to the normal state which corresponded with the clinical improvement. The values of T_0', the BMR and the dosage of the treatment are recorded in the diagram. The chemical treatment therefore reduced T_0' from 58 to 6.5% h^{-1}.

In a second example (Fig. 28), a woman 54 years of age, 57 kg with thyrotoxicosis (class +1.5) was treated with daily doses of 35–20 mg "Tapazol" for 6 weeks. The treatment reduced the BMR from +30% to +3%, and T_0' from 66 to 6% h^{-1}. At the end, the patient was considered to be clinically normal again. If we consider the uptake curves

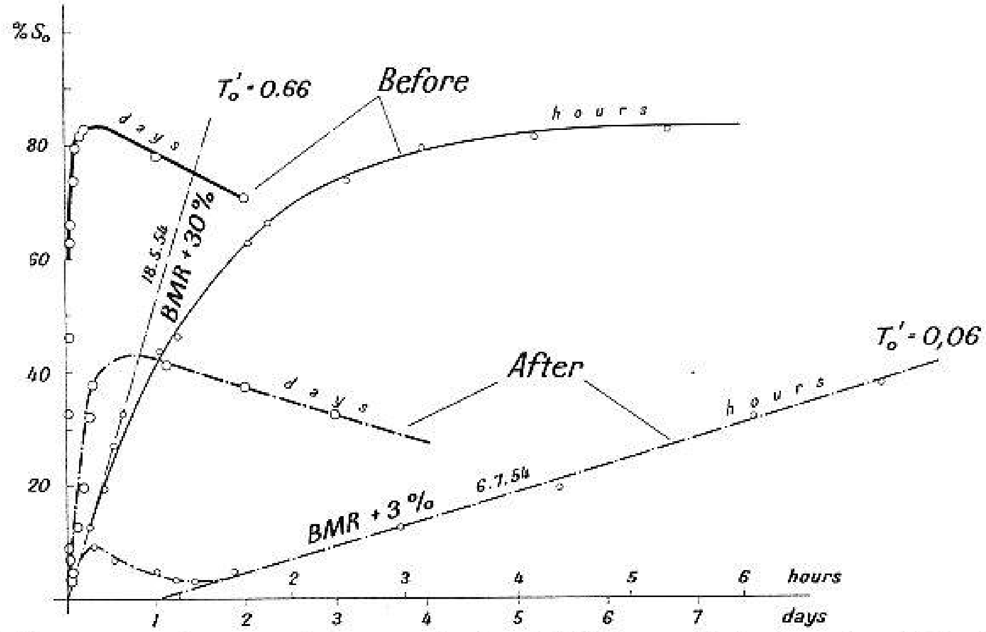

Fig. 28. Treatment of a case of thyrotoxicosis with "Tapazol" for 6 weeks. Fall of T'_0 with the success of the treatment.

plotted on the scale of the days, it must be stressed that the rapid fall after the maximum is not suppressed by the treatment. We see here, too, that the control of the radioiodine tracer is a valuable indication for the supervision of the treatment.

The results of the *treatment* of thyrotoxicosis with *radioiodine* may also be measured and controlled with T_0'. In Fig. 29, a woman 53 years old, 48.5 kg, with thyrotoxicosis (Morbus Basedow) of average intensity

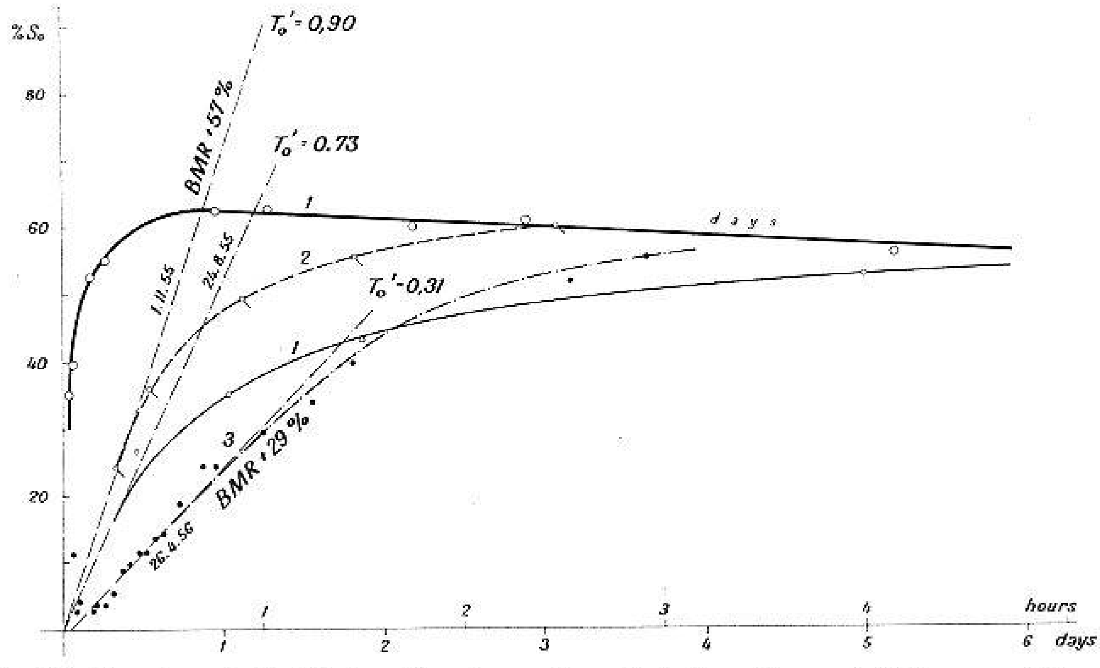

Fig. 29. Treatment of a Morbus Basedow with radioiodine. Curves 1–1 (hours and days scales) before treatment. Curve 2 (hours scale) no effect of the first treatment (4000 rads). Curve 3 (hours) the second treatment (8000 rads) is effective.

(class +2) had a BMR of +55% and a T_0' of 73% h^{-1} at the beginning. She received a first dose of iodine 131 of 10 millicuries, which corresponds —with a gland volume of about 150 cm^3, a maximum uptake of 64% and a biological period of 6.4 days—to an absorbed dose of 4000 rads. This dose was too weak and had no effect at all. The tests carried out two months later showed a BMR of +57%, a T_0' of 90% h^{-1} (fig. 29) and no clinical sign of reduction of the thyrotoxicosis (about the same gland volume). A second dose was given 10 days later and consisted of 16 millicuries, which corresponds—with a volume of 120 cm^3, the same uptake and the same biological period as above—to 8000 rads. This second treatment had a significant effect: the clinical symptoms of toxicosis – with the exception of the ocular symptoms—disappeared, the volume of the gland was reduced to about 50 cm^3, T_0' fell to 31% h^{-1} and the BMR to 29%. The patient is now considered to be in the +1 class with a slight hyperfunction.

The table below gives the results of the tests performed *after* the treatment of 7 other cases of thyrotoxicosis:

Case No.	Treatment	Controls after treatment		
		Clinical Class	BMR %	T'_0 % h^{-1}
120	I^{131}	Normal, 0	+12	8
138	"Thiouracil" 2 months	Nearly normal, +0.5	+10, − 6	22
144	"Tapazol" 30–10 mg 6 weeks	Normal, 0	− 6, −12	7.5
171	"Thiomidil" 2 weeks previously	Normal, 0	+45, +55 (Hypertension)	15
221	"Thiomidil" Tapazol	Normal, 0 (Barker 3.8γ)	− 6, +14	14
209	7.5 mC I^{131}, 3000 rads not effective	Strong hyperfunction, +2.5	+23	140
285	"Tapazol" 4 months previously, not effective	strong hyperfunction, +2.5 (Barker 12.2 γ)	+41, +46	114

In all the 10 cases of treated thyrotoxicosis considered above, the value of the initial tangent agrees very closely with the actual clinical intensity of the function after the treatment. T_0' permits an exact check of the effects of antithyroidal drugs or radioactive iodine.

Grateful aknowledgment is made to all the doctors of The Cantonal Hospital and of the Neumünster Hospital, who have taken a great deal of trouble in completing the questionnaire designed to determine the clinical intensity of the function.

Thanks are due, too, to Mr. Ian Bigland M.A. of The English Institute, Zurich, for correcting this text.

Summary

With the aid of statistics of 249 cases the authors compare the significance of the radioiodine investigation of the thyroid function measured by the initial tangent T'_0 of the uptake curve with the clinical intensity of the function, the basal metabolic rate (BMR) and the PBI determination (Barker). The initial tangent T'_0 is especially valuable—when contact with iodine may be excluded—in cardiac insufficiency and pulmonary diseases, where the BMR can not be used in the evaluation of thyroid function. The comparison of PBI and initial tangent T'_0 is definitely in favour of the latter in our cases. However, PBI was determined only in 91 cases, preferably in the doubtful ones.

The initial tangent T'_0 is influenced by pituitary extracts (TSH) (11 cases), by total hypophysectomy (6 cases) or by the treatment of thyrotoxicosis with chemical drugs or radioiodine (10 cases). T'_0 gives the intensity of the biological function after the treatment with great accuracy.

The statistics of 83 normal cases reveal a symmetrical, nearly normal, distribution with $T'_0 = 4.7$ to $T'_0 = 20.7$ for twice the standard deviation ($P = 0.05$). For the greatest frequency $T'_0 = 10\%\ h^{-1}$.

Résumé

Dans une statistique de 249 cas, les auteurs comparent – pour le diagnostic de la fonction thyroïdienne – la signification de l'examen au radioiode, mesuré par la tangente initiale T'_0 de la courbe d'ascension, avec le métabolisme de base et le taux d'iode du plasma lié aux protéines (Barker). La tangente initiale T'_0 donne généralement la meilleure réponse — quand un contact massif avec l'iode peut être exclu — et tout particulièrement dans les insuffisances cardiaques et respiratoires où le métabolisme de base ne permet pas de diagnostiquer la fonction thyroïdienne. La comparaison de la signification clinique de la tangente initiale T'_0 et de l'analyse de Barker, est nettement en faveur de T'_0. Cependant l'iode protéinique a été déterminé dans 91 cas seulement, dont certains étaient douteux.

La tangente initiale T'_0 est modifiée par les extraits hypophysaires, la TSH (11 cas) par l'hypophysectomie totale (6 cas) ou par le traitement des hyperthyroïdies avec une médication chimique ou le radioiode (10 cas). T'_0 rend compte, avec exactitude, de l'intensité véritable de la fonction après le traitement.

La courbe de fréquence de T'_0 pour 83 cas considérés cliniquement comme normaux est une courbe symétrique, avec distribution quasi

normale. Le double de l'écart quadratique moyen (P = 0,05) est limité par les valeurs $T_0' = 4{,}7$ et $T_0' = 20{,}7\%\ h^{-1}$. La valeur la plus fréquente de T_0' est égale à $10\%\ h^{-1}$.

Zusammenfassung

In einer statistischen Untersuchung, die 249 Fälle erfaßte, vergleichen die Autoren folgende Methoden, welche zur Beurteilung der Schilddrüsenfunktion verwendet werden: den Radiojodtest (wobei die Anfangstangente T_0' der Speicherungskurve der Schilddrüse ermittelt wird), ferner die Grundumsatzbestimmung und die Bestimmung des eiweißgebundenen Jods (PBI) im Plasma. Die Anfangstangente T_0' entspricht im allgemeinen dem klinischen Bild am besten, wenn ein massiver Kontakt des Patienten mit Jod ausgeschlossen werden kann. Dies trifft besonders zu für Fälle mit Lungen- oder Herzinsuffizienz, wo die Grundumsatzbestimmung für die Beurteilung der Schilddrüsenfunktion versagt. Der Vergleich zwischen dem PBI und der Anfangstangente T_0' zeigt in unserer Zusammenstellung eindeutig die Überlegenheit von T_0'. Das eiweißgebundene Jod wurde jedoch nur in 91 Fällen bestimmt, hauptsächlich in solchen, deren Zuordnung zu den verschiedenen Kategorien der Schilddrüsenfunktion im Beginn der Beobachtung zweifelhaft war.

Ein Teil der Fälle erhielt thyreotropes Hormon (TSH: 11 Fälle), Thiouracil oder Radiojod. Bei 6 Fällen wurde die Hypophysektomie durchgeführt. In allen Fällen gab die Anfangstangente T_0' ein zuverlässiges Maß für die Aenderung der Schilddrüsenfunktion.

Die Verteilungskurve von T_0' gibt, für 83 normale Fälle, eine symmetrische Kurve mit einer beinahe normalen Variationsbreite. Die doppelte Abweichung ($P = 0{,}05$) wird durch die Werte $T_0' = 4{,}7$ und $T_0' = 20{,}7\%$ h^{-1} begrenzt. Der wahrscheinlichste Wert von T_0' ist gleich $10\%\ h^{-1}$.

Riassunto

In un esame statistico basato su 249 casi gli autori confrontano il valore diagnostico dei seguenti esami funzionali della tiroide: indagine mediante jodio radioattivo (basata sulla misura della tangente iniziale T_0' della curva di ascesa dello jodio dal sangue alla tiroide), determinazione del metabolismo basale e determinazione del tasso dello jodio plasmatico legato alle proteine.

La tangente iniziale corrisponde in generale al quadro clinico in tutti quei casi in cui un contatto del paziente con rilevanti quantità di jodio può essere escluso. La tangente iniziale dà risultati giusti anche in quei casi nei quali il metabolismo è falsato da fattori estratiroidei come per esempio nell'insufficienza cardio-respiratoria. Il valore diagnostico della determinazione dello jodio plasmatico appare nella nostra casistica inferiore a quello della tangente iniziale.

La tangente iniziale T_0' è modificata dall'ormone tireotropo ipofisario o dagli estratti ipofisari (11 casi), dall'ipofisectomia totale (6 casi) o dalla terapia degli ipertiroidismi con sostanze chimiche o con radiojodio (10 casi). T_0' rispecchia sempre l'intensità reale della funzione dopo la terapia.

La curva di frequenza per 83 casi clinicamente considerati normali è una curva simmetrica, con distribuzione quasi normale. Il doppio dello scarto quadratico medio ($P = 0{,}05$) è limitato dai valori $T_0' = 4{,}7$ e $T_0' = 20{,}7\%\ h^{-1}$. Il valore di T_0' più frequentemente riscontrato è uguale a $10\%\ h^{-1}$.

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