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ATOMIC ENERGY PROJECT
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UNCLASSIFIED

THE CORRELATION OF THE INITIAL RATE OF I^{131} UPTAKE IN THE THYROID WITH THE CLINICAL EVALUATION OF THYROID FUNCTION

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(This is a report of work done in the Spring of 1949 to November 1949)

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Radiation Laboratory
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THE CORRELATION OF THE INITIAL RATE OF I^{131} UPTAKE IN THE THYROID WITH THE CLINICAL EVALUATION OF THYROID FUNCTION

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San Francisco Campus, University of California

October, 1950

Introduction

This paper is concerned with the study of the correlation of the rate of uptake of I^{131} in the thyroid with the clinical evaluation of thyroid function as determined by history, physical examination and other laboratory procedures.

It has become conventional to study the concentration of I^{131} in the thyroid as a function of time and to relate this to the clinical estimate of thyroid function. The maximum concentration and the shape of the concentration curve obtained over a period of several days have been used, with clinical and laboratory evidence from the study of patients, to determine the need for definitive treatment of the patient suspected of having hyperthyroidism. These studies are time-consuming. At the suggestion of A.V.H. in the Spring of 1949, an attempt was made to find a single, more quickly obtained value from the uptake curve that might be as useful as the entire uptake curve in differentiating the normal from the hyperthyroid patient. The rate of uptake of I^{131} in the thyroid during the interval of a few hours after its administration to the fasting patient, expressed as percent-per-hour*, was tried first. Most data were collected on patients around 3 to 6 hours after the administration of the I^{131}. It was realized that the "%/hr" has meaning only if it is used as an average rate of concentration or if the

* "%/hr" is the percent of the total dose of I^{131} collected by the thyroid during the first few hours after its administration (2 to 6 hours) divided by the time between administration and the observation.

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concentration curve is linear. It seemed from the study of the curves of concentration available to us, that these curves were near enough to a straight line during the early hours to make such an observation have meaning. On examination of the data obtained during this study, it was found that, because the early part of the uptake curves was not linear, the so-called "%/hr" was dependent upon the time at which the data were collected. It might still be a useful single value, if the observations on all patients were taken at the same time after the dose was given.

The variation of the "%/hr" with time caused us to restudy the data. In this second approach the total concentration of I^{131} in the thyroid during the first few hours was plotted against time for groups of patients who were normal, who were suffering from diseases other than those of the thyroid, and who were suffering from various diseases of the thyroid. Even though this approach did not make use of a single value, it utilized only data collected within a few hours (up to seven) after the administration of radioactive iodine. A good correlation was found between the high rates of uptake and hyperthyroidism and between the lower rates and absence of hyperthyroidism.

Selection of Patients

Patients were accepted from the Thyroid Clinic, from private physicians of the staff of the University of California and from certain outside physicians. In some of these patients there was a clear-cut clinical estimate of thyroid function stated by the referring physician at the time of referral. In others the I^{131} uptake test was used to help the physician make up his mind about his estimate of thyroid function. For the purpose of the present study, a careful evaluation of case histories and examinations was used in making the division of patients into those in whom there was no

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evidence of toxicity and those in whom there was evidence of toxicity. This was done without reccurse to any laboratory findings. Consultation with the referring physicians at the time of selection of the cases to be used in this study also served as an aid in determining whether or not the patients were really suffering from clinical thyrotoxicosis at the time of the testing. It can be said only that the attempt to make a proper division was as honest as we could make it under the circumstances, and it was made without knowing the value of the I^{131} uptake data. These data are taken from the patient's first I^{131} test only.

All patients who had uptake studies in the early hours after administration of I^{131} are included in the report. These patients were classified in two main groups and several sub groups:

I. Patients sent to the laboratory for study who were considered by the referring physician not to have hyperthyroidism:

a. Non-toxic nodular goiter.
b. Carcinoma of the thyroid with no evidence of hyperthyroidism.
c. Patients sent in because of delayed tooth development but with clinically normal thyroid function.
d. Normal controls.
e. Patients with psychiatric diagnosis and with normal thyroid function.
f. Acromegaly.
g. ? myxedema and hypothyroidism.
h. ? colloid goiter.
i. ? thyroiditis
j. Non-toxic goiter without nodules.
k. Other.

II. Patients sent to the laboratory with the idea that they might have hyperthyroidism:

a. Agree with diagnosis of hyperthyroidism and treated with I^{131}.
b. Agree with diagnosis of hyperthyroidism and treated by methods other than administration of I^{131}.
c. Do not agree with diagnosis of hyperthyroidism but consider euthyroid and not treated.

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d. Not possible to determine whether or not the patient has hyperthyroidism with clinical data available. Patients not treated with radioiodine.
e. Toxic nodular goiter not treated with I^{131}.
f. Toxic nodular goiter treated with I^{131}.

Of a total of 427 patients studied, 292 had observations during the initial seven hours after the administration of I^{131}. The number of these patients who fell into the various sub-groups is shown in Table I.

TABLE I

Group I		Group II	
a.	25	a.	71
b.	38	b.	18
c.	9	c.	4
d.	25	d.	11
e.	44	e.	3
f.	2	f.	3
g.	15		
h.	2		
i.	6		
j.	6		
k.	10		
	182		110

Results of "%/hr" studies

Table II (A and B) shows the results of the "percent-per-hour" determinations without respect to the time at which the observations were made. In some cases the "%/hr" value was obtained at more than one time during the first seven hours. This accounts for the fact that the number of observations exceeds the number of cases.

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TABLE II

The frequency with which the values of the "%/hr" determinations were distributed within the various patient groups.

"A"

"%/hr"	Ia	Ib	Ic	Id	Ie	If	Ig	Ih	Ii	Ij	Ik	TOTAL
0-1	1	0	0	1	1		2		3	0		8
1	5	8	2	5	9	1	5		1	2		38
2	4	20	3	13	30		7			4	4	85
3	6	7	2	8	15	1	5			3	3	50
4	3	6	1	8	15		2		2	2	4	43
5	2	2	0	6	9		0			2		21
6	2	0	1	3	3		0					9
7	3	1	0	3	2		1	1	1		1	13
8	0	1	1	0	1			1				4
9	2	0	1	1	2						1	7
10	1	1		1				1				4
11	0											0
12	0						1				1	2
13	1											1
14	0											0
15	0							1				1
16	0											0
17	1											1
18												0
19											1	1
20												0
21												0
22												0
23												0
24												0
25												0
26								1				1
27												0
28												0
29												0
30												0
31												0
32												1
Observations	31	46	11	49	87	2	23	6	7	13	15	290
Cases	25	38	9	25	44	2	15	2	6	6	10	182

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TABLE II

"B"

"%/hr"	IIa	IIb	IIc	IId	IIe	IIf	Totals
0-1	0			0			1
1	1						1
2	2		1	1			4
3	2		2	2	2	2	10
4	3		1	2			6
5	1		2	1			4
6	1			2			3
7	6			2	1		9
8	4	2		0	1		7
9	10	1		1			12
10	5	1		1			7
11	11	4		2	1	2	20
12	6	2					8
13	7	1					8
14	8	0					8
15	6	1					7
16	4	1					5
17	5	1					6
18	7	2					9
19	3	3					6
20	6	1					7
21	1	1					2
22	2					1	3
23	4						4
24	4	2					6
25	4						4
26	1						1
27	0						0
28	2						2
29	0						0
30	1	1				1	3
31	2						2
33		1					1
35	1						1
39	1						1
50	1						1
Observations	122	25	6	15	5	6	179
Cases	71	18	4	11	3	3	110

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The foregoing data suggest that, in general, there is a difference between the "percent-per-hour" uptake of I^{131} in the thyroid of patients who were considered to have normal thyroid function and those who were considered to be hyperthyroid. The data are plotted in Fig. 1. If attention is narrowed to (a) the group who do not have goiters and have normal thyroid function including the cancer patients, and (b) the group who have goiters and are considered to have hyperthyroidism, the differences between these groups are even more striking. By so limiting the patients to be compared to these two general groups, the ones with the somewhat less certain diagnoses were excluded. These data are plotted on Fig. 2. The results were nevertheless disappointing in that they did not make a sufficiently sharp differentiation between the groups.

Later studies showed that the uptake curve during the early hours is not linear. Therefore, the "%/hr" is not constant but depends upon the time at which the uptake is determined. The effect upon the "%/hr" of the time at which the uptake is determined can be seen in Table III. While we are not at present using the "%/hr" value, it is useful if it is compared only with values obtained at a similar time.

Before the importance of the time for which the "%/hr" was calculated had been appreciated, the "%/hr" was compared with the B.M.R., the P.B.I., and the maximum uptake in a group of 37 normals and 50 hyperthyroid patients. All individuals for whom the 4 measurements were made at approximately the same time are included. It can be seen from Fig. 3 that all the procedures make a relatively good differentiation between the normal and the hyperthyroid patients. In this particular group of patients the "%/hr" determination made the sharpest differentiation between the normal and the hyperthyroid patients.

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TABLE III

The "%/hr" calculated from the maximum values of I^{131} uptake obtained in one normal group (Id) at various times (See Fig. 4)

Hours	1	2	3	4	5	6	7
Maximum percent uptake	11.0	18.0	23.6	27.2	29.6	31.0	32.6
Maximum "%/hr"	11	9	7.9	6.8	5.9	5.1	4.6

Because we were not satisfied with the "%/hr" determination, the following studies were carried out.

Studies of the Concentration of I^{131} in the Thyroid During the First Few Hours after its Administration

Data from patients considered as normal controls (Id) were plotted on a chart, Fig. 4, having time in hours as the abscissa and percent uptake as the ordinate. Single observations were marked with crosses. When more than one observation was available, a straight line was drawn between successive observations. A curve was drawn through the highest observation in the normal group. This curve appears as a heavy line in Fig. 4 through Fig. 15 inclusive and serves as a reminder of the highest observation found in this particular group of normals.

Data from the other groups of patients were plotted in a similar fashion and are shown in Figs. 5 - 15.

With the exception of patients with non-toxic goiters (I a,h,j) it can be seen from Figs. 5 through 9 that in 116 out of 118 patients, the uptakes of those in group I fall within the range found in our normal control group Id (25 cases).

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In Fig. 10 the data which lie above the heavy line represent the two cases thought to have colloid goiters (Ih) and who did not manifest any clinical evidence of thyrotoxicosis. These findings are consistent with iodine deficiency of the thyroid gland.

The other cases shown in Fig. 10 are the 6 patients with non-toxic goiters from group Ij. All the data for these cases lie within the range of normal.

The data from the 25 patients having non-toxic nodular goiters (Ia) are shown in Fig. 11. Observation on 5 of these fall above the range of our normals. Speculation about the explanation of these findings is most interesting but is unfortunately unhempered by the availability of crucial data.

In Fig. 12 (IIa) and Fig. 13 (IIB) are presented data on the I^{131} uptake by 89 patients with thyrotoxicosis. The only difference between group IIa and group IIb lies in the method by which the patients were treated. The plan of treatment was made before the patient was sent for study. Among these patients are five whose findings are clearly in the range of our normals. One was taking propylthiouracil at the time of the test, one patient had been taking quinidine in the past, one is said to have shown spontaneous improvement recently, and one patient was treated at one time for depression at the Langley Porter Clinic. None of these circumstances is offered as an explanation for the normal findings in these patients who were believed to be hyperthyroid. It is interesting, however, that two of these patients became myxedematous after treatment. All of the rest of the observations are clearly above the top range of our normals.

In the group of 6 patients with toxic nodular goiters (II 3 and f) the observations on 3 lie clearly above and those of 3 lie well within the

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range of our normals, Fig. 14. As in the patients with non-toxic nodular goiters, we find that those with toxic nodular goiters also behave in an unpredictable manner in so far as this procedure is concerned.

The group of 11 patients (IId) whose data are shown in Fig. 15 were those in whom there was no clear estimate of thyroid function by the referring physician at the time of referral, nor could we make up our minds about their thyroid status. They were sent to us in order to see whether our procedure would help the physician make up his mind about their diagnosis. The observations on these were scattered without apparent pattern. Nine of these patients were ultimately dismissed as euthyroid. In two the diagnosis of hyperthyroidism was later made. Interestingly, the uptakes of these two patients were not the highest of the 11, but lay in the middle of the range of this group.

The studies reported here suggest that there is a correlation between high uptake of I^{131} in the thyroid in the early hours and the presence of clinical hyperthyroidism in patients whose thyroids do not have nodules. It would be simpler to be able to state the result of the uptake studies on a patient as a single value rather than as a curve. It becomes important then to find out whether such a single value is as reliable as the entire curve for differentiating those patients who have hyperthyroidism from those who do not. To evaluate the possibility of so using a single value the data from the I^{131} uptake curves were re-examined as follows: the previously determined data on certain normal and hyperthyroid patients were selected for analysis. The normals included the patients in groups I b, c, d, e, and II c; the hyperthyroids were those of groups II a and b. The data were taken from Figs. 4,5,6,7,8, 12 and 13. Those falling within the same hour were grouped together. Where only a single observa-

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tion was made on a patient, it was accepted as applying to the time interval in which it was found. Where a line between successive observations on the same patient crosses into a given time interval, the value recorded is that at the midpoint of the time interval; i.e., if the line crosses through the 3 to 4 hour interval, its value was read at 3.5 hours. When necessary, the line was extrapolated to the midpoint of a time interval if it entered but did not reach the midpoint of that interval. The data were plotted as the value of percent uptake against the number of times each particular value occurred within the hour. A similar plot was made for each one hour interval from 2 to 7 hours. The data for the interval between 3 and 4 hours is shown in Fig. 16; this interval is representative of each of the other intervals. In Table IV an analysis of certain data obtained from these plots is presented. As an illustration of the manner in which this table was assembled note how the following information for the 3 to 4 hour interval was obtained from Fig. 16: there were 90 euthyroid patients who had I^{131} uptake measurements made during the interval between 3 and 4 hours after the administration of I^{131}. Eighty-nine of these had uptakes of 27 percent or less at this interval. There were 76 patients with hyperthyroidism who were studied at the same interval and 71 of these had uptakes greater than 27 percent. Five (6.6%) of the 76 hyperthyroids had uptakes that lay within the limits of this group of normals.

From Table IV it would appear that for differentiating those patients who have hyperthyroidism from those who do not, the single value of the uptake determined at any specified time between 2 and 6 hours is useful. If the interval between the oral administration of the I^{131} and the measurement of uptake is too small, there is danger that variation

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in the rate of absorption from the gut will affect the uptake value. It should be born in mind that these patients were fasting when the I^{131} was given and that these statements do not apply to the data obtained from patients with nodular or colloid goiters.

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TABLE IV

Interval in hours after Administration of I^{131}	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7
Number of normal patients who had observations in the interval	27	90	77	65	52
Upper "limit" of normal uptakes* in the interval	21%	27%	30%	30%	30%
Number of normals falling above upper limit of normal	0 (0%)	1(1.1%)	1(1.3%)	0(0%)	1(1.9%)
Number of hyperthyroids who had observations in the interval	54	76	58	54	31
Number of hyperthyroids with uptake below upper limit of normal	2(3.7%)	5(6.6%)	3(5.2%)	4(7.4%)	3(9.7%)
Upper limit of uptake of normals when patients from group Id only are considered (See Fig.3)	20.8%	25.4%	28.4%	30.3%	31.8%

* This limit is arbitrarily selected so that it includes at least 98 percent of the observations.

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Summary and Conclusions

Data were collected on the iodine 131 uptake in the thyroid during the first seven hours after its administration to a group of patients who were considered clinically to have normal thyroid function and to a group who were considered to be suffering from hyperthyroidism. An attempt was made to find a single quickly obtained value from the uptake curve that might be as useful as the entire uptake curve in differentiating between these groups of patients. The uptake as given by the "%/hr" was tried first. It was calculated by taking the percent of I^{131} collected by the thyroid during the first few hours and dividing it by the number of hours between the administration and the observation. It was as useful in these groups of patients as were the determinations of the basal metabolic rate, the protein-bound iodine or the maximum uptake of I^{131} in the thyroid.

It was hoped that the "%/hr" would not be too strongly dependent upon the time at which the observations were made. However, by study of the uptake curve up to 7 hours it was found to be markedly dependent upon the time at which the observations were made. As a consequence, if the value of the "%/hr" is compared only with those taken at similar times, it is even more useful. Similarly, the absolute value of the uptake determined at any particular time between 2 and 7 hours is of use in differentiating patients with hyperthyroidism from those without hyperthyroidism. The result of the tests are unpredictable in patients with nodular goiters and colloid goiters.

Clinical hyperthyroidism is generally considered to be associated with the release of too much thyroid hormone and/or its too great utilization by the body. Even though I^{131} uptake in the thyroid has a good

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positive correlation with the clinical estimate of thyroid function, it measures only one aspect of thyroid function, and in the sense that it does not measure either the release of thyroid hormone from the thyroid nor its utilization by the body, it is not a general test for hyperthyroidism.

This work was performed under the auspices of the Atomic Energy Commission.

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LEGENDS FOR

The Correlation of the Initial Rate of I^{131} Uptake in the Thyroid with the Clinical Evaluation of Thyroid Function.

Fig. 1 Graph showing the number of patients in the normal and hyperthyroid groups having the indicated "%/hr" uptakes of radioiodine in the thyroid. These data were obtained from the observations made within 7 hours after the administration of the radioiodine. No account was taken of the time for which the calculation was made.

Fig. 2 Graph showing the number of patients among a restricted group of normals and hyperthyroids who have the indicated "%/hr" uptake of I^{131} in the thyroid. No account is taken of the time for which these observations were made. All observations were made within 7 hours after the administration of the radioiodine to the patient.

Fig. 3 Comparison of the results of certain laboratory procedures done on normal patients and on patients suspected of having hyperthyroidism. The basal metabolic rates are in percent, the protein-bound iodine determinations are in micrograms percent, the maximum uptake of I^{131} in the thyroid is in percent of the administered dose. All laboratory procedures make a good differentiation between the normal and hyperthyroid groups. The "%/hr" values, even though considered without respect for the time at which the observations were made, provide the sharpest differentiation between this particular group of hyperthyroid and normal patients.

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Fig. 4 Uptake of I^{131} in the thyroid during the first 7 hours after its administration to normal control group Id. The heavy black line goes through the highest observations in this group: it will be repeated as a reference line on curves which follow and is used to remind the reader of the position of the highest observations in this normal group. The abscissa labeled "hours" represents time after the administration of the test dose of radioiodine. 25 patients, 49 observations.

Fig. 5 Uptake of radioiodine in the thyroid in patients with psychiatric diagnoses and clinically normal thyroid fraction (group Ie) in the first 7 hours after the administration of the I^{131}. The heavy line represents the highest observations in the normal control group Id. 44 patients, 87 observations.

Fig. 6 Uptake of I^{131} in group Ic, patients with delayed tooth development and clinically normal thyroid function. 9 patients, 11 observations.

Fig. 7 Uptake of I^{131} in group IIc, patients sent for study with the diagnosis of hyperthyroidism but considered normal by us. 4 patients, 6 observations.

Fig. 8 Uptake of I^{131} in group Ib, patients with carcinoma of the thyroid and clinically normal thyroid function. 38 patients, 46 observations.

Fig. 9 Uptake of I^{131} in 23 patients (32 observations) of groups If, Ig, Ii.

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Fig. 10 Uptake of I^{131} in patients of group Ih and group Ij. The data which are above the heavy line belong to the two cases of colloid goiter in group Ih. The data below the heavy line represent the uptakes on 6 patients with non-toxic non-nodular goiters from group Ij.

Fig. 11 Uptake of I^{131} in patients of group Ia. 25 patients, 31 observations.

Fig. 12 Uptake of I^{131} in patients with hyperthyroidism who were later treated with I^{131}. Group IIa. 71 patients, 122 observations. It will be observed that the data of 4 patients lie clearly below the top range of our normal group Id. The rest of the data lie above this range.

Fig. 13 Uptake of I^{131} in patients with hyperthyroidism who were later treated by methods other than the administration of I^{131}. In this group one of the observations lies clearly below the top level of the range of our normal control group Id.

Fig. 14 Uptake of I^{131} in patients with toxic nodular goiters. Group IIe. 3 patients, 5 observations. Group IIf. 3 patients, 6 observations. The data from this group are scattered above and below the top range of our normal control group Id.

Fig. 15 Uptake of I^{131} in patients in whom the clinical diagnosis of hyperthyroidism was in doubt even after complete study of the patient. Group IId. 11 patients, 15 observations. As would be expected in this group the data are scattered in the top range

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of our normal group. Nine of these were dismissed ultimately as euthyroid. Two, whose data lie at the top range of normal, ultimately showed clear evidence of hyperthyroidism and were treated with I^{131}.

Fig. 16 This graph made between the 3rd and 4th hours, after administration of I^{131}, presents observations on a group of normal and hyperthyroid patients. It shows the number of times any particular value of the percent uptake of I^{131} in the thyroid was found. Of the 90 normal patients, 89 (or 98.8 percent) had an uptake of 27 percent or less. Of the 76 patients with hyperthyroidism who had data at this time there were 71 who had uptakes greater than 27 percent. 6.6 percent of the 76 hyperthyroids had uptakes that lay within the limits of normal of this group.

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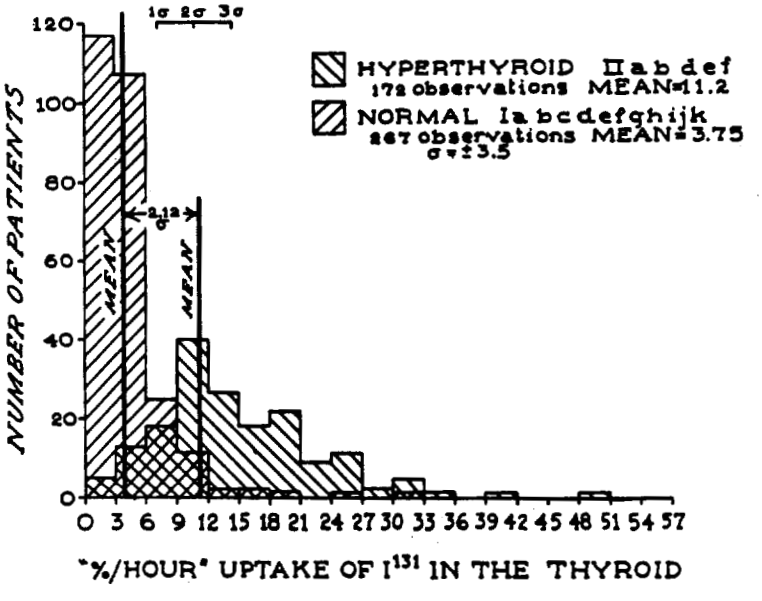

FIG I MU 897

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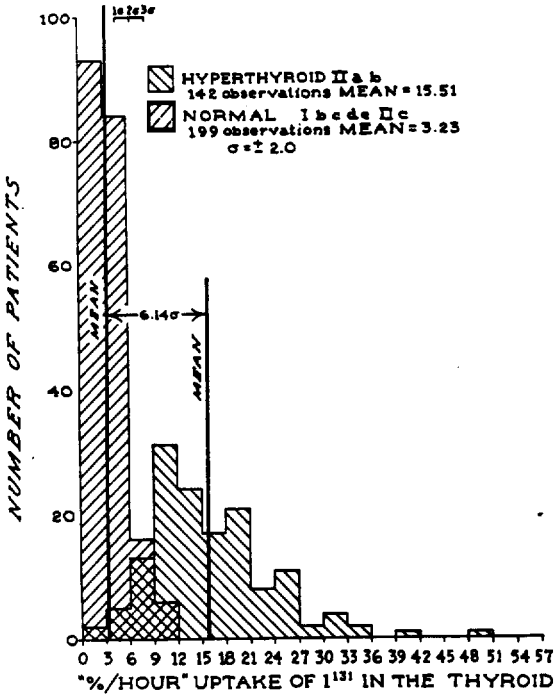

FIG. 2

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LABORATORY DETERMINATIONS OF 37 NORMAL PATIENTS AND 50 PATIENTS WITH HYPERTHYROIDISM

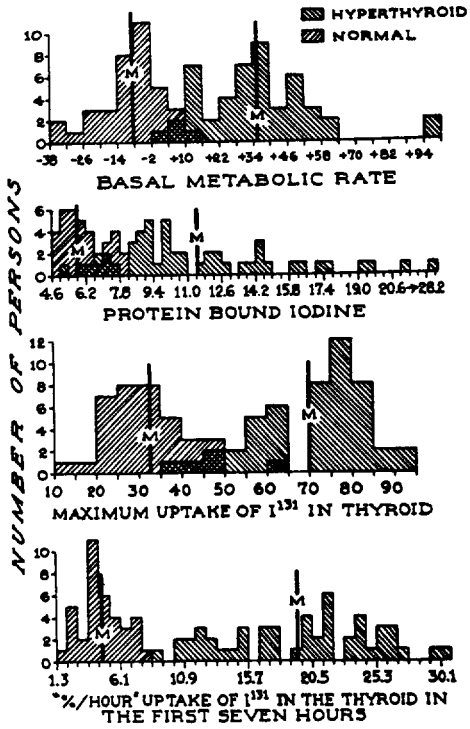

FIG. 3

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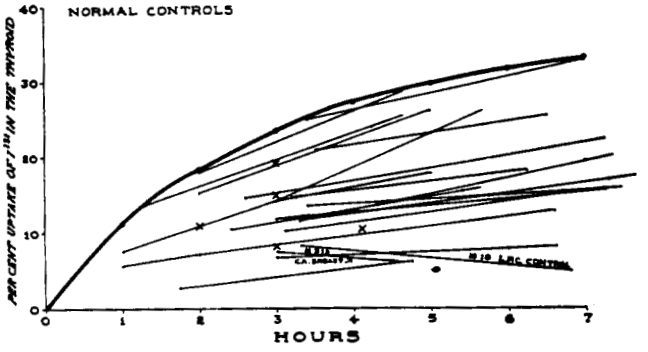

FIG. 4

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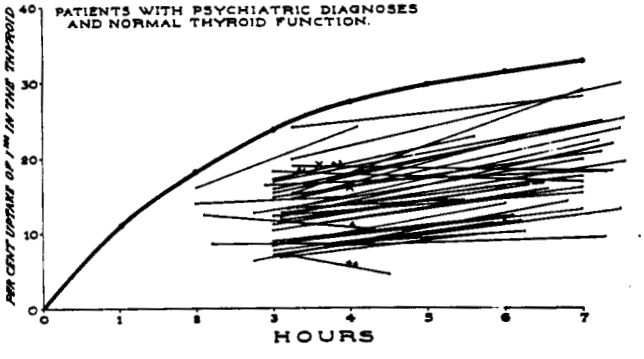

FIG. 5

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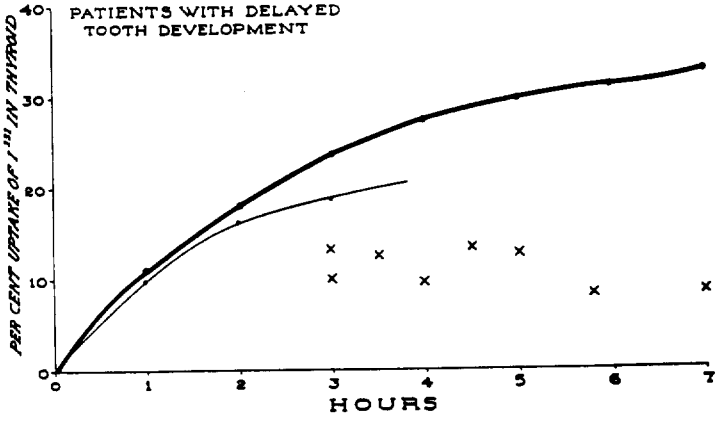

FIG. 6

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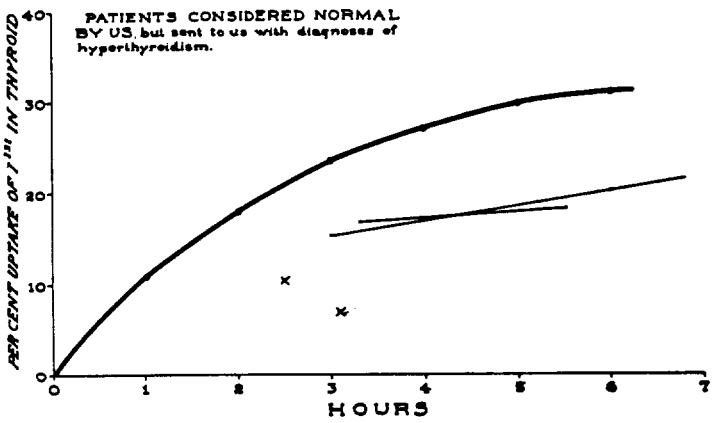

FIG. 7

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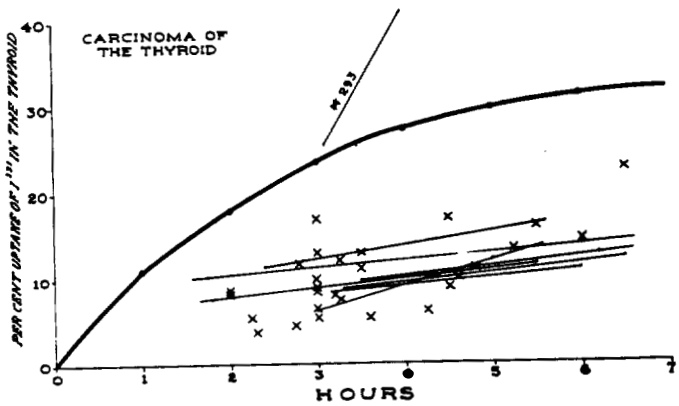

FIG. 8

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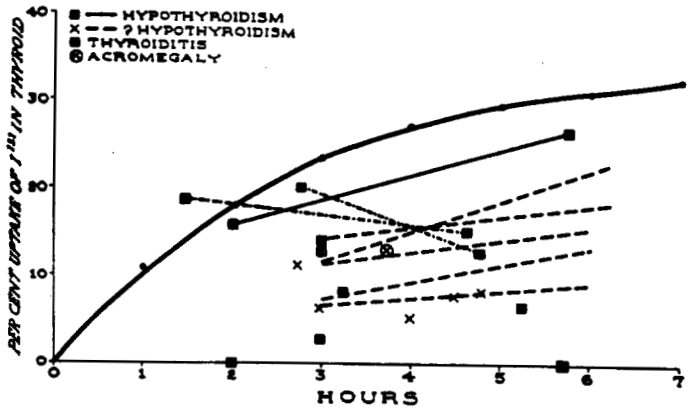

FIG. 9

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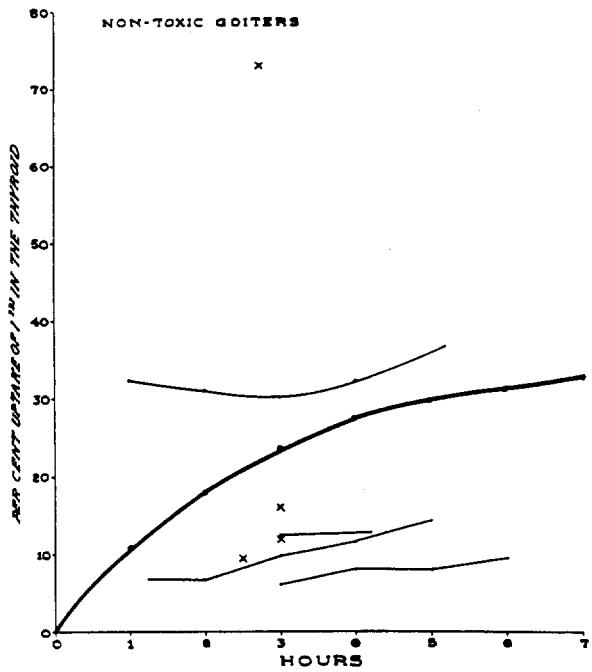

FIG. 10

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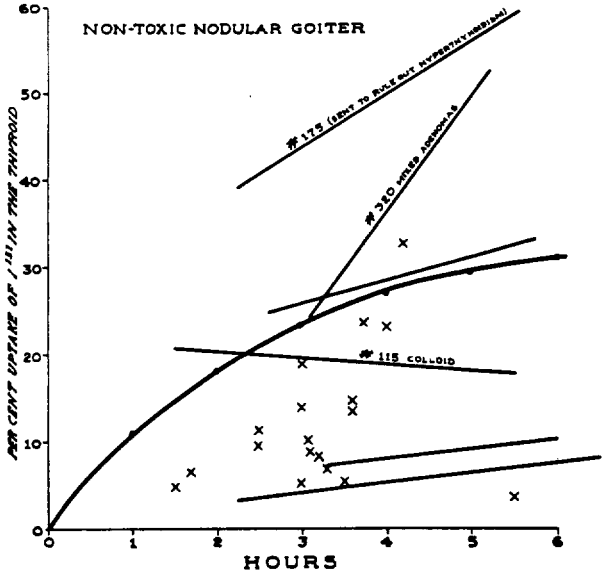

FIG 11

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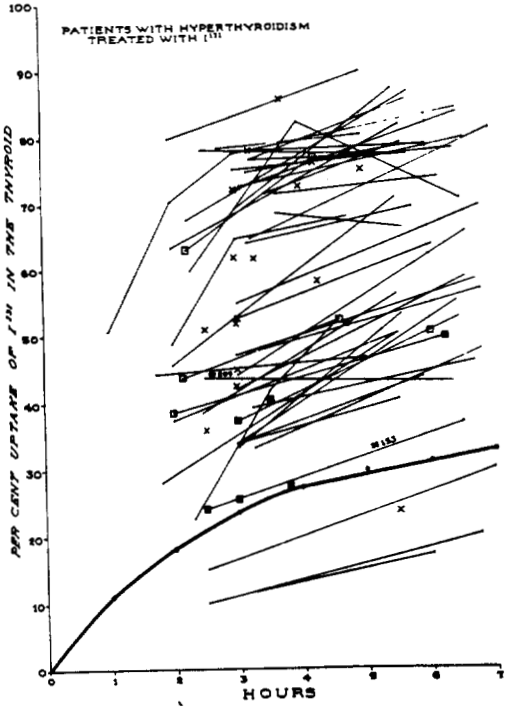

FIG 12

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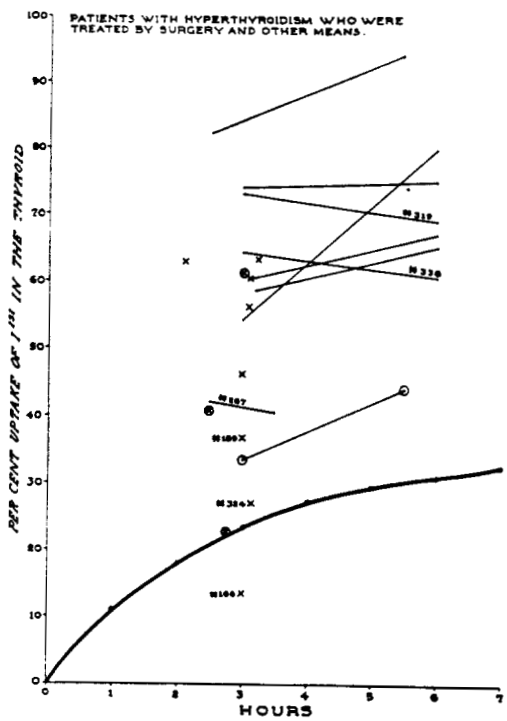

FIG 13

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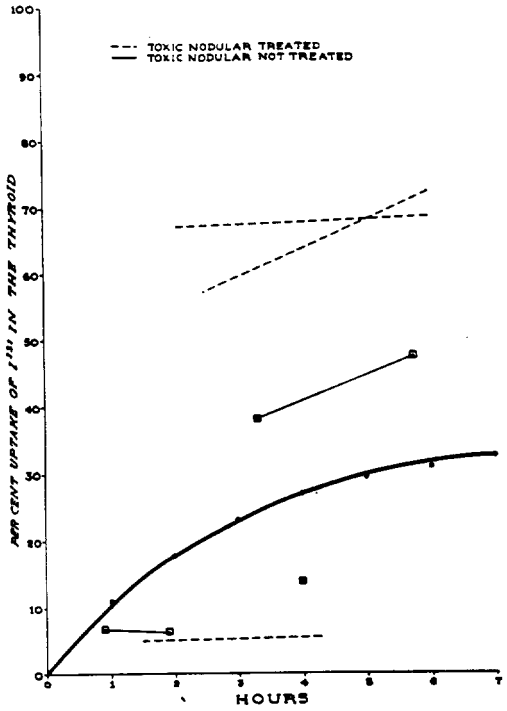

FIG 14

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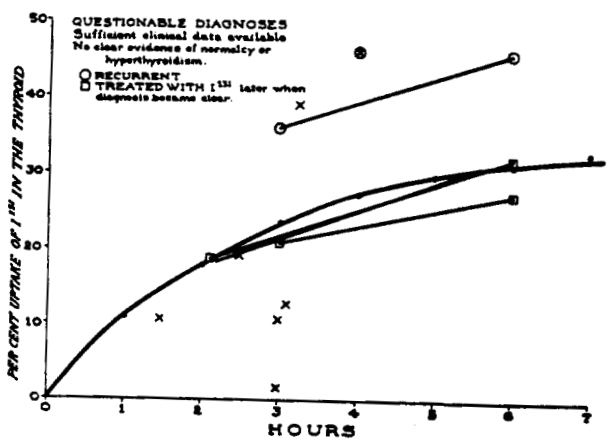

FIG. 15

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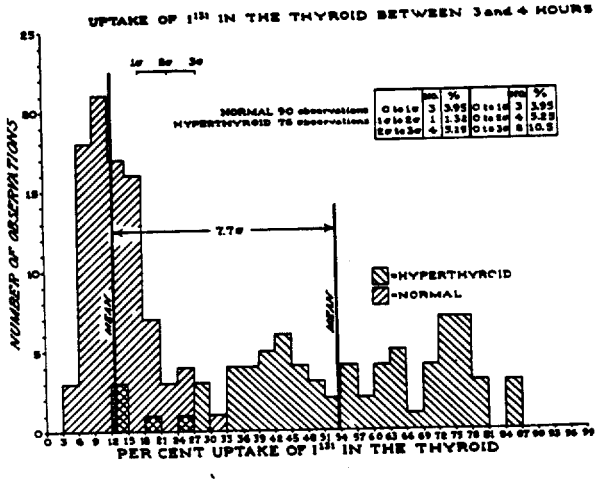

FIG. 16

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