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### Research Article

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# Inhibition by Iodine of the Release of Thyroxine from the Thyroid Glands of Patients with Thyrotoxicosis

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**ABSTRACT** A method has been devised which is free of many of the shortcomings of serial epithyroid counting techniques as an index of the rate of thyroid hormone secretion. By means of this method, the effect of treatment with Lugol's iodine on the rate of thyroïdal secretion of thyroxine ( $T_4$ ) has been assessed in eight patients with thyrotoxicosis due to diffuse or multinodular goiter. The technique involves administration of a tracer dose of inorganic  $^{125}\text{I}$  followed several days later by an intravenous tracer dose of  $^{131}\text{I}$ -labeled  $T_4$ . Serial observations of serum protein-bound (PB)  $^{125}\text{I}$  and  $^{131}\text{I}$  are accompanied by frequent measurements of endogenous serum  $T_4$  ( $T_4$ - $^{131}\text{I}$ ) concentration. Regardless of whether or not its administration was anteceded and accompanied by the administration of large doses of methimazole, iodine induced a rapid decrease in serum  $T_4$ - $^{131}\text{I}$  concentration which could not be explained by an increase in the peripheral turnover of  $T_4$ , as judged from the metabolism of the  $^{131}\text{I}$ -labeled hormone. Hence, the decreased serum  $T_4$  concentration could only have resulted from decreased secretion of the hormone by the gland. Analyses of specific activity relationships between PB $^{125}\text{I}$  or  $T_4$ - $^{131}\text{I}$  and PB $^{131}\text{I}$  made possible estimations of the extent to which iodine had decreased the rate of secretion of  $T_4$ . From such analysis, and in view of other considerations, it is concluded that the rapid decrease in  $T_4$  secretion induced by iodine is not the result of an acute, sustained inhibition of  $T_4$  synthesis, but rather results from an abrupt decrease in the fractional rate of thyroïdal  $T_4$  release.

## INTRODUCTION

The mechanism whereby iodine alleviates thyrotoxicosis in patients with Graves' disease has been a subject of

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long-standing interest and intermittent debate (1-7). The beneficial effect of iodine is usually manifested far more rapidly than would be the case even with very large doses of antithyroid agents. This alone would suggest that iodine does not act by inhibiting hormonal synthesis, if it does so at all, but probably inhibits hormonal release. Attempts to resolve this question through observation of the effect of iodine on the rate of release of glandular radioiodine, as judged by serial epithyroid counting, have led to conflicting results, depending on whether antithyroid agents were administered in association with the iodine (1-5). In view of these discrepancies, and because of both interpretive and technical shortcomings in the technique of serial epithyroid counting, we have devised a method which permits an assessment of the influence of agents, such as iodine, on the rate of release of thyroxine ( $T_4$ ) from the thyroid gland. By means of this technique, iodine has been shown to inhibit abruptly the thyroïdal release of  $T_4$  in patients with hyperthyroidism, an effect which seems adequate to account for its rapid therapeutic action.

## METHODS

Studies were performed in eight patients with untreated thyrotoxicosis due to either diffuse or multinodular goiter. Pertinent clinical and laboratory data are recorded in Table I. All studies were conducted in patients hospitalized on a metabolic ward. Each study consisted of at least two periods, usually three: a control period, a period of iodine administration, and a period after iodine was withdrawn. The total duration of the studies varied from 21 to 30 days (Figs. 1 and 2).

The general experimental protocol was as follows. Each patient was given 150  $\mu\text{c}$  of inorganic  $^{125}\text{I}$  intravenously. Thereafter, bloods were drawn at 12-hr intervals and 12-hr urine collections were made for the duration of the study. Aliquots of serum were subjected to trichloroacetic acid precipitation and both the concentration of protein-bound  $^{125}\text{I}$  in serum (PB $^{125}\text{I}$ ) and total urinary  $^{125}\text{I}$  were measured. When the concentration of PB $^{125}\text{I}$  had reached an approximate plateau (usually at 5-7 days), 50  $\mu\text{c}$  of  $^{131}\text{I}$ -labeled  $T_4$  was

TABLE I  
Clinical Data in Patients Studied

Patient	Age	Sex	Diagnosis	24 hr	Serum
				thyroid <sup>131</sup> I uptake	
				% dose	μg/100 ml
A. J.	33	F	Graves' disease	80	15.8
W. H.	60	M	Toxic multinodular goiter	64	10.8
M. M.	33	F	Graves' disease	82	20.5
K. K.	70	F	Toxic multinodular goiter	62	21.0
E. B.	44	F	Graves' disease	75	20.0
M. D.*	75	F	Toxic multinodular goiter	70	15.1
C. F.*	29	F	Graves' disease	62	13.2
M. D. M.*	49	F	Toxic multinodular goiter	62	17.0

\* Received methimazole (30 mg every 6 hr) during period of study.

administered intravenously in a single dose.<sup>1</sup> Thereafter, both PB<sup>125</sup>I and PB<sup>131</sup>I in serum, as well as urinary <sup>125</sup>I and <sup>131</sup>I, were measured in a dual-channel well-type scintillation counter, corrections being made for crossover of counts from one isotope into the counting range of the other.<sup>2</sup> Values for each isotope were calculated as a per cent of the original dose. Measurements of thyroidal <sup>125</sup>I and <sup>131</sup>I were made daily by means of an external scintillation probe and spectrometer. After a control period of 72-96 hr, Lugol's solution, five drops three times daily, was administered for 6-7 days. In most patients, observations were continued for about 5 days after withdrawal of iodine.

In five patients, studies were carried out precisely as described above. In the remaining three, methimazole (30 mg every 6 hr) was begun 1 or 2 days before administration of the <sup>131</sup>I-labeled T<sub>4</sub> and was continued throughout the period of study.

Estimations of serum stable T<sub>4</sub> (T<sub>4</sub>-<sup>127</sup>I) concentration were made by the method of Murphy, Pattee, and Gold on multiple samples obtained during each experimental period (8).<sup>3</sup>

From the foregoing data a number of calculations were made. The kinetics of the peripheral metabolism of <sup>131</sup>I-labeled T<sub>4</sub> were assessed by methods described in detail elsewhere (9). The fractional rate of peripheral turnover of T<sub>4</sub> was calculated from the semilogarithmic regression slope of the serum PB<sup>131</sup>I, as determined by the method of least squares. T<sub>4</sub> distribution space was calculated from the zero time intercept of the least squares regression equation. Peripheral T<sub>4</sub> clearance rate was calculated as the product of the T<sub>4</sub> distribution space and the fractional turnover rate, and the T<sub>4</sub> disposal rate as the product of the T<sub>4</sub> clearance rate and the serum T<sub>4</sub>-<sup>127</sup>I concentration (10).

The ratio PB<sup>125</sup>I:PB<sup>131</sup>I was calculated for each specimen of serum obtained. In addition, the ratio T<sub>4</sub>-<sup>127</sup>I:PB<sup>131</sup>I was calculated for each of the frequently obtained specimens in

which T<sub>4</sub>-<sup>127</sup>I had been determined. For each treatment period, the slopes and standard errors of the curves described by these ratios were calculated as a semilogarithmic function of time by the method of least squares. For each patient, the significance of the differences between the slopes in the differing treatment periods was calculated by the *t* test. In addition, the paired *t* test was employed to assess the effect of iodine administration on the several functions studied in the group of patients as a whole. The foregoing statistical analyses were based on methods described by Snedecor and Cochran (11).

A formulation was developed from which the maximum fractional rate of T<sub>4</sub> release from the thyroid during the administration of iodine, relative to that present during the antecedent control period, could be calculated. This method and the underlying assumptions are presented in the Appendix.

## RESULTS

*Turnover of exogenous <sup>131</sup>I-labeled T<sub>4</sub> (Table II).* Values for various aspects of the peripheral turnover of exogenously labeled T<sub>4</sub> are shown in Table II, and are characteristic of those found previously in patients with thyrotoxicosis (9, 12, 13). The thyroxine distribution space averaged 11.59 ± 2.28 liters (mean ± SD), a value within the normal range for adults. Fractional rate of T<sub>4</sub> turnover was greater than normal, averaging 16.0 ± 3.0%/day. As a consequence, T<sub>4</sub> clearance rate was also increased (1.83 ± 0.41 liters). Values for T<sub>4</sub>-<sup>127</sup>I concentration during control periods were generally increased (16.7 ± 3.4 μg/100 ml), as was the daily rate of disposal of T<sub>4</sub> (298 ± 68 μg).<sup>4</sup>

In all five patients studied in the absence of anti-thyroid blockade, the curve describing the disappearance of <sup>131</sup>I-labeled T<sub>4</sub> from the serum displayed an apparent slowing during the later portion of each study (Fig.

<sup>4</sup> Throughout this presentation, values for T<sub>4</sub>-<sup>127</sup>I are intended to represent total T<sub>4</sub> concentrations in serum. These can be converted to values for T<sub>4</sub> iodine by multiplying by 0.65.

<sup>1</sup> <sup>131</sup>I-labeled T<sub>4</sub> was obtained from Abbott Laboratories, Chicago, Ill.

<sup>2</sup> Data obtained concerning the urinary excretion of <sup>125</sup>I and <sup>131</sup>I are not employed in the methods of analysis used in the present report, but will be discussed in a later publication.

<sup>3</sup> Performed by the Boston Medical Laboratory, Boston, Mass.

TABLE II  
*Various Aspects of the Peripheral Metabolism of Thyroxine (T<sub>4</sub>) in Patients with Thyrotoxicosis Given Lugol's Iodine*

Patient	Body wt	T <sub>4</sub> space	Fractional T <sub>4</sub> turnover (k)	T <sub>4</sub> clearance	Serum T <sub>4</sub>	T <sub>4</sub> disposal rate
	kg	liters	%/day	liters/day	μg/100 ml	μg T <sub>4</sub> /day
A. J.	42	8.7	16.6	1.45	15.8	229
W. H.	59	16.0	13.4	2.14	11.0	235
M. M.	43	10.1	20.0	2.02	20.5	414
K. K.	40	9.5	13.0	1.23	21.0	258
E. B.	41	10.0	16.9	1.69	20.0	338
M. D.*	43	12.4	20.8	2.58	15.1	390
C. F.*	54	12.8	15.7	2.01	13.2	265
M. D. M.*	53	13.2	11.6	1.53	17.0	260
Mean ±SEM		11.6 ±0.8	16.0 ±1.1	1.83 ±0.14	16.7 ±1.2	300 ±22

\*Received methimazole (30 mg every 6 hr) during period of study.

1). This phenomenon, which has been described previously (9) can be ascribed to thyroidal secretion as T<sub>4</sub> of radiiodine accumulated by the gland after liberation by the peripheral degradation of the exogenous labeled hormone. As would be expected, therefore, no such slowing was evident in the curve of disappearance of <sup>131</sup>I-labeled T<sub>4</sub> from the serum of patients given methimazole during the period of study. In no case did administration of iodine either accelerate the disappearance or

alter the volume of distribution of the exogenous <sup>131</sup>I-labeled T<sub>4</sub>.

*Concentration of T<sub>4</sub>-<sup>127</sup>I.* Before the administration of Lugol's solution, values for the concentration of serum T<sub>4</sub> were essentially constant, regardless of whether or not patients were receiving methimazole during this period. After institution of iodine therapy, serum T<sub>4</sub> concentrations decreased abruptly. This decrease was usually not progressive, however, since values tended to

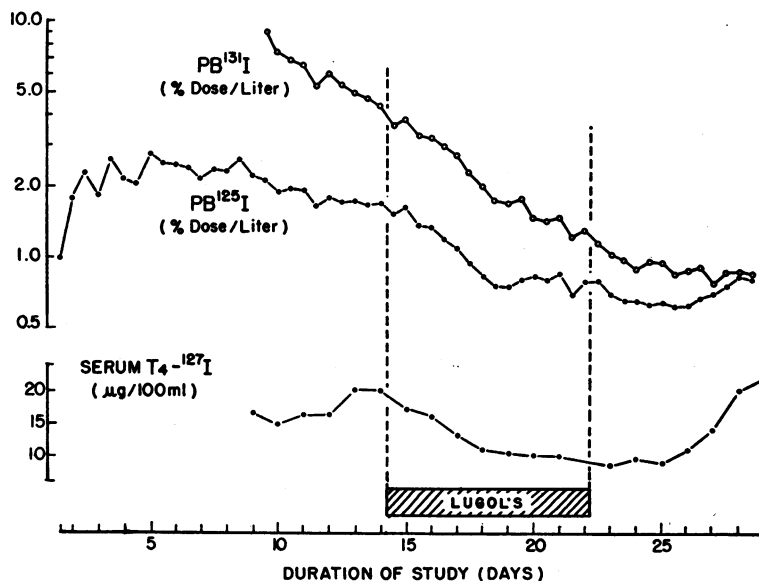


FIGURE 1 The effect of Lugol's iodine on the thyroidal release and peripheral metabolism of thyroxine (T<sub>4</sub>) in a patient (E. B.) with hyperthyroidism. Patient given inorganic <sup>125</sup>I and several days later <sup>131</sup>I-labeled T<sub>4</sub>. Serial measurements made of serum protein-bound <sup>125</sup>I and <sup>131</sup>I and of T<sub>4</sub>-<sup>127</sup>I concentrations.

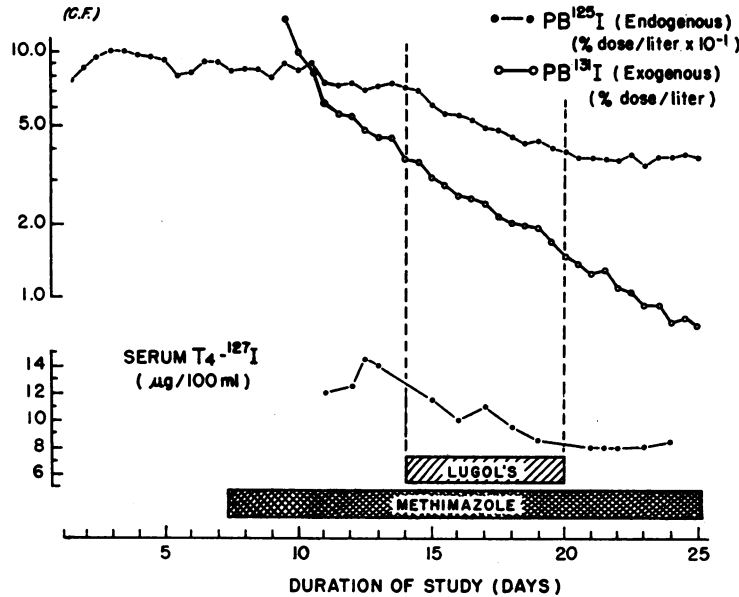


FIGURE 2 The effect of Lugol's iodine in the presence of methimazole blockade on the thyroidal release and peripheral metabolism of thyroxine ( $T_4$ ) in a patient with hyperthyroidism. Patient given inorganic  $^{125}\text{I}$  and several days later  $^{131}\text{I}$ -labeled  $T_4$ . Serial measurements made of serum protein-bound  $^{125}\text{I}$  and  $^{131}\text{I}$  and of  $T_4$ - $^{127}\text{I}$  concentrations.

plateau within 3½–6 days after institution of iodine therapy (Fig. 1). At that time, values had decreased to a mean of  $10.2 \pm 1.9$   $\mu\text{g}/100$  ml from a control mean of  $16.7 \pm 3.4$   $\mu\text{g}/100$  ml. Four patients who received no antithyroid drug during the study were studied after iodine was withdrawn, and in all the sharp rise in serum  $T_4$  concentration into the thyrotoxic range occurred within 4 or 5 days. In contrast, after withdrawal of io-

dine, little or no increase in serum  $T_4$  occurred in two patients who received methimazole (Fig. 2).

*Ratio of  $T_4$ - $^{127}\text{I}$ : $PB^{131}\text{I}$  (Table III).* Before the administration of iodine, the numerical value of the ratio of  $T_4$ - $^{127}\text{I}$ : $PB^{131}\text{I}$  ( $\mu\text{g}/\%$  dose) in the serum increased exponentially with time, since  $T_4$ - $^{127}\text{I}$  remained constant and  $PB^{131}\text{I}$  declined exponentially. In all patients, the slope of the ratio with time decreased markedly when iodine

TABLE III  
*Effect of Lugol's Iodine on the Release of Thyroxine ( $T_4$ ) from the Thyroids of Patients with Thyrotoxicosis as Assessed from the Slope with Time of the Ratio  $T_4$ - $^{127}\text{I}$ : $PB^{131}\text{I}$  after Administration of  $T_4$ - $^{131}\text{I}$*

Patient	A. Control period		B. Lugol's iodine		C. Post-Lugol's period		P values*	
	Slope $\pm$ SEM†	r‡	Slope $\pm$ SEM	r	Slope $\pm$ SEM	r	A vs. B	B vs. C
A. J.	0.230 $\pm$ 0.014	0.99	0.079 $\pm$ 0.011	0.77	0.199 $\pm$ 0.015	0.92	<0.02	<0.05
W. H.	0.180 $\pm$ 0.013	0.96	0.092 $\pm$ 0.015	0.77			<0.05	
M. M.	0.133 $\pm$ 0.009	0.95	0.080 $\pm$ 0.003	0.99	0.162 $\pm$ 0.013	0.93	<0.05	<0.05
K. K.	0.273 $\pm$ 0.017	0.94	0.013 $\pm$ 0.007	0.30	0.132 $\pm$ 0.003	0.98	<0.001	<0.001
E. B.	0.242 $\pm$ 0.009	0.98	0.069 $\pm$ 0.005	0.93	0.197 $\pm$ 0.009	0.97	<0.001	<0.001
M. D.	0.152 $\pm$ 0.005	0.98	0.053 $\pm$ 0.013	0.82			<0.01	
C. F.	0.258 $\pm$ 0.029	0.95	0.056 $\pm$ 0.010	0.82	0.192 $\pm$ 0.010	0.98	<0.01	<0.01
M. D. M.	0.188 $\pm$ 0.019	0.93	0.066 $\pm$ 0.009	0.80	0.166 $\pm$ 0.012	0.97		<0.02

\* Calculated by the *t* test. Only significant differences are shown.

† Standard error of the slope with time (fraction/day) of the  $T_4$ - $^{127}\text{I}$ : $PB^{131}\text{I}$  ratio ( $\mu\text{g}/\%$  dose); calculated by the method of least squares.

‡ Correlation coefficient of the  $T_4$ - $^{127}\text{I}$ : $PB^{131}\text{I}$  ratio vs. time.

|| Received methimazole (30 mg every 6 hr) during period of study.

was administered. During the control period, slopes averaged  $20.7 \pm 4.8\%$ /day, whereas during treatment with iodine the mean slope decreased to  $6.4 \pm 2.2\%$ /day. After withdrawal of iodine, the slope of the  $T_4$ - $^{127}\text{I}$ :  $\text{PB}^{131}\text{I}$  ratio with time increased markedly, averaging  $17.5 \pm 2.4\%$ /day in the six patients studied, as compared to an average of  $6.0 \pm 2.3\%$ /day in the same patients during the administration of Lugol's solution.

Despite the pronounced increase in serum  $T_4$  concentration which occurred after withdrawal of iodine in the four patients not given methimazole, the slope of the  $T_4$ - $^{127}\text{I}$ :  $\text{PB}^{131}\text{I}$  curve was not as great as during the control period. This resulted from the tailing of the  $\text{PB}^{131}\text{I}$  disappearance curve during the latter portion of the study, as described earlier. Typical curves for specific activity ratios obtained in the absence or presence of methimazole blockade are shown in Fig. 3.

*Ratio of  $\text{PB}^{125}\text{I}$ :  $\text{PB}^{131}\text{I}$  (Table IV).* Ratios of the  $\text{PB}^{125}\text{I}$ :  $\text{PB}^{131}\text{I}$  concentrations also increased progressively with time in all patients during the control period. As with the slope of the curve of the  $T_4$ - $^{127}\text{I}$ :  $\text{PB}^{131}\text{I}$  ratios, the slope of the  $\text{PB}^{125}\text{I}$ / $\text{PB}^{131}\text{I}$  curve decreased abruptly during administration of iodine, regardless of whether methimazole was being given. After withdrawal of iodine, the slope of the curve describing this ratio with time increased abruptly in those patients given methimazole. Little or no increase was seen in patients given no methimazole, probably as a result of tailing of the  $\text{PB}^{131}\text{I}$  disappearance curve.

*Thyroidal release of  $^{125}\text{I}$ .* In the five patients studied without methimazole blockade, sequential epithyroid counts did not define a clearly discernible  $^{125}\text{I}$  release curve, and neither acceleration nor retardation of the curve was evident during or after the administration of iodine. In the three patients given methimazole, in con-

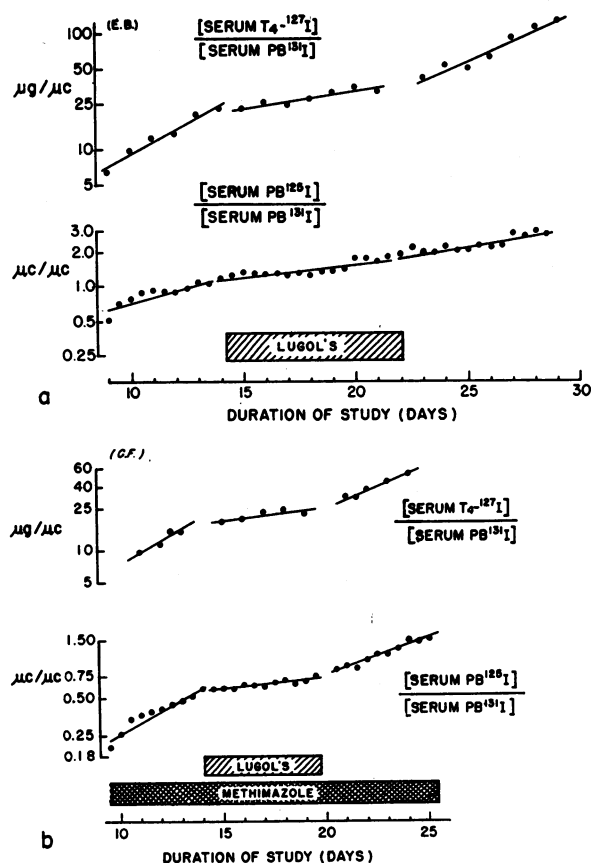


FIGURE 3 The effect of Lugol's iodine on thyroxine ( $T_4$ ) release in patients with hyperthyroidism as judged from the ratios of serum  $T_4$ - $^{127}\text{I}$  and serum  $\text{PB}^{125}\text{I}$  concentrations to the concentration of  $\text{PB}^{131}\text{I}$ . Patients received inorganic  $^{125}\text{I}$  followed by  $^{131}\text{I}$ -labeled  $T_4$ . Patients whose results are depicted in Fig. 3a and 3b are the same as those in Figs. 1 and 2, respectively.

TABLE IV

*Effect of Lugol's Iodine on the Release of Thyroxine ( $T_4$ ) from the Thyroids of Patients with Thyrotoxicosis Given Inorganic  $^{125}\text{I}$  and  $T_4$ - $^{131}\text{I}$  Assessed from the Slope with Time of the Ratio  $\text{PB}^{125}\text{I}$ :  $\text{PB}^{131}\text{I}$  in Serum*

Patient	A. Control period		B. Lugol's iodine		C. Post-Lugol's period		P values*	
	Slope $\pm$ SEM $\ddagger$	r $\S$	Slope $\pm$ SEM	r	Slope $\pm$ SEM	r	A vs. B	B vs. C
A. J.	$0.249 \pm 0.008$	0.96	$0.051 \pm 0.004$	0.79	$0.023 \pm 0.006$	0.21	<0.001	
W. H.	$0.151 \pm 0.004$	0.97	$0.089 \pm 0.004$	0.93			<0.01	
M. M.	$0.227 \pm 0.003$	0.98	$0.109 \pm 0.002$	0.99	$0.084 \pm 0.002$	0.96	<0.001	<0.02
K. K.	$0.127 \pm 0.003$	0.96	$0.052 \pm 0.002$	0.96	$0.053 \pm 0.003$	0.79	<0.001	
E. B.	$0.127 \pm 0.007$	0.90	$0.052 \pm 0.002$	0.84	$0.074 \pm 0.003$	0.90	<0.001	
M. D.	$0.185 \pm 0.003$	0.97	$0.028 \pm 0.003$	0.65			<0.001	
C. F.	$0.211 \pm 0.007$	0.96	$0.041 \pm 0.002$	0.89	$0.142 \pm 0.003$	0.98	<0.001	<0.001
M. D. M.	$0.185 \pm 0.006$	0.94	$0.029 \pm 0.004$	0.48	$0.110 \pm 0.002$	0.98	<0.001	<0.001

\* *t* test for difference between slopes. Only significant differences shown.

$\ddagger$  Standard error of the slope with time (fraction/day) of the  $\text{PB}^{125}\text{I}$ :  $\text{PB}^{131}\text{I}$  ratio; calculated by the method of least squares.

$\S$  Correlation coefficient of the  $\text{PB}^{125}\text{I}$ :  $\text{PB}^{131}\text{I}$  ratio vs. time.

|| Received methimazole (30 mg every 6 hr) during period of study.

trast, a clearly exponential release curve for  $^{125}\text{I}$  in the thyroid was evident during the control period. As has been previously described, this slowed abruptly during iodine administration and accelerated after its withdrawal (1-3).

*Estimate of fractional inhibition of  $T_4$ - $^{127}\text{I}$  release by iodine.* The formulation described in the Appendix provides an estimate of the rate of fractional  $T_4$  release from the thyroid during the period of iodine administration, relative to that present during the control period. The formulation rests on the assumption that thyroidal  $T_4$  exists in a single pool and does not increase in amount as a result of iodine administration. The former assumption cannot be validated, but probably the latter assumption is nearly the case in patients receiving antithyroid drugs. In patients not receiving antithyroid drugs, thyroidal content of  $T_4$ - $^{127}\text{I}$  almost certainly did increase during administration of iodine. Even so, the assumption of constancy of thyroidal  $T_4$ - $^{127}\text{I}$  would lead to an underestimate of the extent to which fractional secretion rate for  $T_4$ - $^{127}\text{I}$  had been decreased.

In five patients studied in the absence of methimazole blockade, the calculated percentage decrease in fractional  $T_4$ - $^{127}\text{I}$  release rate averaged  $74.1 \pm 12.8$ . In the three patients who were studied during methimazole blockade, the estimated percentage decreases in fractional  $T_4$ - $^{127}\text{I}$  release rates were 61.2, 63.4, and 87.3, respectively (Table V).

## DISCUSSION

The striking discrepancy between the speed with which iodine often ameliorates the manifestations of thyro-

toxicosis and the generally delayed response to antithyroid drugs suggests that these agents differ in their basic mechanisms of action. It has been presumed that the early action of iodine can be explained by an inhibition of the release of hormone from the thyroid gland, a suggestion which is supported by numerous demonstrations of a rapid decline in serum protein-bound iodine (PBI) after iodine administration. This conclusion was strengthened by the findings of Goldsmith and Eisele (1), who employed direct epithyroid counting to demonstrate that in patients with hyperthyroidism who were receiving antithyroid drugs, iodine abruptly decreased the rate of loss of  $^{125}\text{I}$  from the thyroid gland. These findings were subsequently confirmed in other studies similarly conducted (2, 3, 5). More recently, however, the observations of Mitchell, Bradford, and Gilboa (4) have raised some doubt as to whether iodine does indeed inhibit the release of thyroidal radioiodine and, by inference, of  $T_4$ . Among 16 patients studied in the absence of antithyroid blockade, eight displayed an apparent acceleration of radioiodine release during iodine administration, while the remaining eight showed no effect.

This discrepancy highlights certain shortcomings of the serial epithyroid counting technique as an index of the rate of thyroid hormone release. Accurate measurement of glandular radioiodine release rates, especially in hyperthyroid patients, requires administration of antithyroid agents to prevent secondary reaccumulation of radioiodine which has already traversed the thyroid, been secreted as hormone, and been liberated as iodide by peripheral deiodination. Such recycling would retard and obscure the primary glandular radio-

TABLE V  
*Inhibition by Lugol's Iodine of the Fractional Rate of Release of Thyroxine ( $T_4$ ) from the Thyroids of Patients with Thyrotoxicosis*

Patient	Control serum $T_4$ $\mu\text{g}/100\text{ ml}$	Serum $T_4$ at time t $\mu\text{g}/100\text{ ml}$	Days to time t*	Fractional rate of $T_4$ turnover; $k$ $\%/day$	Per cent inhibition of fractional $T_4$ release rate†
A. J.	15.8	9.0	6.5	16.6	65.0
W. H.	10.8	8.0	4.0	13.4	63.0
M. M.	20.5	14.0	3.5	20.0	63.0
K. K.	21.0	11.0	6.0	13.0	87.8
E. B.	20.0	11.0	4.0	16.9	91.5
M. D.§	15.1	8.5	6.0	20.8	61.2
C. F.§	13.2	8.5	5.0	15.7	63.4
M. D. M.§	17.0	11.5	4.0	11.6	87.3
Mean $\pm$ SEM	$16.7 \pm 1.2$	$10.2 \pm 0.7$	$4.9 \pm 0.4$	$16.0 \pm 1.1$	$72.8 \pm 4.4$

\* Approximate duration of Lugol's iodine therapy at which serum  $T_4$  concentration no longer continued to decrease.

† See Appendix for method of calculation from the primary data shown in this table.

§ Received methimazole (30 mg every 6 hr) during period of study.

iodine release curve. In studies of the effects of iodine in the absence of antithyroid blockade, inhibition by stable iodine of radioiodine reaccumulation would tend to accelerate the net loss of  $^{131}\text{I}$  from the thyroid and could thereby obscure any slowing in primary  $^{131}\text{I}$  release which iodine might produce. On the other hand, as Mitchell and coworkers suggested, it is possible that antithyroid agents alter intrathyroidal iodine metabolism in such a way as to change the response of over-all  $^{131}\text{I}$  release rates to either pharmacological agents or disease, thus explaining the apparently different effects of iodine in the presence or absence of methimazole blockade (4). Other shortcomings of the serial epithyroid counting technique are also apparent. It provides no information concerning the nature of the iodinated materials being released, an important consideration since iodinated materials other than  $\text{T}_4$  are released from both the normal and diseased thyroid gland (14<sup>6</sup>). Finally, the technique makes no allowance for the specific activity of the radioiodinated materials released, a consideration which becomes particularly cogent in studies of the effects of iodine administration.

The method which we have described is free of the shortcomings of serial epithyroid counting as a technique for demonstrating changes in the rate of  $\text{T}_4$  release, and involves few, if any, intrinsic assumptions. Basically, we have demonstrated that Lugol's iodine<sup>6</sup> abruptly decreases the serum concentration of  $\text{T}_4$ - $^{127}\text{I}$  in patients with hyperthyroidism and that this cannot be explained by a change in the distribution or turnover of the hormone in the periphery, since the metabolism of exogenous  $^{131}\text{I}$ -labeled  $\text{T}_4$  was unaffected. This response was observed irrespective of whether complete blocking doses of antithyroid drugs were given before the administration of iodine. Hence, the absolute rate of  $\text{T}_4$ - $^{127}\text{I}$  secretion must have been decreased by iodine if, as seems most likely, the exogenous  $\text{T}_4$ - $^{131}\text{I}$  is a suitable tag for the metabolism of  $\text{T}_4$ - $^{127}\text{I}$  secreted by the thyroid.

A more quantitative evaluation of the influence of iodine on the rate of  $\text{T}_4$  secretion can be obtained by an examination of the curves depicting the change with time of the ratio of  $\text{T}_4$ - $^{127}\text{I}$ :  $\text{PB}^{131}\text{I}$ . As would be expected from the constancy of  $\text{T}_4$ - $^{127}\text{I}$  and the exponential decline in  $\text{PB}^{131}\text{I}$ , the ratios increased exponentially during the control phase. Had iodine produced a complete inhibition of  $\text{T}_4$  release, the serum  $\text{T}_4$ - $^{127}\text{I}$  concentration would have decreased at the same exponential rate as did the concentration of exogenously labeled  $\text{PB}^{131}\text{I}$ . Hence, the slope of the curve depicting the change with time in the ratio of  $\text{T}_4$ - $^{127}\text{I}$ :  $\text{PB}^{131}\text{I}$  would have been zero. In the entire group

<sup>6</sup> Wartofsky, L., and S. H. Ingbar. To be published.

<sup>7</sup> The effects herein demonstrated should not be construed as being due to iodine per se, since they can be reproduced by pharmacological doses of inorganic iodine.

of eight patients in the present study, the slope of the ratio averaged  $20.7 \pm 4.8\%$ /day during the control period and decreased to  $6.4 \pm 2.2\%$ /day during iodine administration. The lowest individual value for the slope observed during iodine administration was  $1.3\%$ /day, indicating almost complete inhibition of  $\text{T}_4$  secretion.

A decrease in  $\text{T}_4$  secretion induced by iodine could have come about in several ways: an inhibition of  $\text{T}_4$  synthesis, a decrease in the fractional rate of  $\text{T}_4$  release, or both. The ability of iodine acutely to inhibit  $\text{T}_4$  synthesis (Wolff-Chaikoff effect) is well known and has been demonstrated to occur in patients with thyrotoxicosis (15, 16). This effect is usually transient (16), and such transiency might be considered as evidence against its primary role in decreasing  $\text{T}_4$  secretion. On the other hand, the transient nature of the Wolff-Chaikoff effect could be taken to be responsible for the observation that serum  $\text{T}_4$  concentration generally did not continue to fall during the entire period of iodine administration. Nevertheless, several lines of evidence indicate that even if a decrease in synthesis occurs during iodine administration, the major effect of iodine is to inhibit the mechanism by which  $\text{T}_4$  is released. First, very large doses of methimazole do not produce the sharp decline in serum  $\text{T}_4$  or PBI that is produced by iodine. This difference is evident in the methimazole-treated patients in the present study, as well as in earlier studies of the peripheral turnover of  $\text{T}_4$  in thyrotoxic patients in whom methimazole was given to prevent recycling of iodine (9).

A second line of evidence is provided by the response of the serum  $\text{T}_4$  to withdrawal of iodine in methimazole-treated and untreated groups. In the former group, serum  $\text{T}_4$ - $^{127}\text{I}$  concentration remained constant or increased only slightly in the 4-6 days after withdrawal of iodine. In the patients who had received no methimazole, in contrast, withdrawal of iodine was followed both by a rapid rise in  $\text{T}_4$ - $^{127}\text{I}$  concentration to values characteristic of thyrotoxicosis and by reappearance of clinical manifestations. If iodine had acted only to inhibit hormonal synthesis, the response to its withdrawal should have been uninfluenced by concomitant methimazole administration. The rapid increase in serum  $\text{T}_4$  which occurred after iodine was withdrawn from patients given no methimazole is more consistent with restoration of a rapid fractional  $\text{T}_4$  release from a pool which had remained unchanged, or even increased, during iodine administration.

The third, and most important line of evidence derives from observations of the endogenously-labeled PBI ( $\text{PB}^{128}\text{I}$ ). In the present technique, an intrathyroidal pool of  $^{128}\text{I}$ -labeled  $\text{T}_4$  was present before iodine administration. As noted earlier, administration of iodine was not accompanied by an abrupt decrease in thyroidal con-



TABLE VI

Estimated Values for the Thyroid Content of Thyroxine ( $T_4$ ) Based on the Assumption of Complete Inhibition of  $T_4$  Synthesis by Lugol's Iodine\*

Patient	Estimated $T_4$ release rate; $r$	Estimated $T_4$ content, $V_0$	Estimated thyroid weight	Predicted $T_4$ content; $V_p$ †	$V_p/V_0$
	%/day	$\mu\text{g } T_4$	g	$\mu\text{g } T_4$	
A. J.	32.3	706	100	30,800	43.6
W. H.	53.7	431	35	10,780	25.0
M. M.	60.3	687	65	20,020	29.1
E. B.	224.7	150	50	15,400	103.0
K. K.	103.7	250	25	7,700	30.8
M. D.§	29.9	1301	30	9,240	7.1
C. F.§	45.0	589	40	12,320	20.9
M. D. M.§	164.1	159	35	10,780	67.8

\* Estimations of thyroid content of  $T_4$  ( $V_0$ ) and fractional rate of  $T_4$  release ( $r$ ) based on formulation and assumptions presented in Appendix and upon values for serum  $T_4$  concentration and duration of Lugol's iodine therapy shown in Table V.

† Based upon the estimated gland weight and upon analyses by Braasch, Albert, Keating, and Black (17), which revealed a mean  $T_4$  concentration of 20  $\mu\text{g } T_4$  iodine/100 mg wet wt in untreated diffuse toxic goiter.

§ Received methimazole (30 mg every 6 hr) during period of study.

tent of  $^{125}\text{I}$ . Hence, the abrupt decrease in  $T_4$ - $^{125}\text{I}$  secretion during iodine administration, evident from an examination of  $\text{PB}^{125}\text{I}:\text{PB}^{131}\text{I}$  ratios, is best explained by a decrease in the fractional rate of  $T_4$ - $^{125}\text{I}$  release, and not a decrease in its synthesis.

Finally, the Appendix presents a mathematical formulation relating the size of the intrathyroidal  $T_4$  pool and its fractional rate of release to the size and turnover rate of the extrathyroidal  $T_4$  pool. As indicated above, the formulation has demonstrated a marked reduction in the fractional rate of  $T_4$  release during iodine administration, assuming no change in the intrathyroidal  $T_4$  pool (Table V). The same formulation can be employed to calculate the content of the glandular  $T_4$  pool which must have been present had iodine decreased the serum  $T_4$  to the observed extent, not by affecting its fractional rate of release, but solely by inhibiting new  $T_4$  synthesis (see Appendix). The values thereby derived are far below available estimates of thyroidal  $T_4$  content in Graves' disease (17), making the assumption of a predominant effect of iodine on synthesis rather than release of  $T_4$  highly unlikely (Table VI).

For these reasons we would conclude that a decrease in the fractional rate of  $T_4$  release is at least the major reason that iodine acutely decreases  $T_4$  secretion, thereby decreasing serum  $T_4$  and ameliorating the clinical manifestations in patients with thyrotoxicosis. Nevertheless, several aspects of the action of iodine in such patients remain unclear. It is uncertain why, after a few days of treatment,  $T_4$  secretion rate is adjusted to maintain a euthyroid state and a normal concentration of serum  $T_4$ .

Also unexplained is the later reemergence of thyrotoxicosis in many patients, despite continued iodine administration (16). Additional and more prolonged observations will be required to clarify the origin of these responses.

## APPENDIX

Let

- $V_0$  = glandular content of thyroxine ( $T_4$ ) during the control period;
- $V$  = glandular content of  $T_4$  at time  $t$ ;
- $P_0$  =  $T_4$  content of peripheral  $T_4$  pool during the control period;
- $P$  =  $T_4$  content of the peripheral  $T_4$  pool at time  $t$ ;
- $t$  = time after initiation of Lugol's iodine therapy;
- $r_0$  = fractional rate of glandular  $T_4$  release during the control period ( $\text{day}^{-1}$ );
- $r$  = fractional rate of glandular  $T_4$  release during Lugol's iodine therapy; and
- $k$  = fractional rate of turnover of peripheral  $T_4$  pool (unchanged by Lugol's iodine therapy).

The equations governing changes in the content of the peripheral  $T_4$  pool ( $P$ ) are

$$V \xrightarrow{r} P \xrightarrow{k} \quad (1)$$

$$dp/dt = rV - kP \quad (2)$$

During the control period a steady state exists; hence

$$dp/dt = rV - kP = 0 \quad (3)$$

and

$$r_0V_0 = kP_0 \quad (4)$$

A. If Lugol's iodine therapy is introduced, and if Lugol's iodine does not change the glandular pool of  $T_4$  ( $V = V_0$ ), but changes only the fractional release rate for  $T_4$ , then

$$dp/dt = rV_0 - kP \quad (5)$$

The solution for this equation is

$$P = e^{-kt} \left[ \frac{rV_0}{k} (1 - e^{-kt}) + P_0 \right] \quad (6)$$

Rearranging:

$$r = \frac{k}{V} \left( \frac{P - P_0 e^{-kt}}{1 - e^{-kt}} \right) \quad (7)$$

Under these conditions, from equations 7 and 4, the ratio of fractional release rates

$$\frac{r_0}{r} = \frac{(1 - e^{-kt})}{(P/P_0 - e^{-kt})} \quad (8)$$

B. On the other hand, it can be assumed that the only action of Lugol's iodine is to inhibit the synthesis of  $T_4$ . The equation describing the changes in the content of the peripheral  $T_4$  pool under these conditions has been derived and presented in an earlier publication (18).

$$P = e^{-kt} \left[ \left( \frac{rV_0 e^{(k-r)t}}{(k-r)} \right) + \left( P_0 - \frac{rV_0}{k-r} \right) \right] \quad (9)$$

Rearranging:

$$P = e^{-kt} \left[ \frac{rV_0}{k-r} (e^{(k-r)t} - 1) + P_0 \right] \quad (10)$$

Since the assumption dictates that during Lugol's iodine therapy  $r = r_0$ , equations 4 and 10 can be solved simultaneously to determine the two unknowns,  $r_0$  and  $V_0$ .

Equation 10 is rearranged to yield

$$Pe^{kt} = \frac{rV_0}{k-r} (e^{(k-r)t} - 1) + P_0 \quad (11)$$

from whence

$$Pe^{kt} - P_0 = \frac{rV_0}{k-r} (e^{(k-r)t} - 1) \quad (12)$$

Let

$$X = k - r. \quad (13)$$

By substitution into equation 12

$$Pe^{kt} - P_0 = \frac{rV_0}{X} (e^{Xt} - 1) \quad (14)$$

Whence

$$\frac{Pe^{kt} - P_0}{rV_0} = \frac{e^{Xt} - 1}{X} \quad (15)$$

Let

$$Y = \frac{Pe^{kt} - P_0}{rV_0} \quad (16)$$

Substituting into equation 15 and rearranging, we arrive at the transcendental equation

$$e^{Xt} - YX = 1 \quad (17)$$

Equation 14 is solved for the root  $Y$ . Since  $k$  is known,  $r (= r_0)$  can be determined from equation 13 and  $V_0$  from equation 4.

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