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

LEONARD WARTOFSKY, BERNARD J. RANSIL, and SIDNEY H. INGBAR

From the Thorndike Memorial Laboratory, Harvard (Second and Fourth) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts 02118

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 thyroidal 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}I followed several days later by an intravenous tracer dose of ^{131}I-labeled T_4. Serial observations of serum protein-bound (PB) ^{125}I and ^{131}I are accompanied by frequent measurements of endogenous serum T_4 (T_4-^{127}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-^{127}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}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 $PB^{125}I$ or T_4-^{127}I and $PB^{131}I$ 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 thyroidal T_4 release.

INTRODUCTION

The mechanism whereby iodine alleviates thyrotoxicosis in patients with Graves' disease has been a subject of 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 thyroidal 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 μc of inorganic ^{125}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 trichloracetic acid precipitation and both the concentration of protein-bound ^{125}I in serum ($PB^{125}I$) and total urinary ^{125}I were measured. When the concentration of $PB^{125}I$ had reached an approximate plateau (usually at 5–7 days), 50 μc of ^{131}I-labeled T_4 was

This work was presented in part at the Annual Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 1968.

Received for publication 19 June 1969.

TABLE I

Clinical Data in Patients Studied

Patient	Age	Sex	Diagnosis	24 hr thyroid ^{131}I uptake	Serum thyroxine
				% 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.[1] Thereafter, both $PB^{125}I$ and $PB^{131}I$ in serum, as well as urinary ^{125}I and ^{131}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.[2] Values for each isotope were calculated as a per cent of the original dose. Measurements of thyroidal ^{125}I and ^{131}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 ^{131}I-labeled T_4 and was continued throughout the period of study.

Estimations of serum stable T_4 (T_4-^{127}I) concentration were made by the method of Murphy, Pattee, and Gold on multiple samples obtained during each experimental period (8).[3]

From the foregoing data a number of calculations were made. The kinetics of the peripheral metabolism of ^{131}I-labeled T_4 were assessed by methods described in detail elsewhere (9). The fractional rate of peripheral turnover of T_4 was calculated from the semilogarithmic regression slope of the serum $PB^{131}I$, as determined by the method of least squares. T_4 distribution space was calculated from the zero time intercept of the least squares regression equation. Peripheral T_4 clearance rate was calculated as the product of the T_4 distribution space and the fractional turnover rate, and the T_4 disposal rate as the product of the T_4 clearance rate and the serum T_4-^{127}I concentration (10).

The ratio $PB^{125}I$: $PB^{131}I$ was calculated for each specimen of serum obtained. In addition, the ratio T_4-^{127}I : $PB^{131}I$ was calculated for each of the frequently obtained specimens in which T_4-^{127}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_4 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 ^{131}I-labeled T_4 (Table II). Values for various aspects of the peripheral turnover of exogenously labeled T_4 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_4 turnover was greater than normal, averaging 16.0 ± 3.0%/day. As a consequence, T_4 clearance rate was also increased (1.83 ±0.41 liters). Values for T_4-^{127}I concentration during control periods were generally increased (16.7 ±3.4 μg/100 ml), as was the daily rate of disposal of T_4 (298 ±68 μg).[4]

In all five patients studied in the absence of antithyroid blockade, the curve describing the disappearance of ^{131}I-labeled T_4 from the serum displayed an apparent slowing during the later portion of each study (Fig.

[1] ^{131}I-labeled T_4 was obtained from Abbott Laboratories, Chicago, Ill.

[2] Data obtained concerning the urinary excretion of ^{125}I and ^{131}I are not employed in the methods of analysis used in the present report, but will be discussed in a later publication.

[3] Performed by the Boston Medical Laboratory, Boston, Mass.

[4] Throughout this presentation, values for T_4-^{127}I are intended to represent total T_4 concentrations in serum. These can be converted to values for T_4 iodine by multiplying by 0.65.

TABLE II

Various Aspects of the Peripheral Metabolism of Thyroxine (T_4) in Patients with Thyrotoxicosis Given Lugol's Iodine

Patient	Body wt	T_4 space	Fractional T_4 turnover (k)	T_4 clearance	Serum T_4	T_4 disposal rate
	kg	*liters*	*%/day*	*liters/day*	*μg/100 ml*	*μg T_4/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_4 of radioiodine 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 ^{131}I-labeled T_4 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 ^{131}I-labeled T_4.

Concentration of T_4-^{127}I. Before the administration of Lugol's solution, values for the concentration of serum T_4 were essentially constant, regardless of whether or not patients were receiving methimazole during this period. After institution of iodine therapy, serum T_4 concentrations decreased abruptly. This decrease was usually not progressive, however, since values tended to

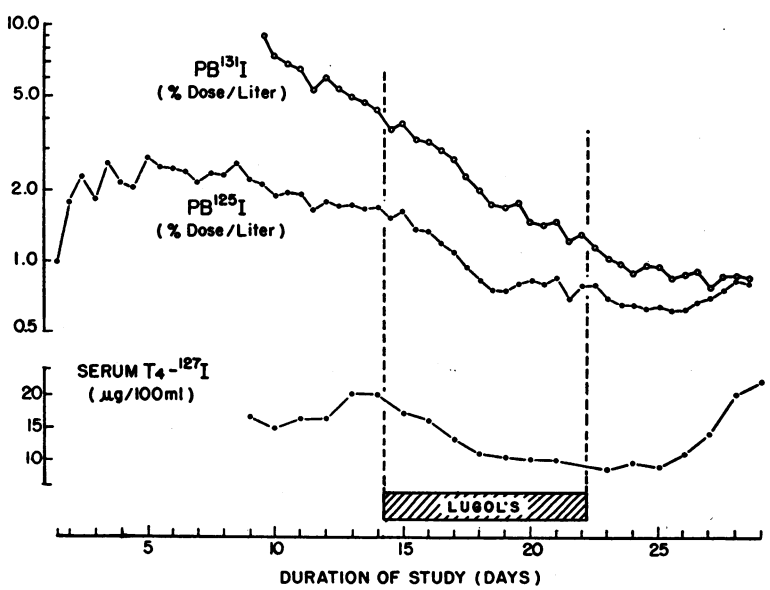

FIGURE 1 The effect of Lugol's iodine on the thyroidal release and peripheral metabolism of thyroxine (T_4) in a patient (E. B.) with hyperthyroidism. Patient given inorganic ^{125}I and several days later ^{131}I-labeled T_4. Serial measurements made of serum protein-bound ^{125}I and ^{131}I and of T_4-^{127}I concentrations.

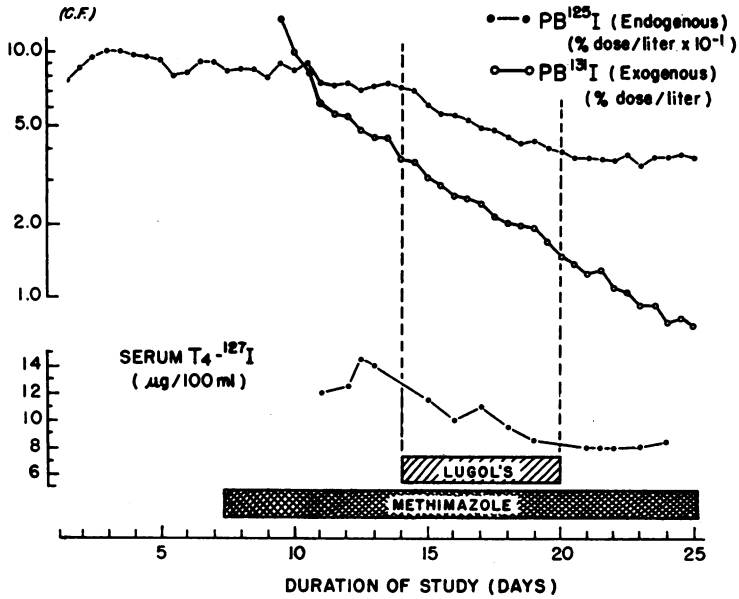

FIGURE 2 The effect of Lugol's iodine in the presence of methimazole blockade on the thyroidal release and peripheral metabolism of thyroxine (T_4) in a patient with hyperthyroidism. Patient given inorganic ^{125}I and several days later ^{131}I-labeled T_4. Serial measurements made of serum protein-bound ^{125}I and ^{131}I and of T_4-^{127}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 ±1.9 μg/100 ml from a control mean of 16.7 ±3.4 μg/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 iodine, little or no increase in serum T_4 occurred in two patients who received methimazole (Fig. 2).

Ratio of T_4-^{127}I: $PB^{131}I$ (Table III). Before the administration of iodine, the numerical value of the ratio of T_4-^{127}I: $PB^{131}I$ (μg/% dose) in the serum increased exponentially with time, since T_4-^{127}I remained constant and $PB^{131}I$ 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}I:$PB^{131}I$ after Administration of T_4-^{131}I

Patient	A. Control period		B. Lugol's iodine		C. Post-Lugol's period		*P* values*	
	Slope ±SEM‡	*r*§	Slope ±SEM	*r*	Slope ±SEM	*r*	A vs. B	B vs. C
A. J.	0.230 ±0.014	0.99	0.079 ±0.011	0.77	0.199 ±0.015	0.92	<0.02	<0.05
W. H.	0.180 ±0.013	0.96	0.092 ±0.015	0.77			<0.05	
M. M.	0.133 ±0.009	0.95	0.080 ±0.003	0.99	0.162 ±0.013	0.93	<0.05	<0.05
K. K.	0.273 ±0.017	0.94	0.013 ±0.007	0.30	0.132 ±0.003	0.98	<0.001	<0.001
E. B.	0.242 ±0.009	0.98	0.069 ±0.005	0.93	0.197 ±0.009	0.97	<0.001	<0.001
M. D.‖	0.152 ±0.005	0.98	0.053 ±0.013	0.82			<0.01	
C. F.‖	0.258 ±0.029	0.95	0.056 ±0.010	0.82	0.192 ±0.010	0.98	<0.01	<0.01
M. D. M.‖	0.188 ±0.019	0.93	0.066 ±0.009	0.80	0.166 ±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}I:$PB^{131}I$ ratio (μg/% dose); calculated by the method of least squares.

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

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

was administered. During the control period, slopes averaged 20.7 ±4.8%/day, whereas during treatment with iodine the mean slope decreased to 6.4 ±2.2%/day. After withdrawal of iodine, the slope of the T_4-^{127}I : $PB^{131}I$ ratio with time increased markedly, averaging 17.5 ± 2.4%/day in the six patients studied, as compared to an average of 6.0 ±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}I : $PB^{131}I$ curve was not as great as during the control period. This resulted from the tailing of the $PB^{131}I$ 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 $PB^{125}I$: $PB^{131}I$ (Table IV). Ratios of the $PB^{125}I$: $PB^{131}I$ 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}I : $PB^{131}I$ ratios, the slope of the $PB^{125}I/PB^{131}I$ 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 $PB^{131}I$ disappearance curve.

Thyroidal release of ^{125}I. In the five patients studied without methimazole blockade, sequential epithyroid counts did not define a clearly discernible ^{125}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-

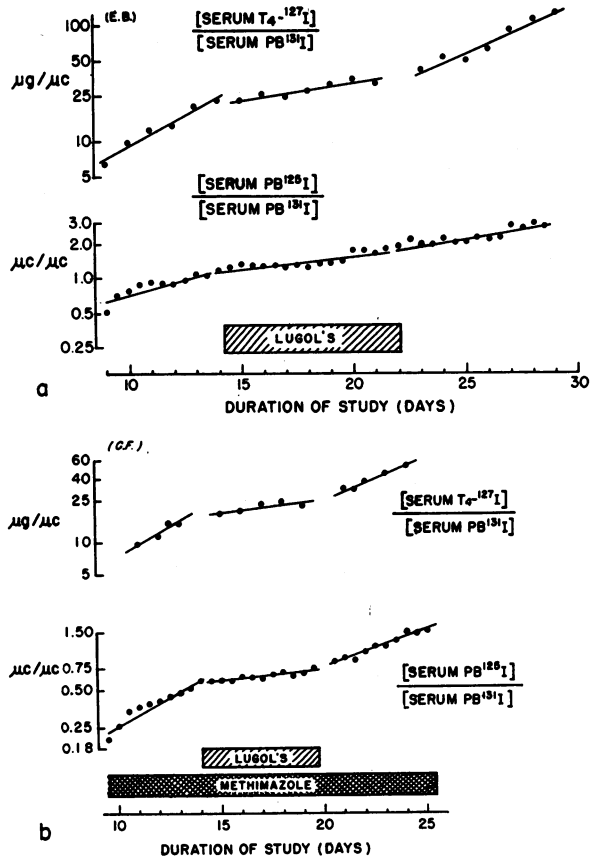

FIGURE 3 The effect of Lugol's iodine on thyroidal thyroxine (T_4) release in patients with hyperthyroidism as judged from the ratios of serum T_4-^{127}I and serum $PB^{125}I$ concentrations to the concentration of $PB^{131}I$. Patients received inorganic ^{125}I followed by ^{131}I-labeled T_4. Patients whose results are depicted in Fig. 3 *a* and 3 *b* 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}I and T_4-^{131}I Assessed from the Slope with Time of the Ratio $PB^{125}I$: $PB^{131}I$ in Serum

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

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

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

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

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

trast, a clearly exponential release curve for ^{125}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}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}I almost certainly did increase during administration of iodine. Even so, the assumption of constancy of thyroidal T_4-^{127}I would lead to an underestimate of the extent to which fractional secretion rate for T_4-^{127}I had been decreased.

In five patients studied in the absence of methimazole blockade, the calculated percentage decrease in fractional T_4-^{127}I release rate averaged 74.1 ±12.8. In the three patients who were studied during methimazole blockade, the estimated percentage decreases in fractional T_4-^{127}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 thyrotoxicosis 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 ^{131}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	Serum T_4 at time t	Days to time t*	Fractional rate of T_4 turnover; k	Per cent inhibition of fractional T_4 release rate‡
	μg/100 ml	*μg/100 ml*		*%/day*	
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 ±SEM	16.7 ±1.2	10.2 ±0.7	4.9 ±0.4	16.0 ±1.1	72.8 ±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}I from the thyroid and could thereby obscure any slowing in primary ^{131}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}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 T_4 are released from both the normal and diseased thyroid gland (14[5]). 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 T_4 release, and involves few, if any, intrinsic assumptions. Basically, we have demonstrated that Lugol's iodine[6] abruptly decreases the serum concentration of T_4-^{127}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}I-labeled 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 T_4-^{127}I secretion must have been decreased by iodine if, as seems most likely, the exogenous T_4-^{131}I is a suitable tag for the metabolism of T_4-^{127}I secreted by the thyroid.

A more quantitative evaluation of the influence of iodine on the rate of T_4 secretion can be obtained by an examination of the curves depicting the change with time of the ratio of T_4-^{127}I: $PB^{131}I$. As would be expected from the constancy of T_4-^{127}I and the exponential decline in $PB^{131}I$, the ratios increased exponentially during the control phase. Had iodine produced a complete inhibition of T_4 release, the serum T_4-^{127}I concentration would have decreased at the same exponential rate as did the concentration of exogenously labeled $PB^{131}I$. Hence, the slope of the curve depicting the change with time in the ratio of T_4-^{127}I: $PB^{131}I$ would have been zero. In the entire group of eight patients in the present study, the slope of the ratio averaged 20.7 ±4.8%/day during the control period and decreased to 6.4 ±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 T_4 secretion.

A decrease in T_4 secretion induced by iodine could have come about in several ways: an inhibition of T_4 synthesis, a decrease in the fractional rate of T_4 release, or both. The ability of iodine acutely to inhibit 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 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 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 T_4 is released. First, very large doses of methimazole do not produce the sharp decline in serum 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 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 T_4 to withdrawal of iodine in methimazole-treated and untreated groups. In the former group, serum T_4-^{127}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 T_4-^{127}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 T_4 which occurred after iodine was withdrawn from patients given no methimazole is more consistent with restoration of a rapid fractional 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 ($PB^{125}I$). In the present technique, an intrathyroidal pool of ^{125}I-labeled T_4 was present before iodine administration. As noted earlier, administration of iodine was not accompanied by an abrupt decrease in thyroidal con-

[5] Wartofsky, L., and S. H. Ingbar. To be published.

[6] 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.

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	*μg T_4*	*g*	*μg 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 μg 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}I. Hence, the abrupt decrease in T_4-^{125}I secretion during iodine administration, evident from an examination of $PB^{125}I$: $PB^{131}I$ ratios, is best explained by a decrease in the fractional rate of T_4-^{125}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 (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:

$$r = \frac{k}{V}\left(\frac{P - P_0e^{-kt}}{1 - e^{-kt}}\right) \quad (7)$$

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).

$$P = e^{-kt}\left[\left(\frac{rV_0e^{(k-r)t}}{(k - r)}\right) + \left(P_0 - \frac{rV_0}{k - r}\right)\right] \quad (9)$$

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.

ACKNOWLEDGMENTS

This work was supported in part by Research Grant No. AM-09753 from the National Institute of Arthritis and Metabolic Diseases and by Grant No. FR-76 from the Division of Health Resources and Facilities, National Institutes of Health, Bethesda, Md.

REFERENCES

1. Goldsmith, R. E., and M. L. Eisele. 1956. The effect of iodide on the release of thyroid hormone in hyperthyroidism. *J. Clin. Endocrinol. Metab.* **16**: 130.
2. Greer, M. A., and L. J. DeGroot. 1956. The effect of stable iodide on thyroid secretion in man. *Metabolism.* **5**: 682.
3. Solomon, D. H. 1956. Factors affecting the fractional rate of release of radioiodine from the thyroid gland in man. *Metabolism.* **5**: 667.
4. Mitchell, M. L., A. H. Bradford, and Y. Gilboa. 1966. Paradoxical response of the unblocked hyperthyroid gland to iodide. *J. Clin. Endocrinol. Metab.* **26**: 639.
5. Goldsmith, R., C. Herbert, and G. Lutsch. 1958. The effect of iodide on the release of thyroid hormone in hyperthyroidism: further observations. *J. Clin. Endocrinol. Metab.* **18**: 367.
6. Ansell, G., and H. Miller. 1952. Influence of iodine on the release of thyroid hormone in thyrotoxicosis. *Lancet.* **2**: 5.
7. Volpé, R., and M. W. Johnston. 1962. The effect of small doses of stable iodine in patients with hyperthyroidism. *Ann. Intern. Med.* **56**: 577.
8. Murphy, B. E., C. J. Pattee, and A. Gold. 1966. Clinical evaluation of a new method for the determination of serum thyroxine. *J. Clin. Endocrinol. Metab.* **26**: 247.
9. Ingbar, S. H., and N. Freinkel. 1955. Simultaneous estimation of rates of thyroxine degradation and thyroid hormone synthesis. *J. Clin. Invest.* **34**: 808.
10. Ingbar, S. H., and N. Freinkel. 1960. Regulation of the peripheral metabolism of the thyroid hormones. *Recent Progr. Hormone Res.* **16**: 353.
11. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods. Iowa State Univ. Press, Ames. 6th edition.
12. Sterling, K., and R. B. Chodos. 1956. Radiothyroxine turnover studies in myxedema, thyrotoxicosis, and hypermetabolism without endocrine disease. *J. Clin. Invest.* **35**: 806.
13. Ingbar, S. H., and N. Freinkel. 1958. Studies of thyroid function and the peripheral metabolism of I^{131}-labeled thyroxine in patients with treated Graves' disease. *J. Clin. Invest.* **37**: 1603.
14. DeGroot, L. J. 1966. Kinetic analysis of iodine metabolism. *J. Clin. Endocrinol. Metab.* **26**: 149.
15. Childs, D. S., Jr., F. R. Keating, Jr., J. E. Rall, M. M. D. Williams, and M. H. Power. 1950. The effect of varying quantities of inorganic iodide (carrier) on the urinary excretion and thyroidal accumulation of radioiodine in exophthalmic goiter. *J. Clin. Invest.* **29**: 726.
16. Harden, R. McG., D. A. Koutras, W. D. Alexander, and E. J. Wayne. 1964. Quantitative studies of iodine metabolism in iodide-treated thyrotoxicosis. *Clin. Sci.* **27**: 399.
17. Braasch, J. W., A. Albert, F. R. Keating, Jr., and B. M. Black. 1955. A note on the iodinated constituents of normal thyroids and of exophthalmic goiters. *J. Clin. Endocrinol. Metab.* **15**: 732.
18. Ingbar, S. H., and N. Freinkel. 1956. ACTH, cortisone, and the metabolism of iodine. *Metabolism.* **5**: 652.