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FROM AUTONOMOUS THYROID NODULES**

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## THE EFFECT OF IODIDE ON THE RATE OF RELEASE OF I<sup>131</sup> FROM AUTONOMOUS THYROID NODULES \*

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After a tracer dose of I<sup>131</sup> has been accumulated by the thyroid gland, and further organification of radioiodine has been inhibited by antithyroid agents, thyroidal radioactivity declines with time, describing an exponential disappearance curve. The slope of this curve is a measure of the fractional rate of loss of glandular organic I<sup>131</sup>.<sup>1</sup> If the accumulated I<sup>131</sup> is uniformly distributed in the glandular organic iodine pool and if proteolysis of thyroglobulin liberates iodinated amino acids in the same proportion as they are present in the intact thyroglobulin molecule, then the loss of organic I<sup>131</sup> will accurately measure the proportion of hormonal stores secreted per unit time. These limiting assumptions have not been conclusively validated and, indeed, there is evidence that suggests they may not be true (4, 5). Nevertheless, it seems reasonably certain that the fractional loss of glandular organic I<sup>131</sup> varies directly with the velocity of those reactions by which thyroid hormone is liberated into the circulation.<sup>2</sup>

The foregoing technique has therefore gained wide acceptance in the study of factors affecting

the thyroidal secretory process, in particular iodides and thyrotropin (TSH) (6-11). It has been shown, for example, that pharmacological doses of iodide induce an abrupt and pronounced decrease in the rapid fractional disappearance of organic I<sup>131</sup> from the thyroid which characteristically occurs in patients with diffuse toxic goiter (7-9); exogenous TSH overcomes the slowing of disappearance rates induced by iodide in such patients (7, 9). In normal individuals fractional disappearance rates are usually so slow that further slowing is difficult to demonstrate (9), although recent studies indicate that iodide can indeed have such an effect (11). When the fractional disappearance of organic I<sup>131</sup> in the euthyroid subject is accelerated by exogenous TSH, however, an inhibitory effect of iodide is readily demonstrable (8, 9).

These findings are consistent with a reciprocal action of TSH and iodide on the secretory mechanism, and have led to the suggestion that "the slowing of thyroid hormone release by stable iodide administration appears to be predominantly due to antagonism at the thyroid level of the release accelerating action of thyrotropin" (8).

However, none of the foregoing observations excludes the possibility that iodide exerts an action on the secretory process that is not dependent on prior stimulation by TSH. This problem is difficult to study because, in the absence of TSH, disappearance of organic I<sup>131</sup> is usually extremely slow (10, 12). However, it is generally agreed that certain thyroid adenomas are autonomous of TSH and can reach a level of thyroid hormone production sufficient to suppress TSH ("hot nodules") (13-15). Thus, it appeared that such hyperfunctioning adenomas might afford a unique opportunity to determine whether iodide can inhibit the thyroidal secretory process in the absence of TSH.

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<sup>1</sup> Although a portion of the I<sup>131</sup> lost from the thyroid under these conditions actually escapes in the form of inorganic iodide (1, 2), this iodide almost certainly is drawn from organic sources, arising from the deiodination of free iodotyrosines (3).

<sup>2</sup> This function has often been called the "hormonal release rate." While this term has the advantage of common usage and brevity, it is not strictly accurate. Accordingly, in the present communication, it will be referred to as the fractional rate of disappearance of organic I<sup>131</sup>.

The present studies in patients with hyperfunctioning adenomas comprised two phases. The first was the selection of patients in whom the complete suppression of TSH secretion could be inferred from indirect evidence. The second phase was the determination of the effect of iodide on the fractional rates of disappearance of organic  $I^{131}$  from the thyroid glands of these patients.

#### SUBJECTS AND METHODS

*Characterization of clinical material.* The six subjects ultimately chosen for this report were selected from patients with nodular goiters seen on the wards and in the Endocrine Clinic of the Boston City Hospital. In addition to careful clinical evaluation, determinations of serum protein-bound iodine (PBI),<sup>3</sup> 24-hour thyroidal uptake of radioiodine, and basal metabolic rate were made in all patients. Three patients were felt to have definite thyrotoxicosis, one was questionably thyrotoxic, and two were probably euthyroid.

Localization of  $I^{131}$  within the thyroid was determined from scintigrams. On the basis of the 24-hour uptake, a dose of  $I^{131}$  was calculated that would result in the accumulation of 50  $\mu$ c within the gland. Scanning was done on the day after administration of this dose.<sup>4</sup> Scintigrams were then correlated with palpatory findings in the neck.

Thyroid suppression tests were performed in four patients. L-3,5,3'-triiodothyronine ( $T_3$ ), 75 to 100  $\mu$ g daily, was administered for 2 or 3 weeks. This dose is thought to cause a complete inhibition of TSH secretion (16, 17). At the end of the treatment period, thyroidal  $I^{131}$  uptakes were redetermined. The two patients in whom suppres-

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

<sup>4</sup> Kindly performed by Dr. Belton A. Burrows, Massachusetts Memorial Hospital, Boston, Mass.

sion tests were not performed were considered to be thyrotoxic.

After radioactivity in the thyroid from previous doses of  $I^{131}$  had largely disappeared, the influence of TSH on the glandular localization of  $I^{131}$  was determined. Ten U of TSH was administered intramuscularly daily for 2 or 3 days, and a scanning dose of  $I^{131}$  was given on the last day of this treatment. On the next day a second scintigram was obtained.

In two patients the adenoma was surgically removed. Postoperatively, function of residual thyroid tissue was assessed by radioiodine uptakes, scintigrams, and suppression tests.

*Studies of the fractional rate of disappearance of organic  $I^{131}$ .* Each patient received 50 to 150  $\mu$ c of carrier-free  $I^{131}$ . One to 3 days later methimazole was started, 120 mg daily in divided doses, to block further accumulation of radioiodine by the thyroid gland. At regular intervals thereafter, usually once or twice daily, the thyroidal content of radioiodine was measured with a directional scintillation probe placed 20 cm from the neck. Radioactivity over the midhigh was subtracted from that over the neck to "correct" for extrathyroidal radioactivity. Sufficient counts above background were obtained to insure a counting error of less than 1 per cent. However, since a major source of error was variation in position of the patient, at each determination the patient and the probe were re-positioned, and counting was repeated until successive counts agreed within 3 per cent. Corrections for physical decay were obviated by comparing thyroidal radioactivity with that of a suitable dilution of the administered dose of radioiodine. After an adequate control period Lugol's solution was administered for 6 to 11 days, in a dose of 24 or 30 drops daily. In two patients observations were continued for 9 and 16 days, respectively, after Lugol's solution was withdrawn.

The disappearance of  $I^{131}$  from the thyroid was assumed to be a semilogarithmic function of time. The slope of the semilogarithmic disappearance curve ( $k$ ) and its standard error were calculated by the method of least

TABLE I  
*Clinical and laboratory findings in patients with autonomous thyroid nodules*

Patient, Age (all ♀)	Thyroid gland nodule	Clinical impression	PBI $\mu$ g%	BMR %	$I^{131}$ uptake/ 24 hrs % dose	$I^{131}$ uptake during sup- pression test %	Postoperative studies	
							$I^{131}$ uptake %	Uptake during sup- pression %
I.O., 66	2 × 4 left lobe	Hyperthy.	9.2	+29	63			
M.L., 64	5 × 5, rt. lobe; left lobe 1.5 × normal size	Hyperthy.	9.2	+40	81		47	17
A.T., 37	3 × 4 left lobe	Hyperthy.	10.1	+16	45	35		
M.D., 51	3.5 × 3.5? rt. lobe	Hyperthy.	8.0	+19	48	33		
R.S., 74	2 × 2, lower pole, rt. lobe	Euthyroid	6.6	+14	52	62		
D.S., 60	3 × 3 isthmus	Euthyroid	5.3	- 1	67	52	30	2

squares, employing the first through the last points obtained during each treatment period. The significance of the change in disappearance rate induced by iodide was assessed in individual patients. Statistical methods employed were those described by Snedecor (18).

#### RESULTS

*Characterization of clinical material.* Clinical observations on the six patients are included in Table I. Each patient had a single prominent thyroid nodule. In five patients the remainder of the gland was either impalpable or subnormal in size; in Patient M.L. the remainder of the gland was slightly enlarged and on later pathological examination was found to be multiple colloid adenomatous goiter.

Scintigrams were performed in all patients, and all showed uptake of radioiodine only in the area of the prominent nodule (Figures 1 and 2). The finding of such a "hot nodule" was the major criterion for inclusion in this study.

In the four patients in whom suppression tests were performed, the marked decrease in thyroidal  $I^{131}$  uptake normally seen did not occur (Table I).

In three patients TSH markedly altered the localization of  $I^{131}$  within the thyroid gland. After TSH, scintigrams clearly demonstrated accumulation of  $I^{131}$  in extranodular areas where accumulation of  $I^{131}$  could not be demonstrated previously (Figure 1).

In both patients whose hyperfunctioning adenomas were removed,  $I^{131}$  uptake and scintigrams revealed a prompt return of function in the residual tissue (Figure 2, Table I). This activity was normally suppressible by triiodothyronine.

*Disappearance studies (Table II).* Seven disappearance studies were performed in six patients. Control disappearance rates were determined during six studies in five patients; they varied from 5.8 to 18.5 per cent per day (average, 10.1). Iodide induced a highly significant slowing in all patients (in each case,  $p < 0.001$ ), and the inhibitory effect of iodide on fractional disappearance was clearly manifest within 3 days of the initiation of treatment.<sup>5</sup> During administration of Lugol's solution, fractional disappearance rates

<sup>5</sup> The time of onset and offset of iodide effect was estimated by the point of intersection of the disappearance curves calculated by the method of least squares (18).

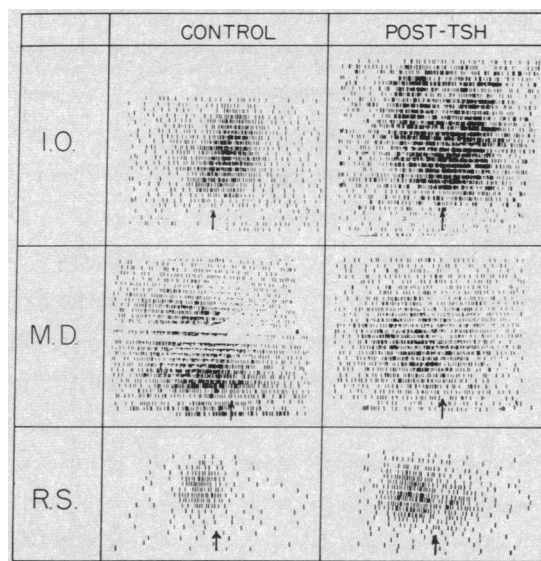


FIG. 1. SCINTIGRAMS OF  $I^{131}$  LOCALIZATION IN THYROID GLANDS BEFORE AND AFTER ADMINISTRATION OF TSH TO PATIENTS WITH HYPERFUNCTIONING THYROID ADENOMAS.

ranged from 0.9 to 4.0 per cent per day (average, 2.3).

In two patients fractional disappearance rates were determined after cessation of iodide treatment. In both patients a significant acceleration occurred ( $p < 0.005$  in M.D., and  $p < 0.001$  in I.O.), and this was manifest within 3 days. In Patient I.O. the postiodide slope was less than

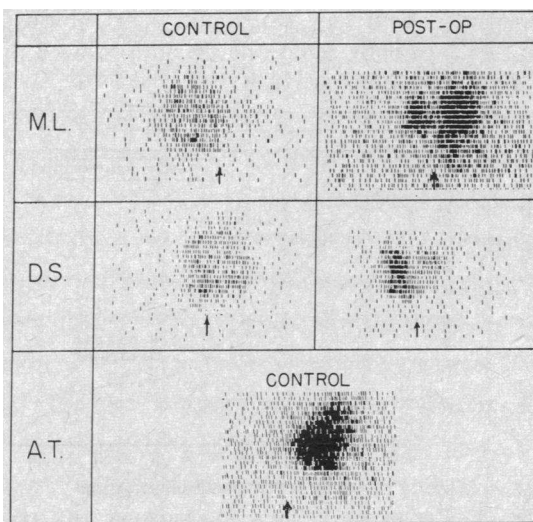


FIG. 2. SCINTIGRAMS OF  $I^{131}$  LOCALIZATION IN THYROID GLANDS IN THREE PATIENTS WITH HYPERFUNCTIONING THYROID ADENOMAS. In upper 2 patients, localization of  $I^{131}$  in thyroid glands after removal of adenomas is also shown.

TABLE II

Effect of Lugol's solution on the fractional rate of disappearance of organic  $I^{131}$  from hyperfunctioning autonomous thyroid nodules

Patient	Lugol's sol.	Duration	Disappearance rate
	q8h		
I.O.	drops	days	%/day*
	0	12	$5.8 \pm 0.2\ddagger$
	10	11	$0.9 \pm 0.3$
	0	5	$7.5 \pm 0.5\ddagger$
M.L.	10	9	$2.3 \pm 0.2$
	0	16	$6.3 \pm 0.3\ddagger$
	0	6	$8.7 \pm 0.3\ddagger$
A.T.	8	10	$2.6 \pm 0.3$
	0	6	$12.0 \pm 0.8\ddagger$
M.D.	8	8	$1.3 \pm 1.0$
	0	2	
R.S.	10	6	$3.0 \pm 0.3$
	0	9	$5.3 \pm 0.3\ddagger$
	0	4	$8.5 \pm 0.5\ddagger$
D.S.	8	6	$2.2 \pm 0.3$
	0	9	$18.5 \pm 0.7\ddagger$
	8	7	$4.0 \pm 0.5$

\* Values shown together with standard error of slope.

† Significantly different from value obtained during administration of Lugol's solution ( $p < 0.001$ ).

‡ Significantly different from value obtained during administration of Lugol's solution ( $p < 0.005$ ).

that obtained before iodide; the difference was possibly significant ( $0.02 < p < 0.05$ ). In Patient M.D. the preiodide period was too short for statistical evaluation. Two studies were performed in Patient I.O., 21 months apart (Figures 3 and 4). In both, iodide significantly slowed the

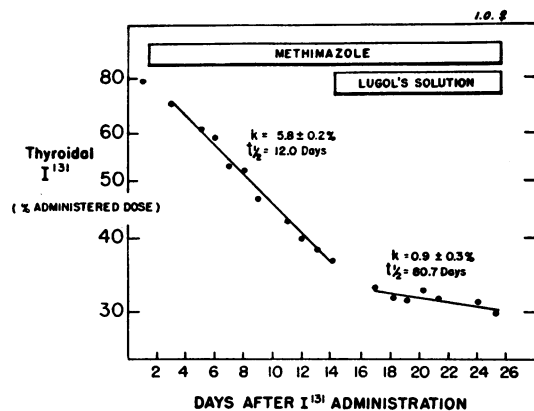


FIG. 3. EFFECT OF LUGOL'S SOLUTION ON THE FRACTIONAL RATE OF DISAPPEARANCE OF ORGANIC  $I^{131}$  FROM AN AUTONOMOUS THYROID NODULE. First study in Patient I.O. Disappearance curves calculated by method of least squares. Values represent calculated disappearance rate  $\pm$  standard error.

disappearance rate, although rates during control and iodide-treatment periods in the second study differed significantly from those obtained during comparable periods in the first study.

#### DISCUSSION

The purpose of this investigation was to assess the effect of iodide on the disappearance of organic  $I^{131}$  from the thyroid gland in the absence of TSH. Therefore, the validity of the conclusions drawn from the data hinges upon the assumption that secretion of TSH was indeed entirely suppressed in these patients. Three types of observations support this conclusion: 1) the locali-

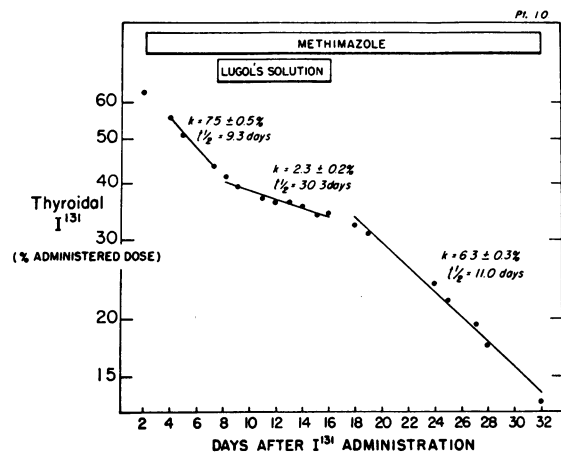


FIG. 4. EFFECT OF LUGOL'S SOLUTION AND ITS WITHDRAWAL ON THE FRACTIONAL RATE OF DISAPPEARANCE OF ORGANIC  $I^{131}$  FROM AN AUTONOMOUS THYROID NODULE. Second study in Patient I.O., performed 21 months after study in Figure 3. Disappearance curves calculated by method of least squares. Values represent calculated disappearance rate  $\pm$  standard error.

zation of  $I^{131}$  within the thyroid gland before and after administration of TSH; 2) studies of iodine metabolism obtained postoperatively; and 3) results of suppression tests. Recourse to such indirect evidence was necessary, since existing techniques do not permit differentiation of normal and subnormal levels of TSH in the circulation by direct assay.

First, TSH induced function in extranodular tissue, which had previously accumulated too little radioiodine to be detected by scintigrams. This implied that endogenous TSH was either absent or present in concentrations too low to support significant function in the potentially active extranodular tissue.

The possibility could be entertained that small amounts of TSH were produced continuously in these patients, independent of the quantity of thyroid hormone secreted, and that this quantity of TSH supported nodular function. Especially in thyrotoxic subjects this would imply a disturbance in the normal mechanism for regulating secretion of TSH. Such a disruption of normal homeostatic controls seemed unlikely, however, in view of the data obtained postoperatively in two patients, one of whom had been thyrotoxic. Normal suppressibility of the thyropituitary axis was unmasked by removal of the adenoma.

Finally, in the euthyroid patients small amounts of TSH could have been secreted by the pituitary in response to normal homeostatic controls. However, failure of  $T_3$  to suppress  $I^{131}$  uptake suggested that such was not the case.

On the basis of these findings it was concluded that, within a reasonable certainty, secretion of TSH was completely suppressed in these patients. Support for this conclusion is provided by previous studies of other patients with this disorder (13-15). These demonstrated similar abnormalities in the response to  $T_3$ , and changes in the localization of  $I^{131}$  after stimulation by TSH or removal of the "hot nodule." Indeed, the capacity of some single thyroid nodules to continue their function and even to produce thyrotoxicosis, in hypophysectomized patients, provides strong evidence of their autonomy from TSH stimulation (19).

The abrupt slowing in the disappearance of organic  $I^{131}$  from the thyroid, which iodide induced in the present studies, suggests strongly that iodide had inhibited the thyroidal secretory process. However, other interpretations merit consideration. Possibly, during the administration of Lugol's solution, appreciable quantities of stable iodine were incorporated into organic moieties, despite the concomitant administration of large doses of antithyroid agents (20). This newly formed hormone would lower the specific radioactivity of organically bound  $I^{131}$ . Thus, the decreased rate of disappearance of organic  $I^{131}$  may have resulted not from a direct inhibitory effect of iodide on the hormonal secretory process but from an increase in the organic iodine pool, the quantity of hormone released remaining unchanged. Although this possible interpretation, equally ap-

plicable to all previous studies of the effect of iodide on hormonal release, cannot be conclusively excluded, two observations make it seem unlikely. First, in patients with diffuse toxic goiter, the slowing of the disappearance of glandular organic  $I^{131}$  which iodide induces is accompanied by a rapid decline in serum PBI (21), suggesting that the quantity of hormone secreted is actually decreased. Second, this explanation for the slowing of the disappearance rate would imply that hormonal secretion is directed toward the release of a constant quantity, rather than a constant proportion of the hormonal pool. This possibility, extensively considered elsewhere (8) and deemed unlikely, would not be consistent with the exponential disappearance of organic  $I^{131}$  which is seen during antithyroid blockade of new hormone synthesis.

Data obtained by other workers have indicated that there may sometimes occur a spontaneous progressive slowing in the fractional rate of disappearance of organic  $I^{131}$ , as measured by the techniques used in the present study (12). Factors responsible for this slowing, which have also been observed in this laboratory, are unknown. However, spontaneous slowing in the disappearance of organic  $I^{131}$  does not appear a likely cause of the slowing that occurred during iodide administration in the present study. First, the spontaneous slowing which has been reported has been of a gradual nature, contrasting markedly with the abrupt slowing that followed administration of iodide. Second, in the patient reported here in whom two studies were performed, the slow phase of the disappearance curve was clearly not related to the time elapsed after the administration of  $I^{131}$  and methimazole, but was closely correlated with the exhibition of iodide. During the first study there was no significant difference in disappearance rates between the first 5 days ( $k = 5.64 \pm 0.96$ ) and the following 6 days ( $k = 5.60 \pm 0.40$ ) of the control period, whereas, during the second study, the introduction of iodide after 5 days induced a striking decrease in the disappearance rate (Figures 3 and 4). Finally, the accelerated disappearance of organic  $I^{131}$  that followed the withdrawal of iodide in two patients implies that iodide had truly inhibited hormonal release.

Thus, it seems most likely that iodide did in-

hibit the thyroidal secretory process in the present patients. Since secretion of TSH in these patients was probably completely suppressed, it appears that iodide can exert its inhibitory action in the absence of concomitant stimulation by TSH. These findings do not exclude the possibility that iodide and TSH exert their antagonistic effects at the same locus of action. However, they appear to invalidate the inference that TSH must be stimulating the release of hormone from any thyroid gland in which iodide inhibits release. Therefore, the effectiveness of iodide in slowing that loss of organic  $I^{131}$  from the thyroid of patients with Graves' disease cannot be construed as evidence for the mediation of TSH in the pathogenesis of this disorder.

#### SUMMARY

Studies were performed in six patients in whom thyroidal accumulation of  $I^{131}$  was localized to a single nodule. Thyroid suppression tests, scintigrams before and after administration of TSH, and studies of iodine metabolism after surgical removal of the nodule provided evidence that secretion of TSH was suppressed in these patients.

Studies of the disappearance of organic  $I^{131}$  from the nodules in these patients were performed before, during, and after administration of Lugol's solution. In all instances, fractional disappearance rates were markedly retarded during administration of iodide.

It is concluded that iodide is capable of inhibiting the thyroidal secretory process in the absence of concomitant stimulation by TSH.

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