THE TEMPORARY NATURE OF THE INHIBITORY ACTION OF EXCESS IODIDE ON ORGANIC IODINE SYNTHESIS IN THE NORMAL THYROID[1]

J. WOLFF,[2] I. L. CHAIKOFF, R. C. GOLDBERG,[3] AND J. R. MEIER

From the Division of Physiology of the University of California Medical School

BERKELEY

In 1944, Morton *et al.* observed that when 300 mg. of sheep thyroid slices were incubated in 3 cc. of a bicarbonate-Ringer medium to which various amounts of I^{127} as inorganic iodide had been added, inhibition of thyroxine and diiodotryosine formation occurred when the added I^{127} exceeded 20 gamma. The resemblance of this *in vitro* effect to the action of excess iodide in Graves' disease in man led us to investigate this phenomenon in the normal intact thyroid (Wolff and Chaikoff, 1948a). In addition to confirming the inhibitory action of excess iodide upon thyroxine synthesis in intact thyroids, the investigation showed that such inhibition by a *single injection* of iodide was related to the level of plasma iodine (Wolff and Chaikoff, 1948b). So long as the concentration of plasma iodine exceeded 20–35 gamma per cent, organic binding of iodine failed to occur in the gland, and only when the concentration fell below this critical range did the gland resume its function of depositing iodine in an organic form. These observations in rats have been confirmed recently by Stanley (1948).

Evidence of an inhibitory action of excess iodide on thyroid function has also been obtained by a different approach. Purves and Griesbach (1946) have shown in rats that excess iodide (one mg. per day) potentiates the antithyroid action of a weak goitrogen. The administration of thiourea alone resulted in a slight degranulation of the acidophils of the anterior pituitary. But when large amounts of iodide were given along with the thiourea, the anterior pituitary presented a picture typical of complete thyroidectomy, i.e., complete degranulation of the acidophils. Mackenzie (1947) also has observed that the antithyroid effect of another weak goitrogen, sulfaguanidine, is augmented in rats fed a diet containing 500 gamma of iodine per gram.

It is well known that in the thyrotoxic patient, administration of excess iodide results in a return of the hyperplastic gland to a more

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[2] U. S. Public Health Fellow.

[3] Atomic Energy Commission Fellow.

normal state and in an increase in both total and thyroxine iodine of the gland (Gutman *et al.*, 1932). But in the normal rat, excess iodide, as judged by its ability to depress thyroxine formation in the thyroid, *in vitro* (Morton *et al.*, 1944) as well as *in vivo* (Wolff and Chaikoff, 1948b), appeared, rather, to resemble the action of antithyroid substances such as thiourea or its congeners. This resemblance between the effects of excess iodide and the antithyroid substances raised the question: does the maintenance of plasma iodide concentrations, well above 35 gamma per cent, for long periods induce histological changes in the thyroid and pituitary glands characteristic of a deficiency in circulating thyroid hormone? Although several attempts have already been made to study the effects of the administration of large amounts of iodide (Gray and Loeb, 1928; Weil, 1936; Hall, 1946), no reports have yet appeared in which the concentration of plasma iodide is shown to have been maintained at such high levels *without interruption* for as long as one month. Insurance against any interruption whatsoever is necessary because it was found that organic binding of iodide in the thyroid gland (i.e., hormone formation) is resumed when the plasma iodide falls below a critical level in the neighborhood of 20–35 gamma per cent.

A. THE EFFECTS OF INJECTIONS OF 500, 1,000 AND 2,000 GAMMA OF I^{127}, THREE TIMES DAILY FOR 1–4 WEEKS, UPON THE STRUCTURE OF THYROID AND PITUITARY GLANDS

Twenty-seven female rats of the Long-Evans strain, weighing from 166 to 232 grams, were injected intraperitoneally every eight hours for periods of one to four weeks with either 500, 1000, or 2,000 gamma of I^{127} as KI in 0.9 per cent saline (Table 1). All rats were sacrificed 10 hours after the last injection in order to insure adequate testing of blood iodine levels at a time which was two hours beyond the interval between successive injections. They were anesthetized with sodium pentobarbital. Blood was then removed from the heart.

TABLE 1. CONCENTRATIONS OF PLASMA TOTAL IODINE FOUND IN RATS INJECTED INTRAPERITONEALLY WITH IODIDE THREE TIMES DAILY

Amounts of iodide injected every 8 hours	Duration of injections	Plasma total iodine 10 hours after last injection
gamma	days	gamma per cent
500	1	156 –205
500	2	137 –175
500	3	165 –394
500	5	125 –269
500	14	555
500	21	225– 425
1000	14	540– 580
1000	21	265 –375
2000	14	675–1060
2000	21	535– 735

Total blood iodine was determined on two cc. samples of plasma, according to the method of Taurog and Chaikoff (1946).

After exsanguination, the thyroids were rapidly excised, weighed, and fixed in Bouin's. They were embedded in paraffin and prepared in multiple sections five micra thick. These were stained with hematoxylin and eosin. Liver, kidney, and heart were similarly treated.

Immediately after excision of the thyroids, the pituitary glands were removed, fixed in Zenker-Formol (9:1), embedded in paraffin, and prepared in sections 2–3 micra thick. They were stained by the method of Martins (1933) modified according to Griesbach (personal communication). The percentages of acidophils, basophils, and chromophobes were determined by a method similar to those employed Griesbach and Purves (1943) and by Floderus (1944). At least 2,000 cells were counted in each gland.

Table 1 lists the total plasma iodine values of animals killed at 1–5 days, and at two and three weeks after the start of the iodine injections. It will be seen that a minimum plasma iodine value of about 150 gamma per cent is established as early as 24 hours (i.e., after three injections of 500 gamma of iodine as KI), and is maintained at levels far in excess of that previously found necessary to prevent organic binding in the thyroid gland following single injections of 500 gamma of iodine.

Thyroid Histology (*Figs. 1 and 2*).—No evidence of hypersecretion of thyrotropic hormone was observed, i.e., epithelial hypertrophy or hyperplasia, or decrease in follicular colloid. On the contrary, reduction of follicular cell height and an increase in follicular colloid was a consistent finding in all animals that had received the iodide injections for one or more weeks.

Pituitary Cytology (*Figs. 3 and 4*).—Cytological examination of the anterior pituitary glands from these animals was undertaken as a more sensitive means of detecting a goitrogenic effect, if any, of a prolonged high plasma iodide level.

The sensitive response of this gland to very slight thyroxine deficiency has been clearly demonstrated in a series of studies by Griesbach and coworkers (1945, 1949) in thyroxine deficient rats. A decrease of 0.1–0.2 gamma in the amount of injected thyroxine necessary to maintain the anterior pituitary in a normal state can be detected by a significant increase in the percentage of the basophils. A more severe thyroxine deficiency (induced either by subtotal thyroidectomy or by the administration of a weak goitrogen) results in the appearance of large hyalinized basophils (thyroidectomy or signet ring cells) and some degranulation of the acidophils. Complete degranulation of the acidophils occurs only after total thyroidectomy or after prolonged treatment with a highly active goitrogen such as propylthiouracil. (fig. 4).

In Table 2, the anterior pituitary cell counts of the iodide-injected rats are compared with results obtained from the following types of

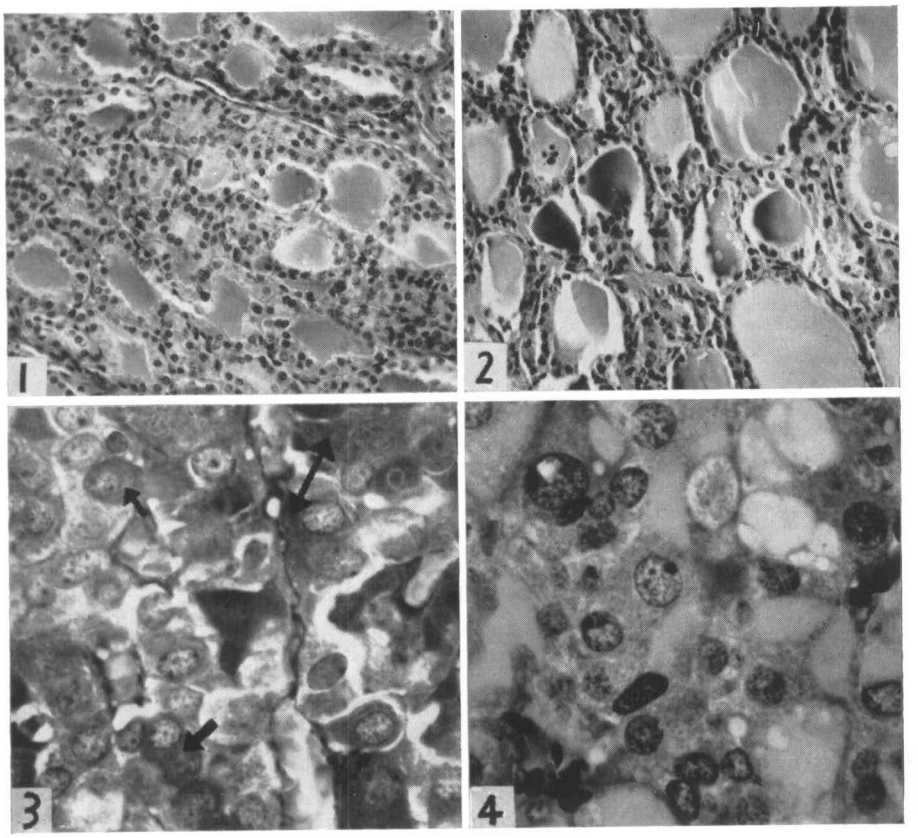

FIG. 1. Thyroid from control rat, maintained on diet containing 0.3 gamma iodide per gram. Note columnar epithelium and large vesicular nuclei. Hematoxylin and eosin; x275.

FIG. 2. Thyroid from rat injected with 2000 gamma iodide every eight hours for three weeks. Note flattened epithelium and smaller deeper staining nuclei. Hematoxylin and eosin; x275.

FIG. 3. Anterior pituitary from animal injected with 1000 gamma iodide every eight hours for three weeks. Arrows in upper portion of picture point to granulated acidophils which appear gray. Arrow at lower left points to a normal basophil. This does not differ from control pituitaries. Martins; x750.

FIG. 4. Anterior pituitary from rat maintained on diet of 0.2 per cent prophythiouracil for one month. The basophils contain large hyaline vacuoles (thyroidectomy cells) and constitute 20 per cent of the total number of cells. All other cells are chromophobes. Martins; x750.

rats: (1) controls, i.e., rats fed the same diet but not injected with iodide; (2) rats totally thyroidectomized; and (3) rats fed for one month a diet containing 0.2 per cent propylthiouracil.

The percentages of the various cell types found in the injected rats were well within the range found for control animals. When the anterior pituitaries of rats exhibiting thyroxine deficiency are compared with those of rats injected repeatedly with large amounts of iodide for periods up to four weeks, it becomes clear that the latter suffer from no deficiency in circulating thyroid hormone.

TABLE 2. DIFFERENTIAL CELL COUNTS OF ANTERIOR PITUITARIES OF RATS

Treatment	Anterior pituitary cell counts*			Remarks
	Acidophils†	Basophils	Chromophobes	
	per cent of total	per cent of total	per cent of total	
Control (untreated)	38–43	5–9	50–57	Cells of normal appearance.
500, 1000, 2000 gamma I^{127} thrice daily for 2 weeks	33–38	6–10	54–56	Cells of normal appearance.
500, 1000 2000 gamma I^{127} thrice daily for 3 weeks	35–41	6–10	48–57	Cells of normal appearance. See fig. 3.
500, 1000, 2000 gamma I^{127} thrice daily for 4 weeks	36–39	5–9	52–58	Cells of normal appearance.
One month after total thyroidectomy	0.7–1.1	21–29	70–78	Complete acidophilic degranulation. Majority of basophils of thyroidectomy type.
0.2 per cent propylthiouracil diet for one month	1.0–1.8	18–28	70–80	Complete acidophilic degranulation. Majority of basophils of thyroidectomy type. See fig. 4.

* At least 2000 cells were counted per gland.
† Degranulated acidophils were included in total per cent chromophobes.

B. FOR HOW LONG CAN THE THYROID GLAND BE INHIBITED WHEN A HIGH LEVEL OF PLASMA IODINE IS MAINTAINED?

It was shown in a previous report that the injection of a *single* dose of 500 gamma of iodide in the normal rat inhibited the formation of organic iodine for about 17 hours (Wolff and Chaikoff, 1948a). When the excretion of the iodide was prevented by nephrectomy, this effect of a *single* injection was prolonged to 32 hours (Wolff and Chaikoff, 1948c). But our failure to observe histological signs of thyroid deficiency in the preceding experiment led us to question the permanence of the inhibitory effect of excess iodide upon thyroxine formation in the gland. The following experiments were therefore designed to determine how long the normal rat thyroid can be inhibited by excess iodide.

A stock solution of KI, containing 500 gamma of I^{127} per cc. and an initial radioactivity of about 20 microcuries of I^{131} per cc., was prepared. One cc. of this *same* solution (i.e., 500 gamma I^{127}) was injected intraperitoneally into normal rats at eight-hour intervals for periods up to 111 hours. The levels of plasma total iodine[4] established by this

[4] Only a small fraction of this iodine is protein bound.

procedure (Table 3 and 4) are so high that dilution by the amount of iodine contributed by diet and breakdown of thyroxine is negligible. As a result, the specific activity of plasma remains the *same* as that of the injected dose throughout the experiment. Because of this, it was possible to calculate the amount of new organic iodine in the thyroid (Wolff and Chaikoff, 1948a).

Experiment 1—The rats used in this experiment weighed 150–222 gm. and, since weaning, had been fed a low iodine diet containing 0.3–0.4 gamma of iodine per gram. They had access *ad libitum* to this diet throughout the period of observation. The animals were sacrificed at 9, 18, 26, 50, 74, and 111 hours after the *first* injection and from 7 to 10 hours after the *last* injection. Blood was obtained from the heart, and the iodine content of plasma determined, as already described. The thyroids were excised and weighed. The organic and inorganic iodine fractions of the thyroids were separated, by means of trichloro-

TABLE 3. THE DURATION OF THE INHIBITORY ACTION OF EXCESS IODIDE IN THE THYROID GLAND

EXPERIMENT 1

(The rats were injected every 8 hours with 500 gamma of I^{127}-labeled I^{131})

Time after first injection	Plasma total iodine*	New† I^{127} in thyroid as:					
		Inorganic		Organic		Total	
hours		gamma	mg. per cent	gamma	mg. per cent	gamma	mg. per cent
9	68	2.9	11.2	0.18	0.69	3.1	11.9
	113	1.2	7.2	0.14	0.87	1.3	8.1
	100	4.0	13.8	0.11	0.38	4.1	14.2
	115	0.98	5.1	0.27	1.4	1.3	6.5
18	138	2.7	10.0	0.31	1.1	3.0	11.1
	183	1.9	11.9	0.42	2.6	2.3	14.5
	185	2.4	12.0	0.38	1.9	2.8	13.9
	140	2.5	11.6	0.30	1.4	2.8	13.0
26	145	2.2	11.4	0.38	2.0	2.5	13.4
	83	0.92	4.6	0.29	1.4	1.2	6.0
	105	2.7	10.4	1.1	4.2	3.8	14.6
	88	3.9	18.1	1.0	6.3	4.9	24.4
50	170	2.3	10.0	2.9	12.6	5.2	22.6
	170	0.89	4.4	5.1	25.5	6.0	29.9
	345	3.2	16.6	1.1	5.8	4.3	22.4
	153	1.7	6.7	2.0	8.0	3.7	14.7
74	252	3.0	15.0	3.4	17.0	6.4	32.0
	302	3.3	13.2	2.6	10.4	5.9	23.6
	178	1.3	7.6	4.6	27.0	5.9	34.6
	240	1.4	6.5	5.8	27.6	7.2	34.1
111	172	1.6	5.6	10.7	38.2	12.3	43.8
	190	1.6	6.7	4.6	20.0	6.2	26.7
	78	0.65	3.8	7.0	41.1	7.7	44.9
	300	0.83	4.0	11.4	54.2	12.2	58.2

* Only a small fraction of this iodine is protein-bound.

† Refers to I^{127} as calculated from the radioactivity recovered in the gland.

acetic acid, as described in an earlier report.[5] The results of this experiment are recorded in Table 3.

It was shown that when the gland escaped from the inhibitory effects of a single injection of excess iodide, the amount of *new* I^{127} organically bound in the thyroid gland was always well in excess of one gamma (see fig. 6 of Wolff and Chaikoff, 1948a). During inhibition, on the other hand the amounts of *new* I^{127} so bound were below this amount. Hence for the present study, we have considered the gland to have escaped from inhibition when the total amount of *new* I^{127} bound organically exceeded one gamma.

In experiment 1 (Table 3), inhibition occurred during the earlier intervals, after the establishment of a high plasma iodine level. In two of the rats, more than one gamma of *new* organic iodine had accumulated in the thyroids 26 hours after the start of the injections. By the time 50 hours had elapsed, the gland showed a renewed capacity to bind iodine organically—*this occurred while the plasma iodine was still high.* At later intervals, more and more of the *new* iodine was organic.

Experiment 2—The rats weighed 210–272 gm. and had been raised on the same low-iodine diet as that used for experiment 1. They were injected every eight hours with 500 gamma of I^{131} labeled iodide, prepared as described in experiment 1, above. All rats were sacrificed two hours after the last injection. For this reason, plasma iodine values, as well as the inorganic iodine content of the thyroid glands, are higher than those observed in experiment 1. These results are shown in Table 4.

Up to 26 hours, the amounts of the injected I^{127} organically bound in the thyroid did not exceed one gamma, the value arbitrarily set as the escape level. At 34 hours, the thyroids of two of the rats still showed inhibition whereas in the other three rats examined at this interval, about 1.3 gamma of *new* I^{127} were organically bound.

Inhibition was still observed in two of the four rats examined at 42 hours and in one of the five rats examined at 50 hours. But 58 hours

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[5] It has already been shown (Wolff and Chaikoff, 1948a) that no inorganic iodide appears in the *insoluble* fraction. The nature of the trichloroacetic acid-*soluble* fraction was tested here by a method similar to that described by Taurog *et al.* (1947). Rats were injected with 500 gamma of I^{127} containing I^{131} and were killed five or 22 hours thereafter. Glands of three rats were pooled and ground with one cc. of cold 10 per cent trichloroacetic acid. The resulting precipitate was washed twice with 2.5 cc. of 5 per cent trichloroacetic acid and discarded.

To the combined supernantants (the trichloroacetic acid-soluble fraction) were added 0.1 cc. of a 2N KI solution, as carrier, and 0.5 cc. of 0.1 N KIO_3. The I_2 so formed was then extracted three times with equal volumes of CCl_4. The combined CCl_4-extracts were then re-extracted three times with dilute (0.1 N) sodium thiosulfate. The radioactivity of the trichloroacetic acid-residue, the CCl_4-fraction, and the thiosulfate fraction was measured. Ninety-five per cent of the iodine originally present in the trichloroacetic acid-soluble fraction was recovered in the thiosulfate solution. This finding indicates that the iodine in this fraction must have been either in the form of I^- or I_2. *This was the case in the early intervals while the excess iodide exerted its inhibitory action as well as later when escape from inhibition had occurred in the gland.*

TABLE 4. THE DURATION OF THE INHIBITORY ACTION OF EXCESS IODIDE IN THE THYROID GLAND
EXPERIMENT 2
(The rats were injected every 8 hours with 500 gamma of I^{131}-labeled I^{127})

Hours after first injection	Plasma total iodine*	New† I^{127} in thyroid as:					
		Inorganic		Organic		Total	
hours	gamma per cent	gamma	mg. per cent	gamma	mg. per cent	gamma	mg. per cent
10	440	9.0	45.0	0.42	2.1	9.4	47.1
10	275	8.5	35.4	0.24	1.0	8.7	44.1
10	260	9.0	36.0	0.28	1.1	9.3	37.1
10	240	7.5	31.2	0.14	0.58	7.6	31.8
18	436	11.0	52.3	0.49	2.3	11.5	54.6
18	366	8.5	42.5	0.34	1.7	8.8	44.2
18	410	8.0	36.4	0.80	3.6	8.8	40.0
18	320	9.5	36.5	0.37	1.4	9.9	37.9
18	470	10.0	40.0	0.26	1.0	10.3	41.0
26	340	9.0	40.8	0.70	3.2	9.7	44.0
26	240	5.0	26.3	1.0	5.3	6.0	31.6
26	290	7.5	28.8	0.50	1.9	8.0	30.7
26	240	6.5	20.9	0.70	2.3	7.2	23.2
34	475	6.5	28.2	1.2	5.2	7.7	33.4
34	670	6.5	29.5	0.35	1.6	6.9	31.1
34	360	5.0	23.8	0.75	3.6	5.8	27.4
34	225	5.5	19.0	1.5	5.2	7.0	24.2
34	430	8.5	27.4	1.3	4.1	9.8	31.5
42	400	7.0	29.1	0.32	1.3	7.3	30.4
42	260	3.9	21.9	0.65	3.8	4.6	25.7
42	475	4.4	17.6	2.3	9.2	6.7	26.8
42	270	8.0	38.1	1.4	6.7	9.4	44.8
50	400	2.8	14.7	0.39	2.1	3.2	16.8
50	390	4.8	21.8	3.2	14.5	8.0	36.3
50	385	4.5	18.7	2.5	10.4	7.0	29.1
50	340	4.2	16.8	2.5	10.0	6.7	26.8
50	340	4.2	18.2	2.3	10.0	6.5	28.2
58	295	2.8	11.7	4.5	18.7	7.3	30.4
58	250	5.5	21.1	2.1	8.1	7.6	29.2
58	400	4.4	22.0	3.9	19.5	8.3	41.5
58	230	2.7	15.0	1.5	8.3	4.2	23.3
58	230	3.9	15.6	4.0	16.0	7.9	31.6

* Only a small fraction of this iodine is protein-bound.
† Refers to I^{127} as calculated from the radioactivity recovered in the gland.

after the first injection, escape occurred in all rats; their thyroids contained 2.3–3.2 gamma of *new* organically bound iodine.

DISCUSSION

The inhibitory action of excess iodide on organic-iodine synthesis in the thyroid gland has been confirmed here but shown to be temporary in nature. The maximum duration of this effect was 50 hours. Escape from inhibition was detected as early as 26 hours, even though plasma total iodine was maintained at levels at which inhibition was initially established. Since it is probably the inorganic iodine within the gland that is the immediate agent responsible for the inhibitory

effect,[6] it became pertinent to determine whether escape from inhibition after 26 hours occurred because the gland lost its capacity to hold high concentrations of inorganic iodide. Tables 3 and 4 show, however, that when escape occurred, the concentrations of inorganic iodide in the gland were as high as those which, in the earlier intervals, caused inhibition.

TABLE 5. REACCUMULATION OF ORGANIC IODIDE IN THYROIDS OF RATS TREATED WITH EXCESS IODIDE

(All rats were fed for the first 19 days a diet containing 0.2 per cent propylthiouracil. At the end of this period the first three rats were sacrificed. The remainder were fed a normal diet for nine or 15 days. Half of the animals of each group received by intraperitoneal injection 500 gamma of iodide as KI thrice daily.)

Time after propylthiouracil	I^{127} injected every 8 hours	Thyroid iodine			
		Inorganic	Organic		Total
			Non-thyroxine	Thyroxine	
days*	gamma	gamma	gamma	gamma	gamma
0	0		0.11†	0.22	0.33
0	0		0.14	0.16	0.30
0	0		0.11	0.27	0.38
9	0		0.81	0.17	0.98
9	0		0.63	0.22	0.85
9	0		2.2	0.54	2.7
9	500	5.4	4.8	0.71	10.9
9	500	7.2	1.8	0.40	9.4
9	500	3.0	4.0	1.0	8.0
15	0		2.2	0.45	2.7
15	0		4.3	0.83	5.1
15	0		2.6	0.70	3.3
15	500	4.0	3.8	0.75	8.6
15	500	5.0	3.6	0.45	9.1
15	500	1.2	4.6	1.1	6.9

* Normal rats of this group contained about 1.5 gamma of thyroxine and 4.2 gamma of nonthyroxine iodine.

† In the rats that received no iodide injections the inorganic iodine was not separated from the nonthyroxine fraction.

Although the problem of exchange has been discussed elsewhere (Chaikoff and Taurog, 1948), the fact that we are dealing here with higher concentrations of iodide leads us to reconsider it. It might be argued that prolonged exposure of the gland to high levels of inorganic iodide results in an exchange between inorganic I^{131} and organically bound I^{127}. If this were the case, the recovery of the I^{131} in the organic fraction (Tables 3 and 4) would not be indicative of renewed synthesis or escape. To test this possibility it was necessary to measure the accumulation of organic iodine in the thyroid gland without resorting to the use of I^{131}. The thyroids of rats were first depleted of their iodine stores by feeding 0.2 per cent propylthiouracil in the diet for 19 days. Thereafter, they were fed a normal diet and injected with excess iodide

[6] Cf. *in vitro* experiments by Morton *et al.* (1944).

(500 gamma every eight hours) for 15 days. As shown in Table 5, reaccumulation of organic I^{127} was not prevented by the excess iodide. In addition to confirming the temporary nature of the inhibitory action of excess iodide upon organic binding of iodine by the thyroid gland, these results lead us to conclude that exchange reactions could not account for the increase of organically bound $I^{1\,1}$ shown in Tables 3 and 4.

In view of the temporary nature of iodide inhibition in the normal rat thyroid, we must reopen the question as to whether a block in the formation of organic iodine is an adequate explanation for the characteristic action of excess iodine (Lugol's) in Graves' disease. An answer to this question must now await investigations in the human thyroid. The recent discovery by Stanley and Astwood (1948) that KSCN expels inorganic iodide from the thyroid offers, for the first time, a simple approach to this problem in man without surgical interference. In patients that have been injected with I^{131}, the inorganic iodide can be discharged from the thyroid gland by thiocyanate, and the organic I^{131} measured by external counting.

SUMMARY

Experiments designed to test the duration of inhibition, by excess iodide, on organic binding of iodine in the thyroid gland are described.

It is shown that the inhibitory action of excess iodide on the normal rat thyroid is temporary in nature. Inhibition lasted for about 26 hours. Despite the continued maintenance of a high level of plasma total iodine (100–200 gamma per cent), the formation of significant amounts of organic iodine was resumed after 26 hours.

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