RADIOACTIVE IODINE AS AN INDICATOR OF THE METABOLISM OF IODINE

IV. THE DISTRIBUTION OF LABELED THYROXINE AND DIIODOTYROSINE IN LIVER, MUSCLE AND SMALL INTESTINE[1]

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BY THE USE OF radioiodine it has been shown that circulating iodide rapidly appears in the thyroid gland as organic compounds that can be separated into diiodotyrosine-like and thyroxine-like fractions (1, 2). A larger portion of the gland's radioiodine was always present as diiodotyrosine than as thyroxine. In the plasma these labeled organic iodine compounds were present as early as two hours after the introduction of radioiodine. At this early interval the level of organically-bound radioiodine was low in plasma, and the diiodotyrosine fraction predominates. At later intervals the amount of organically-bound radioiodine increased, and the thyroxine-like fraction in the plasma then far exceeded the diiodotyrosine-like fraction, even though the major fraction of the gland's labeled iodine was still present as diiodotyrosine.

The gland made hyperactive by the injection of thyrotropic hormone was characterized by a greater uptake of circulating radioiodine than the normal gland (2). In addition a larger portion of the thyroid's radioiodine is present as thyroxine in the hyperactive than in the normal gland. At the two-hour interval 10 per cent of the normal gland's radioiodine was found as thyroxine, whereas in the hyperactive gland 20 per cent of its radioiodine was so held. Interestingly enough, at the latest interval investigated, namely 26 hours after the administration of the radioiodine, 80 per cent of the plasma's radioiodine was contained as thyroxine. In other words, circulating radioiodide present at any particular time will be largely converted or replaced by thyroxine-like radioiodine in the course of 24 hours.

The above studies have dealt with the withdrawal of injected iodine by the thyroid gland, its appearance in the gland as organic compounds and the subsequent appearance of these compounds in plasma. The further course of these thyroxine-like and diiodotyrosine-like compounds obviously involves the peripheral tissues.[4] Hence the manner in which administered radioiodine makes its appearance in muscle, liver and small intestine has been made the subject of the present investigation.

EXPERIMENTAL PROCEDURE

In the first series of experiments 12 male guinea pigs averaging 330 gm. (310–350 gm.) were used. They were divided into 2 groups of 6 animals, one group of which re-

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[4] In these studies, the term 'peripheral tissue' refers to any tissue other than thyroid and plasma.

ceived subcutaneously once daily for 4 days 1 mg. of a thyrotropic hormone preparation,[5] and the other served as control. On the fifth day all 12 guinea pigs received intraperitoneally 1 cc. of a solution containing tracer amounts[6] of radioiodine. After 2 hours, 3 thyrotropic-hormone-treated and 3 control animals were killed by a blow on the neck; the other 6 animals were sacrificed at the 26-hour interval. The small intestine was rapidly removed, washed with isotonic saline, weighed and minced, and approximately 5 gm. samples taken for analysis. Liver and gastrocnemius muscle were weighed, chopped and sampled. In some cases somewhat less than 5 gm. of muscle was obtained from both gastrocnemii; in such cases a small amount of muscle was taken from the thigh.

All samples were hydrolyzed on the steam bath with 90 cc. of 2N NaOH for 8 hours. After cooling, they were made up to volume in 100 cc. volumetric flasks. Five or 10 cc. were ashed directly in a manner previously described in order to obtain an independent measurement of the total labeled iodine content present in the tissue (3). The remaining 90 or 95 cc. were separated into 3 fractions according to the method fully described elsewhere (1). The two butyl alcohol extractions used to remove thyroxine were made with a 30 cc. and a 20 cc. portion, after which the combined butyl alcohol layer was washed with two 20 cc. portions of 20 per cent NaOH. In all other respects the method was the same as that previously described (1, 2).

The second series of experiments was carried out on 18 female guinea pigs weighing about 350 gm. Nine of the animals received over a 6-day period 5 injections of 1 mg. of the thyrotropic hormone preparation. On the seventh day all 18 animals received radioiodine intraperitoneally. Three hormone-treated animals and 3 control animals were killed at 2, 26, and 96 hours after I* administration. The 3 hormone-treated ones that were sacrificed at the 96-hour interval had been injected with an additional 1.0 mg. of the thyrotropic hormone preparation 48 hours after they received the radioiodine. Small intestines alone were taken from this series of 18 guinea pigs. The sampling and analyses were carried out as described above.

RESULTS

It should be recalled that tracer amounts of radioiodide were administered. The amount of iodide introduced into the animal in this manner is very minute and in all probability does not affect the concentration of the iodide already present.

Iodine in all its forms is not immediately labeled merely by introducing radioactive *iodide* into the circulation. From the way in which it was prepared from the tellurium target after removal from the cyclotron, it is known that radioiodine was injected as iodide. Hence, its most immediate action after its introduction into the bloodstream is to label plasma *iodide* as well as tissue iodide that comes into rapid equilibrium with plasma.

After inorganic circulating iodine is labeled in this manner, radioactive measurements may fulfill a twofold purpose. First, if the radioactivity of the inorganic iodine

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[5] The thyrotropic preparation used in this investigation was furnished by Dr. Q. Bartz of Parke, Davis and Company, Detroit, Michigan to whom our thanks are due. This fraction assayed 4 guinea-pig units per mg. The unit is defined as the total dose in mg. injected subcutaneously once daily for 4 days into six 180 and 200 mg. guinea pigs, producing on the 5th day minimal but definite hyperplasia of the thyroid in all six animals.

[6] The method by which tracer amounts of radioiodine are prepared has been simplified over that previously described (3). The tellurium, after removal from the target, is placed in a distilling flask and cautiously heated with chromium trioxide and H_2SO_4 until solution is complete. An excess of oxalic acid is added and, after the reaction has stopped, 25 cc. of 1:1 H_2SO_4 is poured in through a side arm. Distillation is then carried out into an alkaline solution containing a small amount of bisulfite. After neutralization, the solution is ready for use.

fraction of a tissue is measured as a function of time, the manner in which inorganic circulating iodine enters and leaves a tissue may be determined. Second, the entrance of iodide into organic compounds may be observed by measuring the radioactivity of the organic fractions.

One difficulty presents itself in the interpretation of results based solely on radioactive measurements. When comparing animals, particularly under different conditions, we may find different levels of circulating iodine. The same quantity of radioactivity may then serve to label different absolute amounts of iodide. Little therefore can be said about the absolute quantity of iodine represented by the transport or conversion of a specified amount of radioactivity. In each animal, however, the fate of a particular portion of I* represents the fate of a certain fraction of the initially labeled total circulating iodide. In other words, the degree to which the entire initially labeled fraction enters into organic compounds may be compared in normal and thyro-

TABLE 1. RADIOIODINE DISTRIBUTION IN LIVER, MUSCLE, AND SMALL INTESTINE

Tissue	Time after I* administration (1)	Normal Guinea Pigs						Thyrotropic-Hormone-Treated Guinea Pigs					
		guinea pig No. (2)	% of administered I* per gm. tissue×10 (3)	% of tissue I* found as				guinea pig No. (8)	% of administered I* per gm. tissue×10 (9)	% of tissue I* found as			
				Thyroxine (4)	Diiodotyrosine (5)	Inorganic (6)	Total (7)			Thyroxine (10)	Diiodotyrosine (11)	Inorganic (12)	Total (13)
Liver	2	57	0.486	3.1	10.3	86.5	100	54	0.492	18.1	18.7	63.5	100
	2	58	0.426	1.01	1.12	97.5	100	55	0.392	16.0	1.93	81.2	99
	2	59	0.460	0.94	4.23	99.5	105	56	0.368	21.0	4.28	77.6	103
	26	63	0.0790	17.9	11.3	70.0	99	60	0.962	61.0	18.6	20.4	100
	26	64	0.0687	20.8	11.7	67.5	100	61	0.920	60.7	18.0	21.3	100
	26	65	0.0598	18.6	13.8	67.6	100	62	1.07	59.3	19.6	21.1	100
Muscle	2	57	0.294	1.5	7.90	90.5	100	54	0.246	6.04	6.39	87.5	100
	2	58	0.283	2.77	2.68	94.5	100	55	0.205	5.42	3.88	86.0	95
	2	59	0.331	2.37	8.06	89.5	100	56	0.188	12.8	2.19	85.0	100
	26	63	0.0527	11.2	7.74	81.4	100	60	0.251	55.6	10.4	34.0	100
	26	64	0.0275	37.8	6.92	55.4	100	61	0.154	61.6	13.0	24.4	99
	26	65	0.0215	35.6	7.76	47.5	91	62	0.0716	68.8	5.86	26.2	101
Small Intestine	2	57	0.932	0.99	5.61	97.0	104	54	1.88	1.90	6.64	87.7	96
	2	58	2.28	0.825	7.22	92.0	100	55	2.44	1.27	7.84	87.6	97
	26	63	0.139	3.94	7.77	87.0	99	60	0.354	73.0	5.16	23.9	102
	26	64	0.0741	14.5	5.42	80.0	100	61	0.216	79.2	4.10	20.3	104

tropic-hormone-treated animals by means of the radioactive measurements, but the absolute amounts of iodide involved in such conversions can be compared only when the actual amounts of initially labeled iodide are known.

The data obtained from liver, muscle and small intestine are shown in table 1. *Columns* 3 and 9 show the percentage of the administered radioiodine recovered per gram of tissue in normal and hyperactive guinea pigs, respectively. These values were obtained by direct determination of the total radioactivity in an aliquot of the tissue hydrolysate. Obviously the figures shown in these columns give only a general picture of iodine movement in and out of a tissue and throw no light on the forms in which iodine appears. For this reason the differences in radioiodine levels observed between hyperactive and normal animals as a function of time are best discussed along with the iodine fractions which make up the total radioiodine content. In *columns* 4 to 6 and 10 to 12 is shown the percentage of the total radioiodine content which is found in the three fractions: thyroxine, diiodotyrosine and iodide. *Columns* 7 and 13 represent the sum of I* recovered by the addition of the 3 separate fractions; this is expressed as a percentage of the value shown in *columns* 3 and 9. *Columns* 7 and 13 thus show the reliability of the recovery of I* after fractionation.

Relation betweeen Organic I and Total I**

Normal animals. Since, at the time of labeling, all radioactivity is in the inorganic fraction, the difference between total I* and inorganic I* at any time indicates the degree to which organic binding has proceeded. In the normal guinea pig tissues, it is seen from table 1, the total radioiodine content is high at 2 hours (as compared with later intervals) and almost all of it is still in inorganic form. Values in *column 6* show that in the liver of the normal guinea pig 86.5 to 99.5 per cent of its radioiodine is in the inorganic form. In muscle and small intestine similar values were obtained, namely 89.5 to 94.5 per cent and 92 to 97 per cent, respectively. These results fall within the same range as those previously reported for plasma (2). In normal guinea pigs, 87 to 99 per cent of the plasma's I* was found as iodide at the 2-hour interval. The results show that in 2 hours that part of the cycle,[7] in which injected iodide enters the circulation, is converted to organic iodine and then appears in these organic forms in the circulation and peripheral tissues, does not occur to any appreciable degree in the normal guinea pig.

Hyperactive animals. The animals treated with thyrotropic hormone present a somewhat different picture. Two hours after the administration of the radioiodine, the total I* contents of liver, muscle and small intestine of the treated animals were similar to those in corresponding tissues of the normal animal. However, a larger proportion of each tissue's I* was organically bound in the hormone-treated than in the normal animal. The most striking difference was observed in the case of the liver (*column 12*), in which 63.5 to 81 per cent of the I* was found in the inorganic fraction; in other words, 20 to 35 per cent was already organically bound at the 2-hour interval. In small intestine and muscle, differences between the normal and hyperactive animals were less marked. This corresponds to the picture previously reported for plasma; more of the plasma's I* was in the organic form in the thyrotropic-hormone-treated animal than in the normal guinea pig. In 2 hours, over 40 per cent of plasma I* was organically bound in the treated animals. The above differences indicate that in the hyperactive animal a larger proportion of the initially labeled iodide is constantly being converted to organic iodine and is making its appearance in organic form in plasma and peripheral tissues.

Turnover of inorganic iodine. Previous studies on normal rats and rabbits showed that soon after the injection of radioiodide tissues other than thyroid showed a maximum retention of total radioactivity, which dropped off rapidly with time (3). The parallelism between tissues and blood was also noted. These findings made it seem likely that the movement of iodine into and out of the tissues was largely a diffusion of iodide between plasma and tissue fluid, a process presumably governed by the level of plasma iodide. This view was previously presented by Wallace and Brodie (4) and was based on the distribution of massive doses of iodide between tissues and plasma. In their studies iodide behaved like chloride and presumably was free to diffuse between plasma and extracellular tissue fluid. However, since it is likely that the organism has a limited capacity for converting iodide to organic iodine, the administration of iodine far in excess of the physiological capacity would be expected to obscure any changes that might occur in the small quantity actually utilized.

In the present study, however, by the use of tracer amounts of radioiodide it is shown that tissue iodide is constantly turning over in more than one respect. As in the above studies (3, 4), it is found that the inorganic iodine does rapidly diffuse into and out of tissues, as evidenced by the rapid appearance of radioactivity soon after

[7] Cycle refers to the sequence of reactions in which inorganic iodine is converted to organic forms and back to iodide.

the administration of radioiodine and by the fact that this radioactivity is largely in the inorganic fraction. On the other hand, as time goes on, the inorganic radioiodine disappears and is replaced by organically bound radioiodine. The possibility that organification of iodine may take place elsewhere than in the thyroid gland must not be overlooked.

In the tissues of normal guinea pigs, the marked drop in radioiodine content between 2 and 26 hours is seen from *column* 3 of table 1. The liver shows a decrease in radioactivity from about 0.45 to 0.07, a 7-fold change, while muscle and small intestine values decrease in comparable manner. *Column* 6 shows that in the liver, small intestine, and in 2 of 3 cases in muscle, radioiodine after 26 hours is still mostly inorganic. Almost 70 per cent of liver's radioiodine is present as iodide, in the small intestine over 80 per cent is in this form, while for muscle the values vary from 48 to 81 per cent. It is therefore reasonable to suppose that the marked drop with time in the tissues of normal guinea pigs represents an outward diffusion of radioiodide as blood radioiodide becomes depleted through withdrawal by the thyroid, excretion.

In the thyrotropic-hormone-treated animals, total I* content of small intestine and muscle did not suffer nearly as great a decrease between 2 and 26 hours as did these tissues in the normal animal, while the livers actually showed an increase (*column* 9). The radioiodine contents of muscle at 2 and 26 hours were, respectively, 0.19–0.25 and 0.07–0.25. In the experiment shown in table 1, the content in the small intestine dropped considerably, but in another experiment (to be described below: table 2, *column* 9), the decrease in radioactivity was similar to that of muscle. The liver (table 1) increased almost twofold in radioiodine content between 2 and 26 hours. In general, it may be stated that the hormone-treated animals maintain their initial high level of tissue radioiodine much better than do the normal animals. However, the relatively high levels at 26 hours are not due to retention of the inorganic iodine which was present at 2 hours. *Column* 12 in table 1 shows that only about 20 to 25 per cent or each tissue's iodine is inorganic at 26 hours. Apparently inorganic radioiodine has left these tissues, as in the normal animals, but it has been replaced by radioiodine recently synthesized into organic compounds. In other words, the radioiodide present at a given time in the tissues of guinea pigs treated with thyrotropic hormone will be largely replaced by organic radioiodine within 24 hours. In contrast, the tissue radioiodide of the normal animal will still be present largely as radioiodide after the same interval.

Thyroxine and Diiodotyrosine

Distribution up to 26 hours. The organically bound I* discussed above represented the difference between total I*and iodide I*and was separated into a thyroxine-like fraction and diiodotyrosine-like fraction. The fraction most affected by time and thyroid activity was thyroxine; the response in diiodotyrosine fraction was more irregular and showed no definite trend with time and thyroid activity.

Again it should be recalled that the inorganic circulating iodine is the first to be labeled with injected I*. The appearance of radioactivity in diiodotyrosine and thyroxine fractions therefore indicates synthesis from inorganic iodine.

In previous studies (1, 2) it was found that the greatest percentage of the thyroid's I* always appeared in the diiodotyrosine fraction. Such was not the case in the plasma. At the end of one day, the percentage of plasma's I*[8] found as thyroxine was greater than that found as diiodotyrosine. This was true for normal animals as well as for those whose thyroid glands were made hyperactive by treatments with thyrotropic

[8] I* and radioiodine are used interchangeably.

hormone. In the present study the distribution of radioiodine between these two organic fractions in liver, muscle and small intestine followed the same general outline as in plasma rather than in the thyroid gland.

In normal guinea pigs, only small amounts of organic radioiodine were present in the tissues at 2 hours, and most of this was in the diiodotyrosine fraction (tables 1 and 2, *columns* 4 and 5). The radio-diiodotyrosine expressed as percentage of the total radioiodine varied from 1.1 to 10.3, with most of the values lying between 5 and 10. Expressed in the same manner, the thyroxine fraction showed values from 0.8 to 3.1.

The thyrotropic-hormone-treated animals showed a somewhat more rapid conversion of their iodide to organic iodine than the normal, the difference in the two types of animals occurring principally in the thyroxine fraction. At 2 hours the percentage of each tissue's I* found as diiodotyrosine did not differ in normal and hyper-

TABLE 2. RADIOIODINE DISTRIBUTION IN SMALL INTESTINE

Time after I* administration	Normal Guinea Pigs					Thyrotropic-Hormone-Treated Guinea Pigs				
	guinea pig No.	% of administered I* per gm. tissue×10	% of tissue I* found as			guinea pig No.	% of administered I* per gm. tissue×10	% of tissue I* found as		
			Thyroxine	Diiodotyrosine	Inorganic	Total			Thyroxine	Diiodotyrosine	Inorganic	Total
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
2	77	0.981	2.41	9.12	91.4	103	68	0.754	5.89	9.40	88.0	103
2	78	1.40	1.13	9.60	90.0	101	69	0.301	11.2	14.9	77.0	103
2	79	1.28	1.44	10.2	87.6	99	70	0.818	6.47	10.2	78.9	96
25	80	0.208	29.7	5.30	65.0	100	71	0.606	62.3	6.23	32.9	101
25	81	0.261	14.2	7.17	79.5	101	72	0.469	61.7	5.02	33.3	100
25	82	0.178	16.6	6.50	78.4	102	73	0.496	60.2	5.94	32.3	98
97	83	0.0444	55.7	11.9	27.7	95	74	0.124	64.2	13.8	25.4	103
97	84	0.0248	56.2	10.6	28.2	95	75	0.0763	60.0	12.2	24.8	97
97	85	0.0423	48.8	13.4	36.2	98	76	0.0905	61.2	14.0	25.9	101

active animals. At this same time-interval, however, thyroxine values in hyperactive animals were considerably higher than in their controls, especially as regards the liver, in which 21 per cent of the total radioiodine was already in the form of thyroxine.

Between 2 and 26 hours there was a great increase in the relative quantity of radiothyroxine in the tissues of both normal and hyperactive animals. Although considerable variations were encountered, between 15 and 30 per cent of the radioiodine was in the form of thyroxine at 26 hours in most of the normal guinea pigs, as compared with 1 to 2.5 per cent at the earlier hour. Hyperactive animals thus showed a much more complete conversion of initially labeled iodide to thyroxine. At 26 hours, 59 to 61 per cent of the liver's I* was in the form of thyroxine, 60 to 79 per cent in the small intestine (tables 1 and 2), and 56 to 69 per cent in muscle.

In contrast to thyroxine I*, the amount of which progressively increases in the plasma and peripheral tissues, diiodotyrosine I* was low at both time intervals. If the conversion of iodide to thyroxine and diiodotyrosine takes place *only in* the thyroid gland, then it follows that there is a preferential output of thyroxine into plasma and into peripheral tissues, since in the gland the amount of newly formed radiodiiodotyrosine exceeds that of newly formed radiothyroxine. If on the other hand, diiodotyrosine can be formed in the peripheral tissues, then it is likely that the thyroid removed diiodotyrosine from the plasma. This follows from the finding that newly formed diiodotyrosine does not accumulate in the peripheral tissues. Of course, diiodotyrosine could be prevented from accumulating in these tissues through other mechanisms, such as breakdown to yield iodide or further synthesis to thyroxine. The likelihood that the latter proceeds to any appreciable extent in tissues other than the thyroid is not very great.

Distribution at later intervals. The latest interval studied was 96 hours. Such extended observations were carried out only in the small intestine. Figure 1 shows the distribution of I* between thyroxine and inorganic fractions in the small intestine at 2, 26 and 96 hours. In the hormone-treated animals the percentage of total I* found as iodide and thyroxine do not change appreciably between 26 and 96 hours; in the normal or control animals the thyroxine I* continues to increase and the iodide I* to decrease between these two time intervals. The more rapid attainment of a steady condition in the small intestine of animals with thyroids made hyperactive may be due

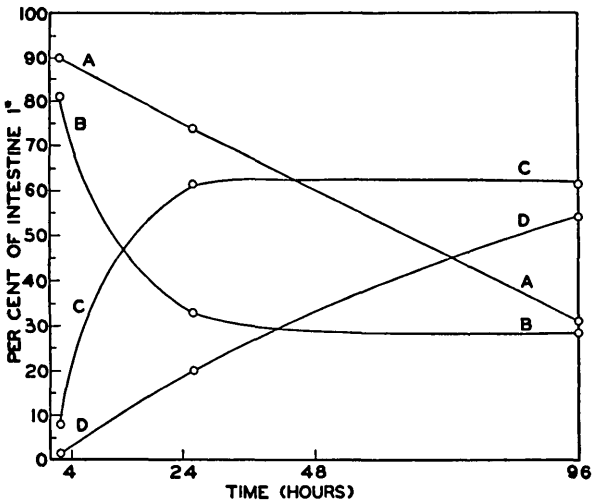

Fig. 1. DISTRIBUTION OF SMALL INTESTINE'S I* between thyroxine and inorganic fractions. *A*, Inorganic I*, normal guinea pig; *B*, inorganic I*, hyperactive guinea pig; *C*, thyroxine I*, hyperactive guinea pig; *D*, thyroxine I*, normal guinea pig. Each point is the average of 3 values shown in table 2.

to a more rapid removal of the initially labeled circulating iodide by the thyroid gland, a more rapid conversion of this to thyroxine, and a more rapid release of thyroxine by the gland into plasma and peripheral tissues.

It should be noted here again that the injection of a tracer dose of I* does not increase the actual content of iodine in the body; hence the transport of I* in its various forms as measured here portrays a phase of endogenous iodine cycle. The decrease in the inorganic I* fraction can only mean that the specific activity[9] of this fraction is decreasing, since it may reasonably be assumed that the total inorganic iodine remains unchanged during the period of observation. The fall in specific activity of the iodide I* is probably the result of two processes: *a*), excretion of labeled iodide, taking place concurrently with intake of unlabeled iodide; and *b*), conversion of iodide I* to organic forms and the regeneration of iodide at the expense of these organic forms. At the very early intervals after the injection of I*, the organic iodine is unlabeled and hence the iodide liberated is unlabeled. The addition of this unlabeled iodide to the system accounts for the rapid drop in specific activities at the early intervals. At somewhat later intervals, the fractions are partially labeled; their breakdown now contributes a certain amount of I*. It can be readily seen that as this process proceeds the drop in specific activity becomes less and less. In a system in which the intake and excretion of iodine are negligible as compared to the amount going through the cycle a time will be reached when the percentage of I* in each fraction will no

[9] Specific activity is defined as I*/I, i.e., the radioactivity associated with unit quantity of iodine.

longer change. When iodine throughout the body is equally labeled, i.e. when unit amounts of iodine in any part of the body will be associated with the same amount of I*, conversion of iodine from one form to another can not change the specific activity of either form. Although for practical purposes we may speak of complete labeling, it should be noted that complete labeling is a limit that is only approached asymptotically.

In figure 1 the distribution of the small intestine's I* between iodide and thyroxine is shown. The results obtained here may be regarded as typical for other peripheral tissues.[10] In the hyperactive animal, a sharp drop in the iodide I* was observed between the first and second intervals; this was accompanied by a sharp rise in the thyroxine-like I*. No appreciable change in the distribution of this tissue's I* between iodide and thyroxine occurred after 25 hours. The values found for the small intestine's I* as iodide were 30 per cent at both 25 hours and 96 hours. The values for thyroxine were 60 per cent at both time intervals. This means that all iodine fractions are about equally labeled in about 24 hours. A longer time is necessary for complete labeling in the normal than in the hormone-treated animal. From the data shown in table 2 and figure 1 it is not possible to state, however, whether *complete* labeling has been attained even in 96 hours.

As pointed out above, all iodine fractions possess the same specific activity when equilibrium is attained, i.e. when labeling is complete. At this time the distribution of I* among its fractions should be in proportion to the distribution of total iodine. Hence when equilibrium is reached, the distribution of I* should be a measure of the relative amounts of iodide, thyroxine and diiodotyrosine. According to this interpretation, the total iodine of the small intestine of the hyperactive animal is distributed among iodide, thyroxine and diiodotyrosine in the ratio of 30:60:10, respectively.

SUMMARY

The deposition of radioiodide, radiothyroxine and radiodiiodotyrosine was measured in liver, muscle and small intestine with radioactive iodine as indicator.

The character of the uptake and loss of total radioiodine by these 3 tissues resembled that of plasma.

The distribution of each tissue's I* among the 3 fractions, iodide, thyroxine and diiodotyrosine, changed with time but at each time interval the distribution resembled that observed in the plasma.

Almost all of the initially labeled iodide in these tissues is replaced by labeled organic iodine in 26 hours by the animal whose thyroid glands had been made hyperactive by injections of the thyrotropic hormone. In the normal animal more than half of the initially labeled iodide is still in the inorganic form at 25 hours.

The percentage of each tissue's I* found as thyroxine increased with time.

The diiodotyrosine fraction as a percentage of each tissue's total I* remained low and relatively uninfluenced by time.

The significance of these findings in relation to the iodine cycle is discussed.

REFERENCES

1. PERLMAN, I., M. E. MORTON AND I. L. CHAIKOFF: *J. Biol. Chem.* 139: 449. 1941.
2. MORTON, M. E., I. PERLMAN AND I. L. CHAIKOFF: *J. Biol. Chem.* 140: 603. 1941.
3. PERLMAN, I., I. L. CHAIKOFF AND M. E. MORTON: *J. Biol. Chem.* 139: 433. 1941.
4. WALLACE, G. B., AND B. B. BRODIE: *J. Pharmacol. & Exper. Therap.* 65: 214. 1939.
5. ELMER, A. W.: Iodine Metabolism and Thyroid Function. London, 1938. P. 269.

[10] It should not be inferred from the above statements that no differences exist in the distribution of I* among thyroxine, diiodotyrosine and iodide in small intestine, liver and muscle. It has been suggested that some tissues other than thyroid (e.g. alimentary tract) may iodinate tyrosine (5).