J. Physiol. (1954) 125, 405–415

SOME DIFFERENCES IN THE METABOLISM OF THYROXINE AND TRIIODOTHYRONINE IN THE RAT

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(*Received* 20 *April* 1954)

The recent discovery by Gross & Pitt-Rivers (1952*a*, *b*; 1953*a*, *b*) and Roche, Lissitzky & Michel (1952*a*, *b*) of the occurrence and metabolic importance of 3:5:3′-triiodo-L-thyronine has created interest in its relationship to thyroxine in the body. It has also provided an explanation of the effects of compounds, such as butyl 4-hydroxy-3:5-diiodobenzoate (BHDB), which antagonize the metabolic action of thyroxine (Sheahan, Wilkinson & Maclagan, 1951; Maclagan & Wilkinson, 1952). Since this drug *enhances* the action of triiodothyronine, it is probably acting by inhibiting the deiodination of both thyroxine and triiodothyronine (Maclagan, Sprott & Wilkinson, 1952; Wilkinson & Maclagan, 1953; Wilkinson, Sprott, Bowden & Maclagan, 1954; Wilkinson & Maclagan, 1954). During the course of this work a considerable amount of information was collected which suggested that triiodothyronine underwent deiodination to a much greater extent than thyroxine. The work described in the present communication was carried out in order to investigate this possibility and also to study the retention of exogenous thyroxine and triiodothyronine in the rat. Observations were also made on the effect of BHDB on these processes.

The rates of deiodination were studied by measuring the radioactivity of the urine of rats injected with either thyroxine labelled in the 3′:5′ positions with ^{131}I or triiodothyronine similarly labelled in the 3′ position. Methods similar to those described in earlier papers were used (Wilkinson *et al.* 1954; Wilkinson & Maclagan, 1954). Together with faecal measurements, the results obtained gave an indication of the total rate of excretion of the two substances. Their retention was also studied by measuring the radioactivity of the whole animal under defined conditions.

METHODS

Materials. 3:5:3′-Triiodo-L-thyronine labelled in the 3′ position with ^{131}I was prepared by the method of Wilkinson & Maclagan (1954). For administration to rats, a concentrate containing 100 μg/ml. in 50% w/v aqueous propylene glycol was diluted with physiological NaCl solution (0·9% w/v NaCl) to produce a solution containing the required dose in 1 ml.

Radioactive thyroxine (3′:5′-^{131}I) in 50% w/v aqueous propylene glycol, purchased from the Radiochemical Centre, Amersham, was prepared for injection in a similar manner.

Immediately before using either solution, paper chromatograms were run in order to check the purity of the materials. These were developed as autoradiographs and by the method of Bowden & Maclagan (1954).

Collection and measurement of radioactivity in excreta. Groups of three male rats were kept in metabolism cages from which the urine and faeces were collected daily and the radioactivity measured. The general procedure was substantially the same as that already described (Wilkinson *et al.* 1954). In all studies involving measurement of the excreta, labelled triiodothyronine or thyroxine was injected subcutaneously.

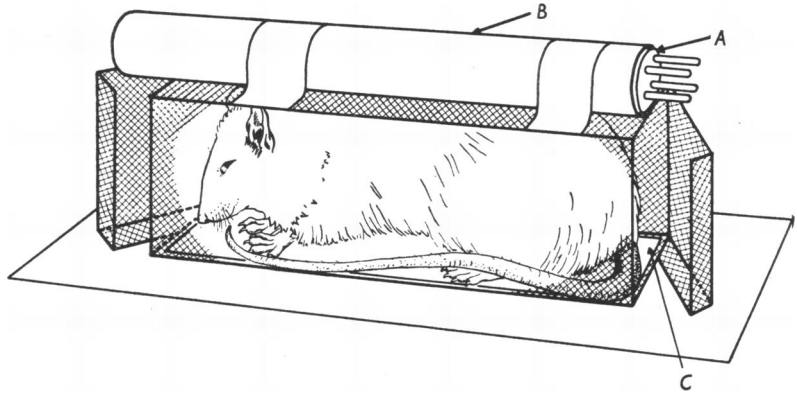

Fig. 1. Special cage used for taking counts of the radioactivity of the whole animal. *A*, G. 10 counter tube; *B*, black paper tube to protect counter against light; *C*, several thicknesses of filter paper to prevent contamination of floor of cage by excreta.

Measurement of retention in whole animal. In these experiments, male rats each weighing 200±5 g, fed on stock diet and tap water *ad lib.*, were kept in ordinary cages and identified by ear clipping. After intraperitoneal injection with ^{131}I-labelled triiodothyronine or thyroxine (approx. 2 μc), each animal was introduced individually into a specially constructed counting chamber which did not permit lateral movement and restricted forward movement to a few millimetres. The upper side of the cage carried clips for a G. 10 counter tube (20th Century Electronics Ltd.) which was protected from light and connected to the scaler. The apparatus is illustrated in Fig. 1. The cage was surrounded by a shield of lead bricks. A background count of about 50/min was obtained. When a rat was introduced the floor of the cage was protected from contamination with excreta by several layers of filter-paper which was changed when necessary. Counts were made at intervals of 2½–5 hr on each animal for a total of 31–35 hr. In order to obviate errors due to excessive movement of the animals, counting was continued for three separate minutes. It was found that the counts rarely differed by more than 5%, but on the few occasions when they did, further 1 min counts were made, and an average taken. After applying a correction for decay, the results were expressed as a percentage of the dose, i.e. the highest count reached for each rat.

RESULTS

Relative rates of deiodination of thyroxine and triiodothyronine in rats. The indication that triiodothyronine releases iodide more readily than thyroxine was obtained from earlier work (Wilkinson *et al.* 1954; Wilkinson & Maclagan, 1954), but the results did not include direct comparisons carried out at the

same time nor was the dosage of the two substances equimolecular. To repair this omission an experiment was carried out in which the urinary iodide of two groups of rats which received radioactive triiodothyronine (10 μg/rat) was compared with that of two similar groups injected with equimolecular doses of labelled thyroxine (12 μg (0·0155 μequiv)/rat). The results of this and previous experiments are summarized in Table 1.

TABLE 1. The urinary radioactivity of rats after single doses of labelled triiodothyronine or thyroxine

(Each row of figures refers to the mean of two or more measurements of the combined excretion of groups of three rats.)

Dose (μg)	Percentage of dose excreted after 24 hr	72 hr	120 hr
	Triiodothyronine		
4	12·2	18·9	19·3
6	14·6	24·2	25·5
10	17·0	25·3	27·1
20	19·1	25·2	26·7
30	17·1	26·9	27·3
50	18·6	24·4	25·7
No. of observations	16	16	16
Range	10·5–23·2	17·1–37·4	17·7–39·5
Mean ± S.E.	16·8 ± 0·96	24·3 ± 1·33	25·5 ± 1·36
	Thyroxine		
4	6·9	16·7	17·7
12	12·4	18·8	19·7
20	18·7	25·5	26·2
30	15·7	23·5	24·7
50	11·1	18·1	18·8
100	7·9	14·4	14·7
No. of observations	14	14	14
Range	5·2–19·3	14·0–26·3	14·6–27·0
Mean ± S.E.	12·1 ± 1·10	19·3 ± 1·10	20·2 ± 1·13
P*	0·001–0·01	0·001–0·01	0·001–0·01

* The probabilities given indicate the significance of the difference between the thyroxine and triiodothyronine results at each time interval.

It will be observed that the percentage of the dose excreted in the urine was higher after triiodothyronine than after thyroxine at all times studied, and also that it was independent of the dose. It has previously been shown that the radioactivity in the urine in such experiments consists almost exclusively of iodide whereas that in the faeces is mainly due to thyronine derivatives (Wilkinson *et al.* 1954).

Faecal excretion of thyroxine and triiodothyronine. The faecal excretion observed in these experiments is recorded in Table 2. In the case of triiodothyronine the percentage excreted appears to be independent of the dose, but after the administration of thyroxine, the percentage excreted increases progressively with increasing dosage.

TABLE 2. The faecal radioactivity after the administration of single doses of labelled triiodothyronine and thyroxine to rats

(Each row of figures represents the mean of two or more observations of the combined excretion of groups of three rats.)

Dose (μg)	Percentage of dose excreted after 24 hr	48 hr	120 hr
	Triiodothyronine		
4	31·3	43·5	49·7
6	40·4	52·7	(57·8 after 72 hr)
10	31·0	41·3	45·8
20	31·2	39·5	43·2
30	27·3	40·0	45·5
50	39·2	48·8	(50·9 after 72 hr)
No. of observations	16	16	
Range	25·8–47·2	36·7–59·3	
Mean ± S.E.	33·8 ± 1·45	44·5 ± 1·47	
	Thyroxine		
4	14·7	31·4	39·2
12	23·7	38·3	45·3
20	28·1	45·9	51·5
30	27·5	49·4	56·0
50	38·5	58·4	64·1
100	51·5	69·6	77·5

Effect of BHDB. The effects of BHDB on the urinary and faecal radioactivity after labelled triiodothyronine and thyroxine are shown in Tables 3 and 4. The figures show that in both cases the marked reduction in urinary output as iodide previously reported (Wilkinson *et al.* 1954; Wilkinson & Maclagan, 1954) is generally balanced by increased faecal excretion. The total rate of excretion both of thyroxine and of triiodothyronine is thus not significantly altered by BHDB. The relation between the percentage of the dose excreted in the faeces and the dose observed in Table 2 in the case of thyroxine seems to apply also in the presence of BHDB, but no such relation holds for triiodothyronine whether BHDB is present or not.

TABLE 3. The effect of BHDB on the total excretion of ^{131}I-labelled triiodothyronine in rats

(Each row of figures refers to the mean of two or more measurements of the combined excretion of a group of three rats.)

Dose of triiodothyronine (μg/rat)	BHDB*	Percentage of dose excreted: Urine	Period of collection (days)	Faeces	Period of collection (days)	Total
6	Absent	25·5	5	57·8	3	83·3
6	Present	11·0	5	64·9	3	75·9
30	Absent	27·3	5	45·5	5	72·8
30	Present	9·8	5	60·4	5	70·2
50	Absent	25·3	4	50·9	3	76·2
50	Present	10·2	4	63·8	3	74·0

* See text for dosage of BHDB.

TABLE 4. The effect of BHDB on the total excretion of ^{131}I-labelled thyroxine in rats

(Each row of figures refers to the mean of two or more measurements of the combined excretion of a group of three rats.)

Dose of thyroxine (μg/rat)	BHDB*	Percentage of dose excreted: Urine	Period of collection (days)	Faeces	Period of collection (days)	Total
4	Absent	17·7	5	39·2	5	56·9
4	Present	8·3	5	50·1	5	58·4
20	Absent	26·0	4	51·0	4	77·0
20	Present	7·4	4	75·6	4	83·0
100	Absent	14·7	5	77·5	5	92·2
100	Present	3·6	5	75·6	5	79·2

* See text for dosage of BHDB.

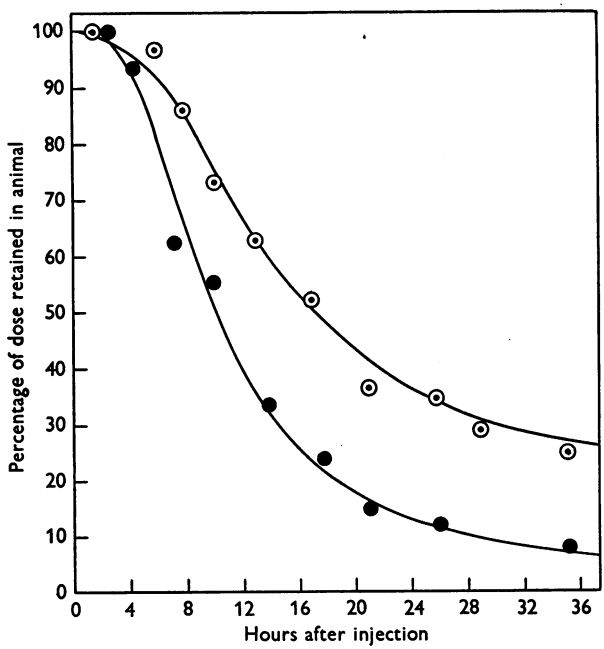

Fig. 2. Typical curves showing the retention of thyroxine and triiodothyronine in the intact rat. ⊙, rat injected with 24 μg 3′:5′-^{131}I-thyroxine; ●, rat injected with 20 μg 3′-^{131}I-triiodothyronine.

Retention of triiodothyronine and thyroxine in rats. The above results indicated that it would be desirable to compare the rates of excretion of triiodothyronine and thyroxine by direct measurement of the amounts retained in the animals. Equimolecular doses (0·031 μequiv, 20 μg 3′-^{131}I-triiodothyronine and 24 μg 3′:5′-^{131}I-thyroxine) were given intraperitoneally and the retained radioactivity was measured by counting the whole animal as described above. Typical curves obtained with single animals are shown in Fig. 2, while the

results obtained with groups of six rats are summarized in Table 5. One of the rats in the triiodothyronine group had to be excluded from the experiment because of refection.

It will be seen that the residual radioactivity was considerably greater at all times studied in the animals treated with thyroxine as compared with those treated with triiodothyronine. This is also shown by the times required for each animal to reach 50% of the initial radioactivity (Table 6) which showed a highly significant difference between the two groups.

TABLE 5. Comparative retention of equimolecular doses (0·031 μequiv) of labelled triiodothyronine and thyroxine in rats

Hours after injection*	Percentage of dose retained: Triiodothyronine (mean of 5 observations ± S.E.)	Percentage of dose retained: Thyroxine (mean of 6 observations ± S.E.)	Significance Student's *t* test
4·7	91·6 ± 3·4	91·6 ± 3·3	N.S.
7·5	62·7 ± 6·5	84·3 ± 1·4	*P* 0·001–0·01
9·9	49·2 ± 4·7	73·3 ± 3·1	*P* 0·001–0·01
13·2	33·0 ± 3·9	61·0 ± 4·6	*P* 0·001–0·01
17·2	23·7 ± 3·4	45·9 ± 6·1	*P* 0·01 –0·02
21	15·4 ± 2·2	37·3 ± 5·6	*P* 0·001–0·01
26	14·0 ± 2·7	32·8 ± 5·0	*P* 0·01 –0·02
29	—	29·2 ± 4·7	—
35	8·5 ± 1·5	21·4 ± 3·5	*P* 0·01 –0·02

* These figures represent the average times at which readings were taken. It required about 1 hr to complete each set of measurements and consequently the times quoted are correct to within 0·5 hr.

TABLE 6. Effect of BHDB on 50% retention times for triiodothyronine and thyroxine in rats

Dose	No. of observations	50% Retention time (hr): Range	50% Retention time (hr): Mean ± S.E.	Significance Student's *t* test
Triiodothyronine (20 μg, 0·031 μequiv)	5	7·2–11·5	9·8 ± 0·61	*P* < 0·001
Thyroxine (24 μg, 0·031 μequiv)	6	11·2–22·2	16·6 ± 1·25	
Triiodothyronine (25 μg)	6	10·9–14·1	11·9 ± 0·48	N.S.
Triiodothyronine (25 μg) + BHDB	6	12·0–17·3	13·8 ± 0·74	
Thyroxine (10 μg)	6	13·8–18·9	16·5 ± 0·72	N.S.
Thyroxine (10 μg) + BHDB	6	13·5–17·8	15·6 ± 0·71	

The figures quoted in Table 5, which depend upon counts of the whole animal, are somewhat different from those which may be deduced from Tables 1 and 2 which depend upon measurements of the excreta. This discrepancy is probably due to differences in rates of absorption from the sites of injection (intraperitoneal in the former and subcutaneous in the latter) and to the relative restriction of movement imposed on the animals kept in metabolism cages during the experiments summarized in Tables 1 and 2. This

difference does not, of course, affect the validity of the conclusions drawn from the two series of experiments since in each case direct comparisons of triiodothyronine and thyroxine were made.

Similar experiments involving the measurement of the radioactivity of the whole animal were carried out to determine the effect of BHDB upon the retention of triiodothyronine and thyroxine. Each animal in the BHDB groups received 50 mg orally the day before the triiodothyronine (8·3 μg) or thyroxine (10 μg) was injected and 25 mg orally on each of the next 2 days. The control groups received triiodothyronine or thyroxine only.

TABLE 7. Effect of BHDB on the retention of radioactive thyroxine and triiodothyronine in rats

Hours after injection	Percentage of dose retained: Thyroxine (mean of 6 observations)	Thyroxine + BHDB (mean of 6 observations)	Significance of difference
6·3	92·4±2·67	94·0±2·98	N.S.
10·1	75·9±2·73	81·2±6·44	N.S.
13·0	64·8±3·74	61·1±5·69	N.S.
16·8	50·2±3·08	46·5±6·01	N.S.
20·4	38·8±1·90	30·6±4·24	N.S.
26·0	36·0±1·27	22·5±4·93	P 0·01–0·02
34·0	24·7±1·66	11·9±1·50	P<0·001
	Triiodothyronine (mean of 6 observations)	Triiodothyronine + BHDB (mean of 6 observations)	
5·3	96·5±1·09	95·6±2·40	N.S.
8·1	90·6±2·50	85·6±2·53	N.S.
10·5	70·2±5·10	81·6±3·20	N.S.
14·0	39·2±3·93	50·4±4·71	N.S.
18·7	25·8±2·20	27·5±3·93	N.S.
24·3	21·7±2·29	17·1±1·48	N.S.
31·2	17·2±2·43	12·1±1·24	N.S.

The results, which appear in Table 7, show that BHDB exerted no significant effect upon the total rate of excretion of thyroxine until after 20 hr, after which rats treated with thyroxine alone excreted it at a slower rate than those which received BHDB as well. This is probably due to greater retention by the thyroid of radio-iodide produced by breakdown of the thyroxine in the former group. This is likely because BHDB, while reducing the extent of this process, must also reduce the amount of radio-iodide available for concentration in the gland. Moreover, by acting as a source of iodide (Wilkinson *et al.* 1954) it would cause the gland to be saturated with non-radioactive iodine, thus supplementing the effect mentioned by reducing the retention of radioactive iodine from the thyroxine.

The table also shows that even less effect was obtained with triiodothyronine, where the accelerating effect of BHDB in the later stages of the experiment was suggestive, but not statistically significant.

The times required for the retention of the dose to fall to 50% in these experiments are included in Table 6. It is noteworthy that small changes in the doses of triiodothyronine and thyroxine have produced no significant alteration in the 50% excretion times, the former still being excreted at a substantially more rapid rate.

DISCUSSION

The results described above show that after the administration of triiodothyronine to normal rats a significantly greater percentage of the dose appears in the urine as iodide than after thyroxine. This is almost certainly due to a difference in the rates of deiodination of the two substances, but we are indebted to the referee for drawing our attention to another possible interpretation. Gross & Pitt-Rivers (1952*b*, 1953*b*) have shown that, in its effects on the inhibition of thyrotrophin secretion by the pituitary, triiodothyronine is about 4 times as active as thyroxine. It is conceivable therefore that, in the rats given triiodothyronine, pituitary inhibition might have been greater than in the case of those injected with thyroxine. The thyroxine-treated animals might therefore accumulate in the thyroid a larger fraction of the iodide produced.

Several factors, however, lead us to reject this alternative explanation. First, all the rats were fed on a diet probably rich in iodine, and any ^{131}I-uptake by the thyroid glands would therefore be minimal. Secondly, the extent of pituitary inhibition with either substance must be related to the dosage and, if these pituitary effects were the correct explanation of the differences in the output of urinary iodide, then the differences should disappear when the doses were large enough to cause maximal pituitary inhibition. In fact the same effects were observed with small (4 μg) as with large unphysiological (100 μg) doses. Moreover, the output of urinary iodide after the administration of thyroxine is only slightly greater in thyroidectomized rats than in intact rats (unpublished work; also Roche, Deltour & Michel, 1953; Wilkinson & Feetham, 1954). We may therefore conclude that triiodothyronine undergoes deiodination at a more rapid rate than thyroxine in intact rats.

This is the reverse of what occurs in simple aqueous solution, for Wilkinson *et al.* (1954) showed that thyroxine solutions contain appreciable quantities of iodide after storage at pH 8–9 for a few days, whilst Wilkinson & Maclagan (1954) found that triiodothyronine was quite stable under the same conditions for 3 weeks or more. The possibility that either substance was contaminated with iodide was excluded by preliminary chromatographic examination, the method used being approximately 10 times as sensitive to iodide as to thyronine derivatives. It would, therefore, appear that deiodination *in vivo* is a function of a biological system the character and location of which are at present unknown. Such a system has previously been suggested to explain the actions of the anti-thyroxine substance, BHDB, on the metabolic effects of thyroxine

(Sheahan, *et al.* 1951) and of triiodothyronine (Maclagan *et al.* 1952; Maclagan & Wilkinson, 1952). Our findings also indicate that these metabolic effects of BHDB cannot have been due to any influence of the drug on the total retention of thyroxine or triiodothyronine by the animals. The hypothetical deiodinating system cannot, however, be identical with the desiodase demonstrated in thyroid and other tissues by Roche, Michel, Michel & Lissitzky (1951) which was shown to catalyse the deiodination of mono- and diiodotyrosine but to have no effect upon thyroxine or triiodothyronine (Michel, 1952).

Our results correlate well with those of Rawson, Rall, Pearson, Robbins, Poppell & West (1953) and Lerman (1953) who showed that the metabolic effects of triiodothyronine were more rapid and less prolonged than those of thyroxine. Rawson *et al.* (1953) measured the disappearance rates of the two substances labelled with ^{131}I in athyreotic euthyroid human subjects and found the half life of triiodothyronine to be 2–5 days whilst that of thyroxine was 6–12 days. These results are to be compared with our figures of 9·8 hr for the 50% excretion times of triiodothyronine and 16·6 hr for thyroxine in normal rats (Table 6).

No other figures for the biological half-life of triiodothyronine have come to our notice, but values for thyroxine in man range from 3·8 days in a cretin (Albert & Keating, 1949) to 8·3 days in a case of untreated myxoedema (Recant & Riggs, 1952; Benua, Albert & Keating, 1952). O'Neal & Heinbecker (1953) obtained a figure of 16·2 hr for the mean half-life for the disappearance of endogenous thyroid hormone in hypophysectomized dogs after treatment with thyrotrophin. O'Neal (1953) found that in thyroidectomized dogs the half-life times for the disappearance of protein bound iodine from the plasma ranged from 6·7 to 13·6 hr after a dose of 5000 μg of thyroxine, and from 18·3 to 27·7 hr after 500 μg. This author has suggested that the much more rapid rate of disposal at the higher dose may be due either to the acceleration by thyroxine of its own metabolic destruction, or to a more rapid rate of excretion after the larger dose. Our measurements of the faecal and urinary output (Tables 1 and 2) show quite clearly that there is a significantly faster rate of excretion at higher dose levels. Moreover, the urinary iodide which is a measure of the extent of metabolic breakdown of thyroxine does not show any such rise with increasing dosage. It appears, therefore, that the second of O'Neal's suggestions is the correct one.

No satisfactory explanation can at present be given for the difference between the effect of dose variation upon faecal excretion (Table 2) in the cases of thyroxine and triiodothyronine. It must, however, be borne in mind that the first stage of reductive deiodination of thyroxine labelled with ^{131}I in the 3′:5′ positions must give rise to a radioactive product, whereas the products of a similar breakdown of 3′-^{131}I-triiodothyronine will be non-radioactive. Measurements of the faecal radioactivity of rats treated with labelled thyroxine

may, therefore, include partially deiodinated material, whilst that from animals treated with labelled triiodothyronine can only consist of the unaltered substance. Similarly, measurements of the urinary iodide in experiments using labelled thyroxine, such as those in Table 1, will include that resulting from further breakdown of the primary product. The results reported in Table 2 with intact rats are quite different from those of Roche *et al.* (1953) who found only traces of radioactivity in the faeces of thyroidectomized rats injected with labelled thyroxine (5 μg/rat).

SUMMARY

1. Thyroxine labelled in the 3′:5′ positions with ^{131}I and triiodothyronine similarly labelled in the 3′ position have been injected into rats and the urinary and faecal radioactivity studied.

2. Triiodothyronine was deiodinated at a substantially greater rate than thyroxine in the intact rat at a number of different dose levels.

3. The percentage of the dose of triiodothyronine excreted in the faeces was independent of the dose, but in the case of thyroxine the percentage of the dose excreted in the faeces increased in proportion to the dose.

4. After single injections triiodothyronine was retained in the animal for a shorter period than thyroxine. With doses of 0·031 μequiv/rat the mean 50% retention times were 9·8 hr for triiodothyronine and 16·6 hr for thyroxine.

5. The anti-thyroxine substance butyl 4-hydroxy-3:5-diiodobenzoate (BHDB) exerted little significant effect upon the overall retention of either substance in rats, with the exception of some acceleration of thyroxine excretion from 26 to 34 hr after injection.

The work was aided by grants from the Governors' Discretionary Fund of Westminster Hospital and from the Medical Research Council, to whom grateful acknowledgement is made. We also wish to thank Miss Shena Anderson for skilled technical assistance.

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