Biliary and Urinary I^{131} Excretion in Euthyroid, Hyper- and Hypothyroid Rats Injected with Labeled Thyroxine. (20184)

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Reports in the literature indicate that thyroxine or its metabolites are excreted in the bile and urine of normal animals(1). The object of the present study is to determine to what extent this elimination is altered in hyper- and hypothyroid animals. The effects of desiccated thyroid treatment, thyroidectomy, and thiouracil administration on the excretion of I^{131} were studied in rats following the injection of I^{131}-labeled thyroxine.

Methods and material. Adult male rats of the Sprague-Dawley strain were used. Normal and thyroidectomized groups were maintained on Rockland Complete Rat Diet. Thyroidectomies were performed under ether anesthesia, with at least 6 weeks allowed for recovery and development of hypometabolism (2). The third group received the same diet supplemented with 2 g of thiouracil per kg of diet for 4 weeks before being used(2). The fourth group was maintained on the basic diet containing 0.2% desiccated thyroid for 3 weeks to allow time for development of marked hypermetabolism. All animals were fed *ad lib.* Two lots of I^{131}-labeled thyroxine (Abbott)* having specific activities of 8.1 and 35.4 mc per mg, respectively, were used. Tracer amounts of about 0.2 μg per kg of body weight were administered subcutaneously. In the first series of experiments, the bile duct was cannulated with polyethylene tubing (inside diameter, 0.011 inch) while the rat was under ether anesthesia. As soon as bile flow was observed, the abdomen was closed, and the animal suspended in a restraining harness. The tracer amount of labeled thyroxine was injected subcutaneously and hourly bile samples were collected. Radioactivity of the whole bile was determined by air drying 0.1 ml aliquots on aluminum plates, and counting in a thin mica window Geiger counter. Urine was collected from a second series of animals placed in metabolic cages. The concentration of I^{131} activity in the urine was determined on 0.5 ml samples and counted in the manner described for bile.

TABLE I. Cumulative 6-Hour Biliary Excretion Following Subcutaneous Injection of I^{131}-Labeled Thyroxine. 4 rats in each series.

Condition	% activity excreted ($x \pm s_x$)*	P†	ml bile excreted*	P†
Normal	11.6±3.08	—	6.1±1.23	—
Desiccated thyroid-treated	12.3±2.38	.703	8.5±1.83	.070
Thyroidectomized	6.2±1.34	.019	3.1±0.78	.006
Thiouracil-treated	3.2±3.02	.009	3.5±2.02	.070

* x = sample mean; s_x = stand. dev. of values.
† Probability of no difference from normal.

Results and discussion. Results with biliary excretion are shown in Table I. Mean excretion of radioiodine in whole bile of normal animals amounted to 11.6% of the injected dose by 6 hours after administration. Taurog and co-workers(3) give a comparable value of about 13% excretion after a subcutaneous injection of 100 μg per kg of I^{131}-labeled L-thyroxine during the same period of time. The radioactivity eliminated in the thyroidectomized and thiouracil-treated rats was reduced significantly to 6.2 and 3.2%, respectively. Desiccated thyroid treatment did not alter significantly the per cent of injected activity excreted in the bile. During the 6-hour collection period the euthyroid animals eliminated 6.1 ml of bile while the excreted volume was reduced to 3.1 and 3.5 ml in the thyroidectomized and thiouracil-treated groups, respectively. An increase to 8.5 ml was found in hyperthyroid rats.

As indicated in Table I, the per cent of injected activity excreted in the bile was measured in 4 thiouracil-treated rats. One animal in this group, however, was more than 3 standard deviations from the mean of the

* The I^{131} used in this investigation was obtained from the Oak Ridge National Laboratory on allocation from the Isotopes Division, U. S. Atomic Energy Commission.

TABLE II. Cumulative Twelve-Hour Urinary Excretion Following Subcutaneous Injection of I^{131}-Labeled Thyroxine.

Condition	No. of rats	% activity excreted ($x \pm s_x$)*	P†
Normal	4	1.3 ± 0.22	—
Desiccated thyroid-treated	4	3.8 ± 1.73	.031
Thyroidectomized	7	1.8 ± 0.79	.261
Thiouracil-treated	4	0.9 ± 0.26	.053

* x = sample mean; s_x = stand. dev. of values.
† Probability of no difference from normal.

remaining animals. Because of the small number of animals used it has been included in the table. By excluding this animal from the group, the mean per cent of I^{131} excreted in the bile becomes 1.7. This mean value is markedly less ($P = .003$) than the corresponding value in the thyroidectomized group. If the apparently atypical animal is included the difference is not highly significant ($P = 0.12$). In comparing the desiccated thyroid-treated group with that of the normal, the former showed an increase in the volume of bile eliminated with no alteration in the per cent of radioactive iodine excreted. The elimination of radioiodine is not related to the amount of bile excreted. However, the volume of bile does appear to be directly related to the thyroid status.

The results of urinary excretion are shown in Table II. Excretion of radioactive iodine in the urine of euthyroid rats amounted to 1.3% of the injected dose of thyroxine by 12 hours after administration. The quantity appearing in the urine of hyperthyroid and thyroidectomized groups was increased to 3.8 and 1.8%, respectively. A decrease to 0.9% was found in the thiouracil-treated rats. Reports in the literature indicate that the kidney plays an important part in the excretion of iodine, but not in the excretion of thyroxine *per se* (1). The increased rates may be due to the marked increase in metabolism which in turn would result in an increase in available radioiodine containing metabolites from the administered thyroxine.

A trend toward a lower rate of excretion in thiouracil animals with respect to thyroidectomized animals is seen in Table II ($P = 0.06$). These results suggest that thiouracil *per se* has an effect on the urinary and biliary excretion of radioiodine in the rat. The ability of the thyroid gland to concentrate iodide is greatly increased by thiouracil treatment(4). In the present series of experimental treatments this might explain the order of urinary radioiodine excretion found among the normal and hypothyroid groups. This does not explain the corresponding values for biliary excretion. Recent investigations(5,6) indicate that thyroxine is eliminated in bile in a free and/or conjugated form. The lowered metabolism of the thyroidectomized and thiouracil-treated groups may be the basis for lower than normal biliary excretion of I^{131}, but the reason for the difference between the 2 hypometabolic groups is not clear. Toxic effects of thiouracil might explain the results found.

Summary. Biliary and urinary excretion of radioiodine was studied following subcutaneous injection of tracer amounts of I^{131}-labeled thyroxine in normal, hypo- and hyperthyroid rats. Thyroidectomized and thiouracil-treated groups showed reduced biliary radioiodine elimination, as well as diminished bile volume during the 6-hour collection period. Hyperthyroid animals showed a marked increase, thiouracil-treated animals a decrease in urinary excretion of radioactive iodine over a 12-hour period. Radioiodine excretion in both bile and urine tended to be lower in the thiouracil-treated animals than in the thyroidectomized groups.

1. Monroe, R. A., and Turner, C. W., *Missouri Agr. Exp. Sta., Res. Bull.*, 1949, v446, 19.
2. Barker, S. B., Kiely, Jr., C. E., Lipner, H. J., *Endocrinol.*, 1949, v45, 624.
3. Taurog, A., Briggs, F. N., and Chaikoff, I. L., *J. Biol. Chem.*, 1951, v191, 29.
4. Vanderlaan, J. E., and Vanderlaan, W. P., *Endocrinol.*, 1947, v40, 403.
5. Taurog, A., Briggs, F. N., and Chaikoff, I. L., *J. Biol. Chem.*, 1952, v194, 655.
6. Klitgaard, H. M., Lipner, H. J., Barker, S. B., and Winnick, T., *Endocrinol.*, 1953, v52, 79.

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