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ESTIMATION OF RADIATION DOSAGE DELIVERED BY A SINGLE  
MASSIVE INJECTION OF I<sup>131</sup> IN THE RAT<sup>1,2</sup>

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## INTRODUCTION

One of the major problems in radiobiology is the search for quantitative relationships between absorbed radiation dose and biological effect. In the case of internally deposited radioactive isotopes such relationships are particularly difficult to assess. After administration, radioisotopes usually undergo complicated patterns of distribution, accumulation, and elimination depending on their chemical form, mode of administration, and in some cases, on the amount of radioactive material administered. In addition to total dose, the rate of dose delivery contributes significantly to the observed biological effect. Following a single injection of a radioactive isotope, the dose rate changes continuously depending upon the rate of radioactive decay and the rates of uptake and elimination from the tissues.

In the course of several investigations in this laboratory a considerable body of knowledge has accumulated on the lethality (1,2) and the acute and chronic pathology (1,3,4) in rats resulting from a single massive injection of  $I^{131}$  (greater than 10  $\mu\text{C/g}$  body weight). It, therefore, seemed desirable to try to determine the radiation dose associated with the observed pathology. Data from three studies of the distribution of a tracer dose of  $I^{131}$  (5-7) were applied to this problem, and the calculated beta radiation doses from a single injection of 90  $\mu\text{C/g}$  body weight of  $I^{131}$  (close to the mean lethal dose at 60 days) ranged from 150 rad in the small glands and lymph nodes to 420 rad in the whole body.<sup>4</sup> If  $\gamma$ -radiation was assumed to contribute as much as 20% to the total dose, the above doses would be increased to 150 rad and 500 rad, respectively. These estimates seemed too low to account for either the acute lethality or the unrepaired damage in the tissues of long-term survivors, particularly when the sparing (or dose reduction) effect of protracted exposure was considered. There appeared to be at least two serious defects in the

foregoing calculations: (a) the extent to which the internal radiation altered the distribution of the isotope was unknown, and (b) the tracer distribution data covered only the first 48 hours and the 7th day.

The studies described in this report were undertaken to provide detailed information on the metabolic behavior of a high-level injection of  $I^{131}$  (50  $\mu\text{C/g}$  body weight) which would permit calculation of the average radiation dose in the whole body and the individual tissues of the rat.

## METHODS

Female rats were obtained from Sprague-Dawley, Inc., Madison, Wis. when 40 days old. Throughout the experiment they were fed Purina Lab Chow and tap water ad lib except during the  $I^{131}$  injection and during daily in vivo retention measurements. When the animals were 52 to 60 days old, and had achieved a mean body weight of about 165 g, each animal received a single injection of  $I^{131}$  via the surgically exposed external jugular vein while under light ether anesthesia. Carrier-free  $I^{131}$  obtained from Oak Ridge National Laboratory was diluted to the desired radioactive concentration with a solution containing 0.85 mg/ml of NaCl and 0.5 mg/ml of  $Na_2SO_3$ . Ten rats that were given 1  $\mu\text{C/g}$  body weight of  $I^{131}$  constituted the low-dose "control" group.<sup>5</sup> Twenty-five rats were given 10  $\mu\text{C/g}$ , 85 rats received 50  $\mu\text{C/g}$  (the average dose was 8.35  $\mu\text{C/rat}$ ), and 39 rats received 90  $\mu\text{C/g}$ . Two extra rats injected at each dose level were immediately sacrificed with chloroform and quick frozen to provide counting standards for the in vivo retention measurements. For the first two weeks after injection, when the animals were highly radioactive, they were housed two to a cage<sup>6</sup> in a modified Berkeley Box with controlled temperature and humidity. The cages were separated from each other by 1/8" lead sheet, and the sides and back of the box were lined with lead sheet.

All the rats could not be injected at one time because of limited hot-animal holding space. Therefore, several animals were injected at each of the high-dose levels on six different occasions during a 3-month period. The 50 rats at the 50  $\mu\text{C/g}$  level that constituted the serial sacrifice group were injected in two lots. Five rats from each lot were sacrificed at 24 and 48 hours postinjection to provide an overlap and an internal check on the time intervals that were not common to both injection days.

Whole-body retention of  $I^{131}$  was measured during the first two weeks after

injection. All animals were counted daily in a whole-animal counting apparatus which consisted of two 2-inch diameter end-window Geiger-Müller tubes<sup>7</sup> mounted on either side of and directed toward an open-ended plastic rat holder. Counting rates were maintained at a statistically accurate level (greater than five times background count rate), but were kept well below the level at which coincidence becomes significant for this combination of self-quenching G-M tube and Tracerlab scaling circuit (6,000 cpm). This was accomplished by varying the tube-to-animal distance and by use of suitable aluminum and lead absorbers.

Fifty of the animals injected at the 50  $\mu\text{C/g}$  level were serially sacrificed in groups of five, and tissue distributions were measured at time intervals from 4 hours to 6 days postinjection. The remaining 110 animals were reserved for other experiments. Terminal whole-body retention was measured by in vivo counting just before sacrifice. The animals were sacrificed with an overdose of chloroform. Blood was drawn from the inferior vena cava. Tissue specimens (listed in Table I) were dissected, examined for gross pathology, and weighed.<sup>8</sup> The small bowel was divided into three portions corresponding roughly to the duodenum, jejunum, and ileum. The contents of the various portions of the tract were expressed by gentle manual squeezing, or in the case of the stomach and cecum, by gentle teasing of the solid matter from the exposed mucosal surface. The eviscerated skinned carcass was cut up into a number of pieces small enough to fit in counting capsules. The tissue samples, depending on their size, were placed either in small capped vials of Bouin's fixative<sup>9</sup> or in open tin bottle caps.

Depending on their size and on the amount of radioactivity estimated to be present, tissue specimens were assayed for  $\text{I}^{131}$  by one of the following four methods: (a) a wall-type scintillation counter, (b) a probe-type scintillation counter, (c) an end-window G-M counter with suitable lead absorbers to screen

out the beta-particles, or (d) the in vivo apparatus described above. The last method was used only for the most active samples, i.e., the thyroid and gastrointestinal contents. Several weeks after the sacrifice of the animal, when most of the  $I^{131}$  had decayed, the above-mentioned samples were reassayed by method (c). Aliquots of the injection solution were measured in the appropriate counting apparatus each time tissue samples were measured.

## RESULTS

Whole-body retention of  $I^{131}$ :

Whole-body retention of a low dose of  $I^{131}$  (1  $\mu\text{C/g}$  body weight or less) and of a massive dose of  $I^{131}$  (10, 50, or 90  $\mu\text{C/g}$  body weight) are compared in Fig. 1.<sup>10</sup> Elimination of the low dose of  $I^{131}$  could be described by a two-component exponential equation. The initial rapid component is assumed to represent excretion of unused iodide and the second component (biologic half life,  $T_E = 12$  days), release of labeled hormone from the thyroid and elimination of both inorganic and protein-bound iodine from the carcass and pelt (6-8). Initially, excretion of a single massive dose of  $I^{131}$  followed the same pattern as the excretion of a low dose--roughly 40% was excreted in the first four hours at all  $I^{131}$  dose levels. Elimination of the higher doses was markedly retarded from the 4th to the 24th hour postinjection, so that by the end of the first day the high-level rats retained twice as much  $I^{131}$  on a percentage basis as those given the low dose. After the first day rapid elimination of a massive dose was resumed, and by the fifth day 96% had been excreted. The low-dose animals had excreted 86% of the injected  $I^{131}$  at this time.

Retention of  $I^{131}$  in the thyroid gland:

The effect of the internal radiation on iodine retention in the thyroid gland after an injection of 50  $\mu\text{C/g}$   $I^{131}$  is shown in Fig. 2. The tracer data (6,7) are shown for comparison. The radiation did not seem to affect accumulation of radioiodine, although there may have been some alteration of the iodine trapping mechanism as judged by the significantly greater uptake of  $I^{131}$  in the heavily irradiated glands at 12 hours ( $P < 0.01$ ). After the first day the irradiated thyroid glands lost  $I^{131}$  at an exceedingly rapid rate ( $T_E < 12$  hours), and only 0.1% of the administered dose remained in the thyroid tissue 4 days after injection. Elevated concentrations of  $I^{131}$  or periods of prolonged

$I^{131}$  retention in the blood and tissues coincided with the release of  $I^{131}$  from the thyroid during the second day after injection.

$\beta$ -radiation dosage in individual tissues:

Radiiodine concentrations (expressed in percent of administered dose per gram wet weight) are shown in Table I for several tissues at intervals from 4 hours to 6 days after injection of 50  $\mu\text{C/g}$  body weight of  $I^{131}$ . During the first 12 hours postinjection the distribution of a massive dose of  $I^{131}$  was similar to that of an  $I^{131}$  tracer (5). From the 12th to the 36th hour the  $I^{131}$  concentrations in the tissues of the high-dose rats remained elevated in contrast to the smooth continuous decline seen after injection of a tracer dose (shown in Fig. 3 for whole blood). The tissues of the high-dose animals lost  $I^{131}$  rapidly after the 36th hour, and by the 4th day their tissues retained a smaller percentage of the injected dose than the tissues of tracer animals.

The biological data were used to evaluate the concentration-time integral in the  $\beta$ -ray dose formula (9):

$$D_{\beta}(t) = 51.2 \text{ rad/d} \times 0.187 \text{ Mev} \int_0^t C(t) dt,$$

where 0.187 Mev is the average energy of the  $I^{131}$   $\beta$ -particle (9, p. 715), and  $t$  is the time after injection in days. It is apparent from the tables of data and from Figs. 3 and 4 that the distribution of a massive dose of  $I^{131}$  in the tissues could not be described by a simple mathematical expression. The experimental distribution data in microcuries per gram  $\pm$  S.D. were plotted as a function of time on a linear scale (shown in Fig. 3 for whole blood), and the concentration-time integrals were determined graphically. The small organs, i.e., adrenal, ovary, and lymph nodes, were assumed to be spheres of about 2 mm radius, which is less than the maximum beta range. A radius of 1 mm was assumed for each lobe of the thyroid. A geometrical correction,  $D_{\text{avg}} = 0.86 D_{\beta}$  (9, pp. 734-735), was therefore applied to the calculated  $\beta$ -ray dose in the small

organs, where  $D_{\beta}$  is the dose inside a large mass with the same  $I^{131}$  concentration. A somewhat larger correction,  $D_{avg} = 0.70 D_{\beta}$  (9, p. 743), was introduced in calculating the thyroid dose because of the deviation of the shape of the rat thyroid from a sphere.

Average doses were calculated for uniform tissue distribution and undoubtedly err on the high side in some parts of a single tissue and on the low side in other parts of the same tissue. Preliminary autoradiographic evidence suggests that shortly after administration radioiodide in the tissues is, for the most part, associated with the blood-vascular or the lymphatic circulation.<sup>11</sup> The maximum error in the calculated average  $\beta$ -radiation dose due to individual variations from the mean  $I^{131}$  tissue concentrations was estimated for several tissues from the areas under the smoothed curves joining the positive and negative standard deviations (see Fig. 3 and Table II).

The  $\beta$ -ray doses to the tissues from an injection of 50  $\mu\text{C/g}$  of  $I^{131}$  were also calculated from tracer data (5,6). The results of these calculations are compared in Table II with the doses estimated from high-level data. Radiation doses based on tracer data were generally lower than those calculated from high-level injection data--by as much as a factor of two in the case of the endocrine glands and lymphatic tissues. There was good agreement only in the case of the two largest highly vascular organs: liver and kidney. The  $\beta$ -radiation doses to the highly vascular tissues were, on the average,  $2/3$  of the  $\beta$ -ray dose calculated for whole blood. These findings confirm similar estimates used by Seidlin et al. (10) in calculating the  $I^{131}$  blood dose in patients. The blood dose, with appropriate corrections for iodide space, appears to be a reliable estimate of the absorbed dose in many of the tissues. However, there were some notable exceptions. The dose to the pelt was almost twice that of whole blood reflecting the presence of an iodide concentrating mechanism in the skin of the adult rat as postulated by Brown-Grant and Pethes (11). The

radiation dosages in the two endocrine organs investigated--adrenal and ovary--were about one-half that for whole blood.

$\beta$ -radiation dose in the gastrointestinal tract:

The gastrointestinal tract plays a special role in the metabolism of iodine. Radioiodide is secreted by the gastric mucosa of the rat (and by the salivary glands in other species), and is later reabsorbed from the small intestine (12-14). The  $I^{131}$  concentrations and weights of the stomach, small intestine, large intestine-caecum, and the contents of each portion of the tract were determined at intervals from 4 to 72 hours after injection of 50  $\mu\text{C/g}$  body weight of  $I^{131}$ . The data are collected in Table III. There were no noteworthy differences in the  $I^{131}$  concentrations in the three segments of small intestine or in their respective contents at any time after injection. The data have therefore been combined and are expressed as small intestine and small intestine contents.

The curves in Fig. 4 demonstrate once again the important influence of acute radiation exposure on gastrointestinal function--in this instance--the metabolism of  $I^{131}$  in the gastrointestinal tract. When a tracer dose of  $I^{131}$  is injected, the maximum accumulation of  $I^{131}$  in the tract is reached about one hour after injection. The  $I^{131}$ -labeled contents move quickly into and through the small intestine, so that only a small percentage of the peak  $I^{131}$  accumulation remains in the tract 24 hours after injection. In the irradiated animals gastrointestinal function appeared to be normal during the first few hours after the  $I^{131}$  injection. However, instead of being passed into the small intestine, the  $I^{131}$  continued to accumulate in the gastric lumen from the 4th to the 12th hour. The mass of the gastric contents slightly more than doubled during this time, indicating a significant reduction in gastric motility (15). After the 12th hour absorption of  $I^{131}$  from the intestinal tracts of the internally irradiated rats (50  $\mu\text{C/g}$   $I^{131}$ ) was

remained but at a rate only one-half of that observed after injection of an  $I^{131}$  tracer. Elimination of  $I^{131}$  from the gastrointestinal tract was almost complete by the 4th day in both the high-level and tracer groups.

The radiation dosages to the stomach and to the small and large intestine (shown in Table IV) were calculated from the  $I^{131}$  concentrations in the tissues themselves and in their contents. The concentration-time integrals ( $\mu\text{C}\cdot\text{hr}/\text{g}$ ) were evaluated graphically as described above. The tissue of the gastrointestinal tract was assumed to be an extended hollow cylindrical shell with an average wall thickness of 1 mm. It was further assumed that the wall of this cylinder approximated a thin plane radiation source. The average dose to the gastric and intestinal mucosa from  $I^{131}$  in the tissue itself was calculated using data given by Loevinger and Hine,  $D_{\text{avg}} = 0.85 D_p$  (9, p. 726). The dose to the mucosal layer from the  $I^{131}$  distributed in the gastric or intestinal contents was estimated to be 0.5 of the average dose in the contents (16,17). The total dose to the mucosal layers of the stomach and intestines, the sum of the dose from the tissue, and the dose from the contents, is shown at the bottom of Table V.

The amount of  $\beta$ -radiation absorbed in the small intestine in the first three days after the  $I^{131}$  injection was about 500 rad, slightly higher than that calculated for whole blood. The gastric mucosa sustained a massive  $\beta$ -radiation exposure--5,600 rad in the first three days after injection of 50  $\mu\text{C}/\text{g}$  of  $I^{131}$  (almost 10,000 rad at the 90  $\mu\text{C}/\text{g}$  level).

#### $\gamma$ -ray dosimetry:

The  $\gamma$ -ray dose from  $I^{131}$  was calculated for the whole body and for certain tissues from the equations given by Loevinger, Holt and Hine (9, p. 861),

$$D_{\gamma} = 0.0546 \int \rho \Gamma \int_0^t c(t) dt,$$

where  $\rho$  is the density of tissue (assumed to be unity),  $\Gamma$  is the dose rate

constant equal to  $2.18 \text{ cm}^2 \cdot r / \mu\text{C} \cdot \text{hr}$  for  $\text{I}^{131}$ ;  $\bar{g}$  is the average geometrical factor which is dependent on the size and shape of the  $\gamma$ -emitting source (9, pp. 850-853); and  $\int C(t) dt$  is the time-integral of  $\text{I}^{131}$  distribution in the tissues. The geometrical factor  $\bar{g}$  which allows  $\gamma$ -ray dose calculation for an extended source is very difficult to evaluate except for the simplest geometrical shapes. Therefore, the following simplifying assumptions were made about the geometrical shape of the whole body and tissues of the rat:

(a) The body of the rat is a circular cylinder of unity density whose dimensions are radius = 1.8 cm and height = 15 cm and for which  $\bar{g}$  was estimated to be  $16.5 \text{ cm}^2$ ; (b) the organs of the rat are spheres of unit density whose radii can be calculated from their masses and for which  $\bar{g} = 3 \pi r \text{ cm}$  (9, p. 857); (c) the intestinal tract is a compact spherical mass containing a uniform distribution of  $\text{I}^{131}$ ; and (d) the full stomach is a sphere containing a uniform distribution of  $\text{I}^{131}$ , and the mucosa (constituting the surface of the sphere) receives a  $\gamma$ -ray dose one-half that at the center.

The  $\text{I}^{131}$   $\gamma$ -ray dose to a tissue is the sum of (a) the  $\gamma$ -ray dose from  $\text{I}^{131}$  contained in the tissue (the  $\gamma$ -ray self-dose), (b) the average  $\gamma$ -ray dose from  $\text{I}^{131}$  in the surrounding tissues (the whole-body dose); and (c) the  $\gamma$ -ray dose from  $\text{I}^{131}$  concentrated in the thyroid gland and stomach.

The average  $\text{I}^{131}$  distribution in the whole body was calculated for various times after administration as follows:

Retention (average) =

Retention (total) - Retention (thyroid) - Retention (stomach and contents).

Experimentally determined values for average total body retention, thyroid retention, and gastric retention of  $\text{I}^{131}$  are given in Figs. 1 and 2 and Table III. The time integral of average body retention evaluated graphically was  $33.8 \mu\text{C} \cdot \text{day/g}$  for the first six days after the  $\text{I}^{131}$  injection, and the  $\gamma$ -ray dose from  $\text{I}^{131}$  distributed throughout the body was approximately 45 r.

The reciprocal dose theorem was used to calculate the contribution to the total  $\gamma$ -ray dose in the whole body and in the tissues other than the thyroid and stomach due to  $I^{131}$  concentrated in the latter organs. This theorem states that "the average dose delivered to a given volume by a given amount of radioactivity at some fixed point equals the dose at that point due to the same amount of radioactivity distributed uniformly inside the specified volume".

The average  $\gamma$ -ray dose to the entire body from  $I^{131}$  concentrated in the stomach was calculated to be  $15 \times \left( \int_0^3 C(t) dt = 13.1 \mu\text{C-day/g} \right)$ . The contribution from the thyroid gland to the whole body  $\gamma$ -ray dose was of the order of 5 rad  $\left( \int_0^6 C(t) dt = 4.1 \mu\text{C-day/g} \right)$ .

Because of the close proximity of the spleen to the stomach (approximately 1 cm), the  $\gamma$ -ray dose to the spleen from  $I^{131}$  concentrated in the stomach was calculated separately using a  $\bar{g}$  value of  $0.09 g_p$  at the center of the stomach.

The  $\gamma$ -ray self-dose, the  $\gamma$ -ray dose from surrounding tissues (considered to be equal to the whole-body dose), the  $\gamma$ -ray dose from  $I^{131}$  concentrated in the thyroid and stomach, and the total absorbed dose--beta radiation plus  $\gamma$ -ray--are shown in Table V for several tissues. The  $\gamma$ -ray contribution to the total absorbed dose in the thyroid and stomach was small, and probably could be neglected. However, the  $\gamma$ -ray dose represented from 15% to 30% of the total dose to the whole body and to the tissues that did not concentrate  $I^{131}$  to a significant degree.

## DISCUSSION

Influence of internal  $I^{131}$  radiation on iodine metabolism:

Measurements of whole-body retention and tissue distribution of  $I^{131}$  revealed that  $I^{131}$  beta-particle radiation altered iodine metabolism in two important ways--the increased rate of release of  $I^{131}$  from the thyroid gland which has been demonstrated previously (19), and the dynamics of gastrointestinal iodine metabolism. Egestion of  $I^{131}$  from the thyroid and delay of intestinal reabsorption of  $I^{131}$  due to suppressed gastric motility appear to account for the elevated blood and tissue concentrations and prolonged whole-body retention.

Massive radiation exposure of the thyroid gland produced such profound tissue destruction that within a short span of time (12 to 36 hours after injection) the disintegrating tissue spilled all the accumulated  $I^{131}$  back into the circulation. The return of 10% to 15% of the injected  $I^{131}$  dose to the circulating blood during a relatively short period significantly increased the radiation exposure of nearly every other tissue. The rise in the  $I^{131}$  concentration of the lymphatic tissues during the thyroid release phase suggests that at least part of the  $I^{131}$  discharged from the thyroid was in a particulate form. Tong et al. (20) have shown that the major fraction of iodine in the plasma of rats 24 to 48 hours after a thyroidectomizing dose of  $I^{131}$  is bound to large protein fragments resembling thyroglobulin.

Within 4 hours after the  $I^{131}$  injection, gastric motility was substantially reduced as evidenced by the large increase in the total mass of gastric contents. Suppression of gastric motility has been observed in the rat both during and for several hours after either whole-body or abdominal x-ray exposure (15,21,22). Ulmer et al. (25) recently demonstrated significant gastric retention of an  $I^{131}$  tracer injected just after 900 r of whole-body x-ray. The extent and early onset of deranged gastric function are not surprising in light of the

magnitude of both the initial dose rate, 200 rad/hr, and the accumulated dose, 5,900 rad during the first three days after injection of 50  $\mu\text{C/g}$  of  $\text{I}^{131}$ .

Correlation of radiation dose with chronic pathology:

Direct measurements were not made of  $\text{I}^{131}$  tissue concentrations at the  $\text{LD}_{50}/60$ -day level (90  $\mu\text{C/g}$  body weight) (1,2). However, it seemed reasonable to estimate the radiation doses to the tissues of rats given 90  $\mu\text{C/g}$  of  $\text{I}^{131}$  at 9/5 the dose calculated for the 50  $\mu\text{C/g}$  group, because whole-body  $\text{I}^{131}$  retention was similar for both groups (see Fig. 1). Thus, at an injected dose of 90  $\mu\text{C/g}$  of  $\text{I}^{131}$ , the whole body absorbed roughly 750 rad, the lymphatic tissues, 550 rad; the kidney, 550 rad; the adrenal glands, 400 rad; and the ovaries, 500 rad.<sup>11</sup>

The chronic pathology exhibited by long-term survivors of a previous experiment (1) involving a single high-level injection of  $\text{I}^{131}$  in rats (10  $\mu\text{C/g}$  to 90  $\mu\text{C/g}$ ) was most pronounced in the endocrine glands, the lymphatic tissues, the liver, and the renal cortex. The data in the present report indicate that the radiation dose to these tissues from an  $\text{I}^{131}$  injection of 50  $\mu\text{C/g}$  or more was great enough to produce significant cell damage.

At the lowest  $\text{I}^{131}$  injection level (10  $\mu\text{C/g}$ ) thyroid destruction was complete (1), and the structural changes in the other endocrine glands were the same as those seen in surgically thyroidectomized rats (23-25). However, as the  $\text{I}^{131}$  dosage was increased, the ovary, pituitary, and adrenal cortex exhibited progressively more severe pathological changes above and beyond those associated with prolonged hypothyroidism. This qualitative indication of the dependence of pathology on radiation dose, and the magnitude of the doses to these organs at the higher  $\text{I}^{131}$  injection levels strongly suggest that these endocrine glands were directly damaged by the radiation.

The endocrine glands are complexly interrelated through feed-back mechanisms

and varying degrees of synergism or antagonism of their hormones. Destruction of the thyroid and structural impairment of the pituitary, adrenal cortex, and ovary (the combined result of radiation damage and thyroid deficiency) almost certainly led to functional impairment and a polyglandular deficiency. It is to be expected that following irradiation, cell regeneration or recovery would be impaired in those tissues or organs which are dependent on the endocrine balance. Although the effects on the lymphatic tissues in the long-term survivors of a massive injection of  $I^{131}$  (reduced cellularity and depression of lymphopoiesis) were originally considered to us to be chiefly radiation effects (1), endocrine deficiency may well have played an important role in their failure to recover. Pituitary growth hormone and thyroxine are both known to support lymphatic tissues and stimulate lymphocyte production (26,27); in their absence, restoration of lymph node structure was inadequate. Secretion of adrenal cortical and ovarian hormones which are lympholytic (27,28) was probably also low, rendering the problem even more complicated. Regeneration in the liver and kidney was probably also adversely affected by the reduced protein anabolic stimulus that resulted from deficient pituitary secretions (growth hormone). Preliminary findings from several groups of rats that received replacement thyroid hormone therapy after irradiation with  $I^{131}$  support the foregoing conclusions (3, 30).

## SUMMARY

1. Young adult female Sprague-Dawley rats were injected with  $I^{131}$  at levels of 1, 10, 50, and 90  $\mu\text{Ci/g}$  body weight. Retention of  $I^{131}$  was determined by in vivo counting for two weeks after injection. Fifty rats that were injected with 50  $\mu\text{Ci/g}$  of  $I^{131}$  were serially sacrificed at intervals from 4 hours to 6 days later. Tissue weights and  $I^{131}$  concentrations were determined, and  $\beta$ -ray and  $\gamma$ -ray doses were calculated for the whole body and several tissues.
2. The internal radiation significantly altered both release of  $I^{131}$  from the thyroid gland and gastrointestinal metabolism of radioiodine. The thyroid glands of the high-dose rats accumulated  $I^{131}$  normally for the first 12 hours. After the 12th hour the heavily irradiated thyroid tissue lost  $I^{131}$  rapidly, so that within a short time (12 to 36 hours postinjection) all the accumulated  $I^{131}$  had been returned to the circulation. When the rapid release of  $I^{131}$  from the irradiated thyroid was taken into account, the calculated  $\beta$ -ray dose to the gland was 25% of that which would be calculated from tracer studies.
3. Gastric motility was reduced during the first 36 hours after the  $I^{131}$  injection, causing a significant delay in reabsorption of  $I^{131}$  from the intestine. Prolonged whole-body retention of  $I^{131}$  and elevated tissue  $I^{131}$  concentrations could be accounted for by delayed reabsorption of  $I^{131}$  secreted by the stomach, and by the release of  $I^{131}$  from the thyroid.
4. The  $\gamma$ -ray contribution to the total dose was significant (19% to 50% of the total dose) in the whole body, and in all tissues except the thyroid and gastric mucosa.

SUMMARY (continued)

5. The total radiation dose in the whole body, and the doses calculated for the individual tissues from a single high-level injection of  $I^{131}$  were generally consistent with previous observations on lethality and pathology of long-term survivors. It is suggested that the pathologic changes previously observed in long-term survivors of a single massive injection of  $I^{131}$  (atrophy and structural derangement of the anterior pituitary, adrenal and ovary, and depletion of the lymphopoietic tissues) are not due to either radiation or endocrine deficiency alone, but are the consequences of both radiation damage and profound and prolonged endocrine deficiency.

FOOTNOTES

<sup>1</sup> This work was performed under the auspices of the U. S. Atomic Energy Commission.

<sup>2</sup> A preliminary report of these studies was presented at the Work in Progress Section of the 42nd Annual Meeting of the Radiological Society of North America, December 1956, and an abstract appeared in *Radiology* **68**, 103-104 (1957).

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<sup>4</sup> The whole-body  $\beta$ -ray dose of 300 rep given for the 90  $\mu\text{C/g}$   $\text{I}^{131}$  group in ref. (1) was calculated, using the gross oversimplification that all of the  $\text{I}^{131}$  retained in the rat was uniformly distributed throughout its body.

<sup>5</sup> This was the lowest  $\text{I}^{131}$  dose for which statistically significant in vivo measurements could be made for as long as 7 days postinjection.

<sup>6</sup> The  $\gamma$ -ray dose to a rat from the  $\text{I}^{131}$  in its cage mate probably did not exceed 4.5 r for the first 6 days. This is the maximum value calculated for the mutual radiation of two unit density spheres ( $V = 165 \text{ cm}^3$ ) provided that they remain tangent during the entire 6-day interval.

<sup>7</sup> The G-M tube used was of the "Scott-type", i.e., with a cylindrical glass wall, a thin mica end window, and filled with one atmosphere of helium saturated with ethyl alcohol vapor. These tubes are approximately 1% efficient for photons.

<sup>8</sup> The lymph node samples consisted of as many lymph nodes as could be dissected from the mesenteric, cervical and axillary regions. Mediastinal nodes were removed from the thymus and discarded.

FOOTNOTES (continued)

<sup>9</sup> The Bouin's-fixed tissue specimens were later embedded in paraffin and prepared for routine pathological examination. The pathological findings will be the subject of a separate report.

<sup>10</sup> The tabular data appear in ref. (4).

<sup>11</sup> M. E. Johnston, C. W. Asling, and P. W. Durbin, University of California Lawrence Radiation Laboratory, unpublished data.

<sup>12</sup> The value for  $\bar{g}$  was calculated from the equation for  $g_p$  at the midpoint of a cylinder (18, p. 435), assuming that  $\bar{g} \approx 0.55 g_p$  for cylinders of  $r > 1.5$  cm.

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Table I.

Retention of a large dose of  $I^{131}$  in the tissues of the rat. Mean values are expressed as percent of administered dose per gram wet tissue  $\pm$  S.D. Groups of five rats (unless otherwise specified) were given 50  $\mu$ C/g body weight of  $I^{131}$  at 52 to 55 days of age

	<u>4-hour</u>	<u>12-hour</u>	<u>24-hour<sup>b</sup></u>	<u>2-day</u>	<u>4-day<sup>c</sup></u>	<u>6-day</u>
Whole blood <sup>a</sup>	.53 $\pm$ .06	.18 $\pm$ .03	.20 $\pm$ .07	.09 $\pm$ .04 <sup>b</sup>	.01 $\pm$ .003	.002
Heart and lungs	.27 $\pm$ .05	.11 $\pm$ .02	.14 $\pm$ .05	.06 $\pm$ .01	.01 $\pm$ .006	.003 $\pm$ .001
Kidney	.20 $\pm$ .03	.09 $\pm$ .02	.10 $\pm$ .04	.06 $\pm$ .01	.02 $\pm$ .007	.006 $\pm$ .002
Liver	.17 $\pm$ .05	.09 $\pm$ .02	.10 $\pm$ .04	.08 $\pm$ .01	.02 $\pm$ .007	.004 $\pm$ .001
Ovary	.24 $\pm$ .06	.12 $\pm$ .02	.12 $\pm$ .04	.06 $\pm$ .02	.01 $\pm$ .004	.005 $\pm$ .004
Adrenal	.17 $\pm$ .03	.08 $\pm$ .02	.08 $\pm$ .02	.04 $\pm$ .01	.01 $\pm$ .004	.01 $\pm$ .01
Spleen	.18 $\pm$ .04	.08 $\pm$ .02	.16 $\pm$ .10	.05 $\pm$ .01	.02 $\pm$ .009	.01 $\pm$ .007
Lymph Node	.25 $\pm$ .04	.11 $\pm$ .02	.15 $\pm$ .06	.07 $\pm$ .01	.02 $\pm$ .01	.01 $\pm$ .003
Thymus	.16 $\pm$ .02	.06 $\pm$ .01	.23 $\pm$ .15	.07 $\pm$ .01	.03 $\pm$ .01	.02 $\pm$ .009
Felt	.37	.21	.30 $\pm$ .05	.18 $\pm$ .02	.14 $\pm$ .01	.11 $\pm$ .04

<sup>a</sup> Whole blood 0.19%/g  $\pm$  .02 and 0.02%/g  $\pm$  .01 at 36 and 72 hours, respectively.

<sup>b</sup> Group of 10 rats.

<sup>c</sup> Group of 4 rats.

Table II

Time integral of  $I^{131}$  content and  $\beta$ -radiation dose accumulated in the tissues of the rat in the first 6 days after an intravenous injection of 50  $\mu\text{C/g}$  of  $I^{131}$ .

	$T = 6$ $\left( \frac{\mu\text{C } I^{131} \text{ injected}}{g} \right) dt$	$\mu\text{C-day/g}$	Integral $\beta$ dose	Integral $\beta$ dose calculated from linear data
Adrenal		18.2	rad	rad
Heart and lungs		28.	150	80
Whole blood		37.	270	160
Kidney		23.6	$350 \pm 85^a$	260
Liver		24.7	$230 \pm 60^a$	220
Lymph nodes		27.7	240	200
Ovary		23.6	230	110
Testis		75.	$200 \pm 50^a$	110
Spleen		24.9	720	490
Thymus		27.8	$240 \pm 90^a$	100
Thyroid		$2.4 \times 10^4$	$270 \pm 130^a$	-
			$1.6 \times 10^5$	$6 \times 10^5$

<sup>a</sup> Maximum error determined graphically.

Table III

Weight and distribution of  $I^{131}$  in the gastrointestinal tract and its contents after intravenous injection of 50  $\mu\text{C/g}$  body weight.  $I^{131}$  content is expressed in percent of administered dose in the whole organ or its contents. Values shown are the mean for 5 rats  $\pm$  S.D.

Gastrointestinal tract						
Hours after injection	Stomach		Small intestine		Large intestine & cecum	
	$I^{131}$ content (% of dose)	Weight (g)	$I^{131}$ content (% of dose)	Weight (g)	$I^{131}$ content (% of dose)	Weight (g)
4	2.8 $\pm$ .6	1.0	1.0 $\pm$ .1	3.1	.34 $\pm$ .09	1.9
12	1.5 $\pm$ .2	1.0	.60 $\pm$ .09	3.2	.17 $\pm$ .04	1.8
24	1.0 $\pm$ .3	.93	.44 $\pm$ .07	3.0	.14 $\pm$ .02	1.8
36	.71 $\pm$ .1	.84	.27 $\pm$ .03	2.2	.12 $\pm$ .01	1.6
48	.80 $\pm$ .6	1.1	.22 $\pm$ .05	2.4	.11 $\pm$ .06	1.8
72 <sup>a</sup>	.16 $\pm$ .2	1.0	.04 $\pm$ .02	2.4	.03 $\pm$ .02	1.7

Gastrointestinal tract						
Hours after injection	Stomach		Small intestine		Large intestine & cecum	
	$I^{131}$ content	Weight	$I^{131}$ content	Weight	$I^{131}$ content	Weight
4	14. $\pm$ 1	2.3	2.0 $\pm$ .2	4.3	.60 $\pm$ .1	3.7
12	21. $\pm$ 4	5.3	1.2 $\pm$ .2	4.3	.51 $\pm$ .1	3.4
24	11. $\pm$ 6	3.1	.94 $\pm$ .2	3.4	.65 $\pm$ .3	4.2
36	6.4 $\pm$ 4	3.1	.81 $\pm$ .1	4.0	.75 $\pm$ .2	3.0
48	1.6 $\pm$ 1	1.2	.47 $\pm$ .1	3.4	.95 $\pm$ .5	3.4
72	1.4 $\pm$ 2	2.3	.11 $\pm$ .03	3.5	.28 $\pm$ .3	3.3

<sup>a</sup> The entire G.I. tract and contents contained 0.72% and 0.12% at 4 and 6 days, respectively.

Table IV

Time integral of  $I^{131}$  content and  $\beta$ -radiation dose accumulated in the gastrointestinal tract of the rat in the first three days after intravenous administration of 50  $\mu\text{C/g}$  of  $I^{131}$ . Average tissue dosages were calculated assuming the sources were thin compared to the  $I^{131}$   $\beta$ -particle range.

	Stomach	Small intestine	Large intestine
$\int_{t=0}^{t=3} \frac{(\mu\text{C } I^{131}\text{-injected})dt}{\text{g tissue}}$	259 $\mu\text{C-day/g}$	35.2 $\mu\text{C-day/g}$	17.3 $\mu\text{C-day/g}$
Average dose from $I^{131}$ in tissue <sup>a</sup> (rad)	2,100	280	130
$\int_{t=0}^{t=3} \frac{(\mu\text{C } I^{131}\text{-injected})dt}{\text{g contents}}$	738 $\mu\text{C-day/g}$	46.2 $\mu\text{C-day/g}$	55.7 $\mu\text{C-day/g}$
Mucosal dose from $I^{131}$ in contents <sup>b</sup> (rad)	3,500	220	270
Total mucosal dose <sup>c</sup> (rad)	5,600	500	400

<sup>a</sup>  $D_{\text{avg}} = 0.83D_{\beta}$  (9, p. 729)

<sup>b</sup>  $D_{\text{mic}} = 0.5D_{\beta}$  contents (9, p. 735)

<sup>c</sup> Values shown on line 5 are sums of lines 2 and 4

Table V

Gamma-ray dose and total absorbed radiation dose ( $\beta + \gamma$ ) in the whole body and tissues of the rat 6 days after a single intravenous administration of  $50 \mu\text{C/g}$  body weight of  $\text{P}^{32}$ .

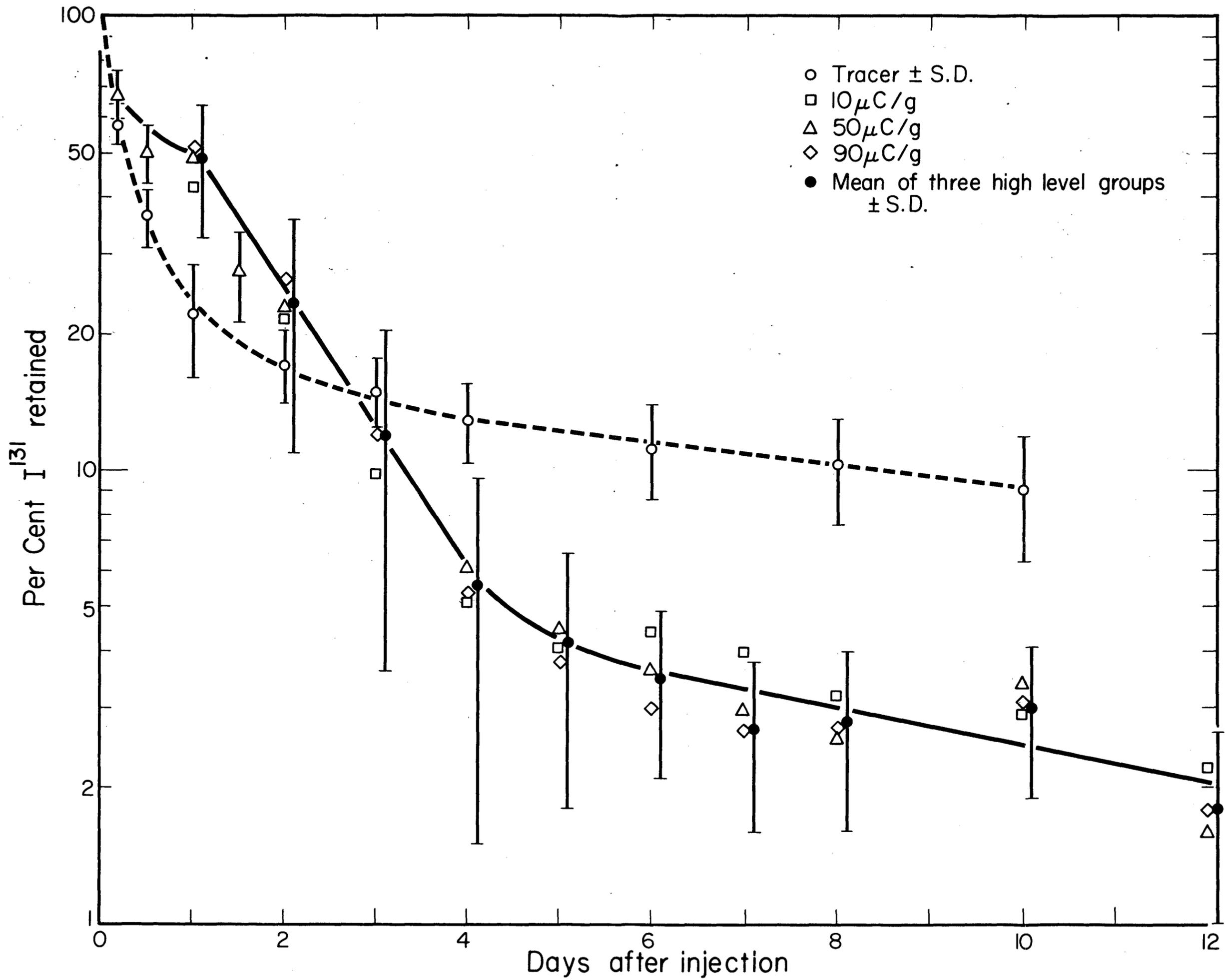
Tissue	$\beta$ dose rad	$\gamma$ self-dose r	$\gamma$ -ray dose from sur- rounding tissues r	$\gamma$ -ray dose from thyroid & stomach r	Total ab- sorbed dose rads	% $\gamma$ -ray con- tribution
Whole body	$350^a$	45	-	5 + 15	415	15
Adrenal	150	< 2	45	5 + 15	215	30
Ovary	200	< 2	45	5 + 15	265	25
Spleen	240	10	45	5 + 45	345	30
Gastric mucosa <sup>b</sup>	5600	260	45	5	5900	5
Small intestine <sup>b</sup>	500	45	45	20	610	18
Kidney	230	10	45	20	305	21
Liver	240	20	45	20	325	26
Thyroid	$1.6 \times 10^5$	20	45	20	$1.6 \times 10^5$	< 0.1

<sup>a</sup> The small difference between the energy absorbed per rad and per roentgen has been neglected, and the  $\beta$ -particle dose (in rads) and the  $\gamma$ -ray dose (in roentgens) are considered to be additive in their effect.

<sup>b</sup> Dose to gastrointestinal tract was calculated for the first three postinjection days.

## FIGURE LEGENDS

- Fig. 1. Retention of  $I^{131}$  in the rat after intravenous injection of a "tracer" dose (open circles, see footnote 4) or one of three massive doses, 10  $\mu\text{C/g}$ , 50  $\mu\text{C/g}$ , or 90  $\mu\text{C/g}$  (open figures). The numerical average for the three high-level doses is also shown (closed circles).
- Fig. 2. Accumulation and release of  $I^{131}$  by the thyroid gland of the rat following intravenous injection of a tracer dose (open circles) and a massive dose, 50  $\mu\text{C/g}$  body weight (closed circles). Tracer data are from Watts and Durbin (6) and Watts (7).
- Fig. 3. Comparison of the concentrations of  $I^{131}$  ( $\mu\text{C/ml}$ ) in the whole blood of the rat after intravenous injection of a tracer dose (open circles) or a massive dose, 50  $\mu\text{C/g}$  body weight (closed circles). Tracer data are from Hamilton et al. (5) and Watts and Durbin (6).
- Fig. 4. Retention of  $I^{131}$  in the gastrointestinal tract of the rat after injection of a massive dose of  $I^{131}$ , 50  $\mu\text{C/g}$  body weight (closed circles). Tracer data of Hamilton et al. (5) are shown for comparison (open circles).



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