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# THE DISTRIBUTION AND ACUTE EFFECTS OF LARGE DOSES OF IODINE-131 IN THE RAT

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## ABSTRACT

The investigation reported herein was undertaken in order to determine the tissues particularly exposed to radiation injury following the administration of a large dose of $I^{131}$.

The isotope distribution in the tissues of rats injected intravenously with 30 μc $I^{131}$ per gram body weight was compared with that found after a dose of 0.33 μc per gram body weight, at 7-, 14-, and 21-day intervals postinjection. The body-weight changes and the results of hematological investigations, as well as histological studies of a wide range of tissues from animals receiving these doses of $I^{131}$, are also recorded.

Apart from the thyroid gland, most of the retained isotope was in the carcass (consisting mainly of muscle, bone, and interstitial tissue) and in the pelt. Except for the pelt, the concentrations of $I^{131}$ in most of the extrathyroid tissues were similar to one another. Only the thyroid gland, the lymphoid organs, and the myelopoietic elements of the bone marrow showed evidence of radiation damage after the larger dose of $I^{131}$. It is concluded that animals exposed to heavy internal irradiation with $I^{131}$ suffer primarily from the effects of whole-body irradiation rather than from the results of specific extrathyroidal localization of $I^{131}$.

# THE DISTRIBUTION AND ACUTE EFFECTS OF LARGE DOSES OF IODINE-131 IN THE RAT

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## INTRODUCTION

The treatment of thyroid carcinoma with $I^{131}$ is now widely practiced, and massive doses are sometimes employed (see, for example, References 1, 2). Hamilton et al.[3] determined the $MLD_{60}$ (median lethal dose at 60 days) for $I^{131}$ in the Sprague-Dawley rat, and reported preliminary observations on the acute injury and mortality pattern of $I^{131}$ in the rat. No other extensive toxicological studies with $I^{131}$ have come to our notice, and the work reported here was undertaken in an attempt to analyze further the toxic actions of large doses of this isotope.

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## METHODS

Female Sprague-Dawley rats, 55 days old, weighing about 150 grams were employed. A pelleted diet (Purina Chow) and water were given ad lib. After the administration of $I^{131}$, the animals were housed in groups of three per cage; the cages were shielded from one another by 2-inch thicknesses of lead and placed about 2 feet apart in order to minimize cross-irradiation between the animals in different cages.

Carrier-free $I^{131}$ (obtained in the form of NaI from Oak Ridge National Laboratory) was dissolved in 0.9% (w/v) NaCl and injected into the surgically exposed external jugular vein under light ether anaesthesia. The doses used were 30 μc per gram of body weight and 0.33 μc per gram of body weight, the groups of animals concerned being designated the high- and low-level-dose groups respectively. Two batches of animals ("A" and "B") were injected, each batch including animals from both dose groups.

The animals in batch "A" were sacrificed at the following time intervals.

| Time (Days after injection) | Number sacrificed: High-level-dose group | Number sacrificed: Low-level-dose group |
|---|---|---|
| 7 | 5 | 5 |
| 14 | 6 | 5 |
| 21 | 7 | 5 |

After skinning, the animals were dissected, and the residue ("carcass") was passed through a meat grinder. The organs were weighed and their radioactivity measured with a gamma-ray scintillation counter.[4] Where the counting rates were too low for accurate measurement, the corresponding organs from two or more rats were pooled for assy. The results were expressed as (a) percentage of the injected $I^{131}$ present per whole organ, and (b) percentage of the injected $I^{131}$ present per gram of wet tissue.

The animals in batch "B" were used for histological and hematological studies. It was originally planned to obtain tissues from three animals in the high-level dose group at each of the time intervals studied (7, 14, and 21 days postinjection). Only seven of the nine animals given $I^{131}$ for this

purpose survived and these were sacrificed as follows — two each at 7 and 14 days after injection, and three at 21 days after injection. Three control animals were given the low-level dose of $I^{131}$. The body weights, red cell counts, hemoglobin levels, and leukocyte counts (total and differential) of all the surviving animals in batch "B" were recorded at weekly intervals. The following tissues were examined histologically — the lymphatic organs (thymus, spleen and lymph node), the salivary, lachrymal, thyroid, and adrenal glands, ovary, liver, kidney, small intestine, stomach, and portions of skin and striated muscle from a region that was anatomically remote from the thyroid gland. Tissue samples were removed immediately post-mortem and fixed in Bouin's fluid, and paraffin sections were stained with hematoxylin and eosin.

## RESULTS

Except for impairment of growth (vide infra) and apart from the two animals in batch "B" that died 3 days after receiving the high-level dose of $I^{131}$ the animals did not appear grossly abnormal.

Batch A: The concentrations of $I^{131}$ and the total amounts of the isotope present in the different organs are shown in Tables I and II respectively.

Batch B: The body weight and leukocyte changes in these animals are summarized in Figs. 1 and 2 respectively. There were no appreciable differences between the red cell counts and hemoglobin values of animals in the low- and high-level-dose groups respectively. The weights of a few of the organs from these animals are presented in Table III.

No abnormalities were detected histologically in any of the tissues from animals in the low-level-dose group. Of the tissues from the animals in the high-level-dose group, only the lymphoid organs and thyroid glands showed changes that could be attributed to radiation injury. The microscopic changes in the lymphoid tissues were similar to those observed following whole-body x-irradiation.[5] The outstanding features were shrinkage of the centers of active lymphopoiesis and diminution in the number of mature lymphocytes present. These changes were most obvious in the tissues obtained one week after the injection of $I^{131}$, progression towards the restitution of normal architecture being apparent two weeks

Table I

The concentration of $I^{131}$ in the organs of rats 7, 14, and 21 days after intravenous injection. The animals in the high- and low-level-dose groups received 30 μc and 0.33 μc $I^{131}$ per gram body weight respectively. The average values for each group are expressed as the percent of the injected dose present per gram of fresh tissue x $10^3$.

| | 7 days | | 14 days | | 21 days | |
|---|---|---|---|---|---|---|
| | Low level | High level | Low level | High level | Low level | High level |
| Bone | 4 | 1.7 | 6 | 1 | 1 | 1 |
| Muscle | 3 | 1.7 | 2 | 0.7 | 1 | 0.5 |
| Pelt | 70 | 59 | 43 | 30 | 18 | 20 |
| Thyroid | 171,700 | 4,000 | 103,400 | ...[a] | 35,000 | 175 |
| Heart | 4 | 2.1 | 1 | 0.9 | 1 | 0.4 |
| Lung | 8 | 3.8 | 4 | 2.6 | 1 | 0.8 |
| Spleen | 1 | 2.9 | 2 | 1.8 | 2 | 0.2 |
| Blood cells | 3 | 0.5 | 2 | 0.2 | ... | 0.3 |
| Blood plasma | 8 | 1.3 | 3 | 0.4 | ... | 0.4 |
| Liver | 7 | 1.2 | 2 | 0.4 | 1 | 0.3 |
| Kidney | 9 | 2.8 | 3 | 1.4 | 1 | 0.2 |
| Stomach | 15 | 4.7 | 33 | 2.3 | 2 | 0.4 |
| Small intestine | 6 | 2.2 | 2 | 0.8 | 1 | 0.3 |
| Large intestine | 5 | 2.4 | 2 | 1.3 | 1 | 0.3 |
| Pancreas | 1 | 1.4 | 1 | 0.8 | 4 | 0.1 |

[a] The thyroid glands in this group were very fragile and for this reason they were not dissected off the adjacent portion of the trachea. The values for their weights therefore are not available.

Table II

The total amounts of $I^{131}$ in the organs of rats 7, 14, and 21 days after intravenous injection. The animals in the high- and low-level-dose groups received 30 μc and 0.33 μc $I^{131}$ per gram body weight respectively. The average values for each group are expressed as the percent of the injected dose present per whole organ or tissue mass x $10^3$.

| | 7 days | | 14 days | | 21 days | |
|---|---|---|---|---|---|---|
| | Low level | High level | Low level | High level | Low level | High level |
| Bone[a] | 57 | 23.3 | 35 | 14.1 | 12 | 16.1 |
| Muscle[b] | 207 | 132 | 157 | 59 | 36 | 39 |
| Carcass | 840 | 600 | 318 | 305 | 183 | 123 |
| Pelt | 1910 | 1390 | 1280 | 885 | 568 | 527 |
| Thyroid | 4010 | 51.4 | 2860 | 1.8 | 928 | 1.8 |
| Heart | 3 | 1.4 | 1 | 0.6 | 1 | 0.1 |
| Lung | 9 | 4.7 | 5 | 3.3 | 1 | 2.8 |
| Spleen | 1 | 1.0 | 1 | 0.6 | 1 | 0.5 |
| Blood cells | 17 | 3.0 | 12 | 1.1 | ... | 1.7 |
| Blood plasma | 54 | 9.6 | 23 | 2.8 | ... | 3.2 |
| Liver | 57 | 9.9 | 22 | 3.2 | 8 | 2.1 |
| Kidney | 13 | 3.5 | 5 | 1.8 | 2 | 1.6 |
| Stomach | 13 | 4.4 | 4 | 2.3 | 1 | 1.4 |
| Stomach contents | 55 | 13.1 | 23 | 5.5 | 2 | 4.6 |
| Small intestines | 27 | 8.8 | 9 | 3.3 | 4 | 3.1 |
| S.I. contents | 55 | 9.2 | 12 | 1.8 | 2 | 3.5 |
| Large intestines | 9 | 4.0 | 4 | 2.4 | 2 | 2.0 |
| L.I. contents | 88 | 7.8 | 21 | 6.0 | 4 | 1.5 |
| Pancreas | 4 | 2.3 | 3 | 1.4 | 9 | 1.4 |

[a] Skeleton assumed to account for 8% of the total body weight.

[b] Muscle assumed to account for 45% of the total body weight.

Table III

The weights of some organs from rats (Batch B) given $I^{131}$ intravenously. The animals in the high- and low-level-dose groups received 30 μc and 0.33 μc per gram body weight respectively.

| Animal (No.) | $I^{131}$ dose level | Interval between injection and sacrifice (days) | Organ weight (mg) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Thyroid | Adrenal | Kidney | Spleen | Thymus |
| 3001 | Low | 21 | 14.8 | 37.2 | 850 | 460 | 350 |
| 3002 | Low | 21 | 14.4 | 34.6 | 780 | 620 | 401 |
| 3005 | Low | 21 | 14.4 | 45.0 | 900 | 500 | 267 |
| 2897 | High | 7 | 6.0 | 33.4 | 700 | 189 | 42 |
| 3000 | High | 7 | ... | 29.6 | 710 | 166 | 78 |
| 3003 | High | 14 | 7.8 | 28.4 | 650 | 410 | 280 |
| 3004 | High | 14 | 5.0 | 29.4 | 730 | 280 | 240 |
| 2898 | High | 21 | 3.4 | 30.5 | 580 | 440 | 396 |
| 2899 | High | 21 | 3.6 | 38.9 | 740 | 280 | 295 |
| 3006 | High | 21 | 2.2 | 32.0 | 650 | 270 | 199 |

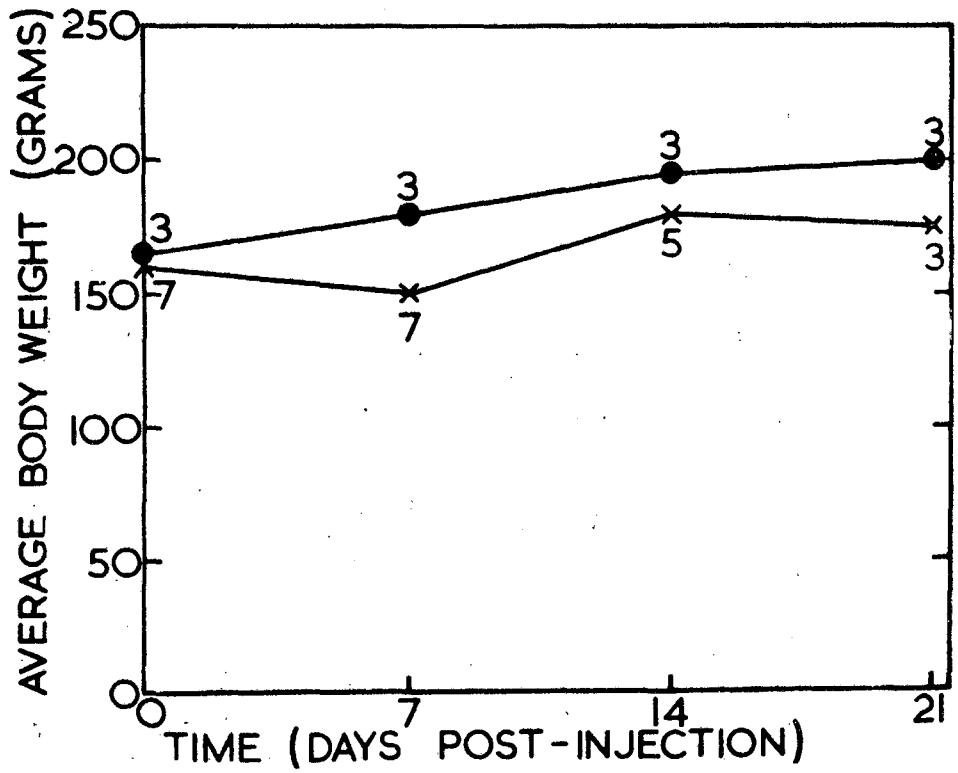


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Fig. 1. Average body weights of rats (Batch B, see text) given $I^{131}$ intravenously.

X—X high-level-dose group (30 μc per gram body weight);
●—● low-level-dose group (0.33 μc per gram body weight).
The figures beside each point indicate the number of animals upon which each average value is based.

after the injection and approaching completion by the third week of the experiment. Restitution of the normal architecture seemed to be occurring more rapidly in the spleen than in the thymus and lymph nodes, but the total number of sections examined was too small to yield conclusive evidence on this point. The thyroid glands showed extensive coagulative necrosis with karyolysis and karyorhexis of the follicular epithelium. Masses of fibrin, extruded erythrocytes, and cellular infiltration (mainly histiocytic) were present in all the sections. Invasion by fibroblasts was apparent in the thyroid remnants from the animals killed 14 days postinjection, and those from the animals killed after 21 days contained, in addition, a few large, bizarre-looking cells with hyperchromatic nuclei.

## DISCUSSION

The "high-level" dose of $I^{131}$ is about one third of the $MLD_{60}$ for the strain of rat used, and exceeds the amount needed to destroy the thyroid gland. The "low-level" dose may have been sufficient to produce a transient change in thyroid function, although no residual damage was detected histologically; the use of a smaller amount of $I^{131}$ would not have permitted accurate measurement of the radioactivity of the systemic tissues at the end of the experiment.

The results of short-term distribution studies[6,7] with tracer amounts of $I^{131}$ indicated that the isotope is widely distributed in the extrathyroidal tissues under these conditions, but could not be extrapolated directly to toxicological experiments because of the possibility that internal $I^{131}$-irradiation *per se* might alter the metabolism of iodine and hence the distribution of the isotope. The possibility of such an effect received some support from the observation that abnormal $I^{131}$-containing compounds, the metabolic fate of which is not precisely known, are present in the blood after $I^{131}$-thyroidectomy,[8,9] and from the difference between the observed behavior of large therapeutic doses of $I^{131}$ and that predicted on the basis of preliminary tracer investigations.[10] Also, toxicological investigations involve long-term experiments in which the animals remain appreciably radioactive for longer

periods of time than in tracer investigations designed to study normal metabolism.

The widespread distribution of the isotope, with the retention of appreciable amounts (Table II) in the pelt and "carcass"--which consisted mainly of muscle, bone, and interstitial tissue--and with low but fairly uniform concentrations (Table I) in most organs and tissues, indicates that a whole-body type of irradiation occurred following the administration of $I^{131}$. The relatively large amount in the pelt may have been due to contamination with urine and saliva, so it is uncertain how large a contribution to whole-body irradiation this would make under conditions in which such contamination did not occur. It appears that the administriation of the high-level dose, as opposed to the low-level dose, did not result in any gross alteration in the over-all picture of $I^{131}$ distribution in the tissues. Destruction of the thyroid gland abolishes the organification of iodine and therefore increases the urinary excretion of $I^{131}$ as iodide. This accounts for the retention of a larger fraction of the injected $I^{131}$ by the animals given the smaller dose of the isotope.

The aseptic necrosis of the thyroid gland was remarkable only for its severity, resembling the most severe lesions described in previous studies of the acute destructive effects of $I^{131}$ (see, for example References 10, 11, 12). Transient minimal histological evidence of renal injury, which was detectable up to one week after the administration of about 3 μc of $I^{131}$ per gram body weight, as well as chronic kidney damage following heavy abdominal x-irradiation, have been reported.[12, 13] We observed occasional areas, in our sections of kidney tissue, where the intensity of staining of the tubular epithelium was somewhat decreased and in which the cell outlines were slightly less distinct than elsewhere. These small changes appeared in all the sections of kidney tissue examined and were unrelated to the dose of the isotope used, or to the survival time of the rats concerned. We concluded, therefore, that it was unjustifiable to attribute them to radiation injury. The diffuse histological lesions in the lymphoid organs of animals given the high-level dose were similar to those observed after whole-body irradiation.[5] This and the profound depression of the lymphocyte count are of interest in view of the suggestion that the lymphocyte count is the most sensitive and reliable index of radiation injury following $I^{131}$-therapy.[14] The small depression of the neutrophile count is considered to indicate transient radiation injury to the myelopoietic elements of the bone marrow.

It is concluded that animals exposed to heavy internal irradiation with $I^{131}$, as in the recent toxicological studies by Hamilton et al.,[3] die primarily from the effects of whole-body irradiation rather than from the results of specific localization of $I^{131}$ outside the thyroid gland. It is also suggested that the findings presented here provide some experimentally derived indication of the type of radiation hazard to which patients given large doses of $I^{131}$, notably in the treatment of thyroid carcinoma, may be exposed.

## SUMMARY

An attempt has been made to analyze the toxic actions of large doses of $I^{131}$ in terms of the organs other than the thyroid gland exposed to the effects of internal irradiation with this isotope.

The distribution of $I^{131}$ in the tissues of rats was studied 7, 14, and 21 days after the administration of 30 μc $I^{131}$ per gram of body weight, and the results compared with data obtained after a relatively small dose of the isotope (0.33 μc per gram of body weight). Histological and hematological observations were made on both groups of animals.

It is concluded that animals exposed to heavy internal irradiation with $I^{131}$ die primarily from the effects of whole-body irradiation rather than from the results of specific localization of $I^{131}$ outside the thyroid gland.

The relationship of these findings to previous toxicological and other work involving the use of large doses of $I^{131}$ is briefly discussed.

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