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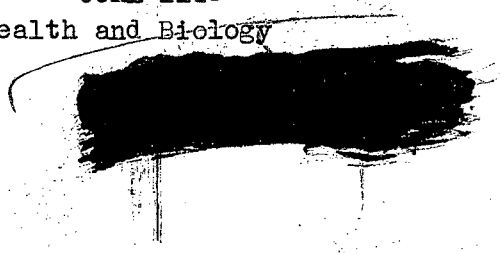

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I THE METABOLIC PROPERTIES OF VARIOUS ELEMENTS

J. G. Hamilton

Project 48A

Tracer Studies

Kenneth G. Scott and Josephine Crowley

A considerable volume of work was accomplished during the past three months in our tracer program, experiments being conducted with At^{211}, carrier-free Bi^{206}, carrier-free Mn^{52}, carrier-free $Mo^{93,99}$, Np^{237}, Ta^{182} of a fair degree of specific activity, carrier-free Sc^{46}, and high specific activity Tm^{170}.

Astatine.

J. G. Hamilton, K. G. Scott, C. W. Asling, P. C. Wallace, and G. Thilo.

The rather formidable difficulties associated with the assay of astatine in biological material has been finally solved by the use of a scintillation counter which detects the K x-rays of the short-lived Po^{211}. The disintegration pattern of At^{211} has been studied in the past by Segrè and his co-workers, and 60 percent of the disintegrations are by orbital electron capture to form Po^{211} which has a half-life of 5×10^{-3} seconds. Concomitantly, this results in the release of 90 kv x-rays. A special circuit was devised to enable the counting of these x-rays with a reasonable signal to noise ratio. The system employed was quite efficient in that approximately 10 percent of all the disintegrations of At^{211} could be counted. The employment of this procedure avoided the laborious and rather inaccurate chemical procedures necessary for the isolation of astatine so that the alpha particle activity could be counted. To insure that no impurities were present, careful decay curves were taken extending over six half-lives and were observed to coincide with the reported 7.5 hour half-life.

Table I summarizes the average values obtained following the intravenous administration of At^{211} in rats. The time intervals of sacrifice were 1, 4, 9, 13, and 24 hours. For each time interval, the values given represent the average for three rats. The rats were young females whose weight averaged 150 grams. The figures given for blood, skeleton and muscle were calculated on a basis of 7, 8, and 45 percent respectively. It will be noted that in the case of the lymph glands, lacrimal gland, and salivary gland, no figures are available on percent per organ accumulation. This arose from the fact that for these three tisues complete dissection was not achieved. Rather wide variations in stomach, small intestine and large intestine contents were noted and the percent per gram values varied over a large range from animal to animal.

In general, it can be said that the metabolic pathways of astatine, including its selective accumulation by the thyroid, resembles that of iodine

TABLE I

DEPOSITION OF AT^{211} IN THE RAT 1, 4, 9, 13, and 24 HOURS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. ANIMALS SACRIFICED AT 1, 4, and 24 HOURS EACH RECEIVED 50 MICROCURIES OF AT^{211}. THE 9 and 13 HOUR ANIMALS EACH RECEIVED 35 MICROCURIES OF AT^{211}.

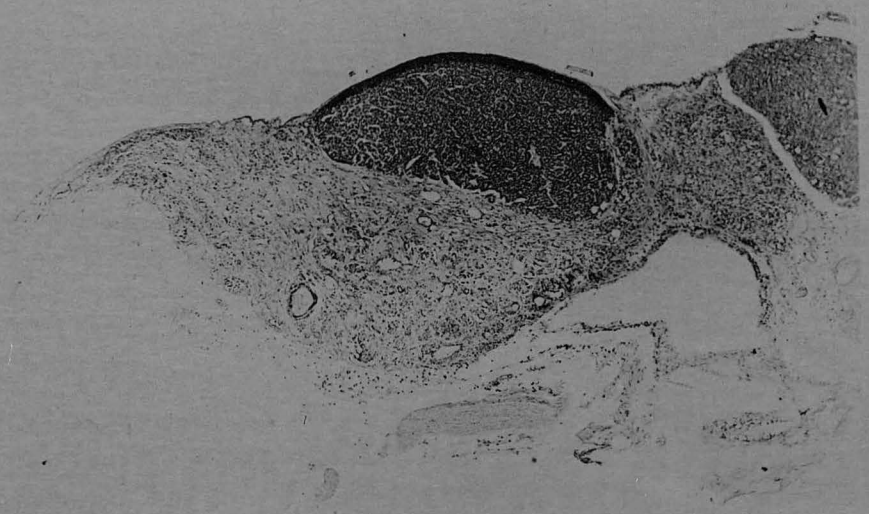
Organ	1 hour		4 hours		9 hours		13 hours		24 hours	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Adrenal	.088	1.83	.080	1.57	.057	1.00	.058	.80	.048	.96
Lymph Gland	-	.60	-	1.23	-	1.18	-	.84	-	1.05
Pituitary	.087	1.13	.020	2.77	.009	1.48	.010	1.25	.011	1.24
Lac. Gl.	-	4.89	-	.76	-	.58	-	.36	-	.84
Ovary	.156	1.81	.142	1.55	.084	1.16	.075	.93	.094	1.45
Sal.Gl.	-	.77	-	.85	-	.63	-	.42	-	.67
Eyes	.12	.43	.093	.33	.063	.24	.048	.19	.087	.32
Pancreas	.72	.94	.51	.64	.30	.47	.218	.40	.512	.61
Brain	.24	.16	.148	.09	.129	.08	.105	.07	.131	.08
Thyroid	1.24	66.7	2.09	129.0	1.88	107.0	2.75	171.0	3.28	188.0
Heart	.77	.97	.41	.60	.40	.51	.36	.51	.47	.77
Lungs	3.74	2.85	3.16	2.71	2.61	2.19	2.72	2.19	2.84	2.66
Spleen	3.61	3.48	3.00	3.10	2.14	1.95	1.31	1.45	1.73	2.54
Cells	2.40	.415	1.88	.368	2.31	.240	2.58	.265	1.51	.301
Plasma	1.71	.296	1.24	.238	1.55	.162	1.43	.145	1.06	.213
Liver	6.12	.87	4.11	.70	7.21	.84	6.33	.82	3.67	.56
Kidney	1.76	1.27	1.53	1.06	1.21	.78	1.09	.72	1.18	.97
Stomach	5.87	4.38	11.0	9.25	8.79	7.15	9.08	7.43	7.25	7.04
Sm.Int.	4.82	1.12	2.95	.88	3.51	.88	3.39	.94	2.65	1.05
Cecum	1.38	.89	.47	.61	.44	.51	.49	.48	.97	1.15
Lg.Int.	1.60	1.19	.87	.71	1.29	.83	1.06	.72	1.12	.93
Stom.Cont.	6.14	8.86	10.9	35.2	9.11	9.25	5.75	12.4	4.52	11.7
Sm.Int.Cont.	2.74	1.09	1.66	1.13	1.61	.97	1.85	1.13	2.95	1.38
Cecum Cont.	.84	.71	1.32	.95	1.00	.81	1.01	1.60	3.83	4.65
Lg.Int.Cont.	.27	1.13	.29	2.20	.08	-*	.09	-*	1.71	11.8
Skeleton	9.89	.748	7.10	.591	4.42	.403	4.74	.424	5.45	.476
Muscle	19.7	.265	16.6	.246	11.5	.186	11.6	.185	13.4	.207
Skin	22.2	.91	19.0	.83	18.4	.80	19.6	.88	18.2	.870
Urine	.94	-	8.55	-	17.9	-	19.6	-	17.3	-
Feces	.03	-	.46	-	1.84	-	2.34	-	3.72	-

*Large intestine empty, activity in organ due to washings only.

in many respects. In addition to the high uptake by the thyroid, there is noted a large concentration of this radioelement in the stomach and small intestinal fluids which has also been observed with iodine. Unfortunately, it was not convenient to secure saliva which would have been of interest since it has been noted by other investigators that following the administration of radio-iodine in man, there is a high concentration in the saliva. The data presented here are by far the most accurate tracer studies that have been done with astatine. Experiments done in the past have shown very poor recovery due to the fact that isolation of astatine from biological material is associated with considerable loss of this highly volatile element in the process of its chemical recovery.

A noteworthy point is that the urinary excretion of astatine is somewhat less than that of iodine since 17 percent was found to be excreted at the 24 hour interval whereas with iodine from 40 to 60 percent is excreted at the corresponding time interval.

Radioautographic studies of rat thyroid tissue markedly damaged by varying doses of At^{211} have been completed and representative photomicrographs are presented in Figs. 1, 2, and 3. These were the animals which had received 150, 100, and 50 microcuries of astatine, respectively. Forty days later they were given 5 microcuries of carrier-free radio-iodine by intraperitoneal injection and sacrificed 24 hours later. The photomicrographs of the sections at the three dose levels presented here revealed undamaged parathyroid tissue with marked destructive effects upon the thyroid. Another measure of the thyroid damage was determined in a parallel series of experiments in which the thyroid uptake of radio-iodine under identical conditions was determined for a wide range of dosages of astatine. Normal control figures average 20 percent in groups of five rats maintained on standard dog chow diet. The radio-iodine uptake value at the 50 microcurie dose level of astatine was found to be 5 percent; at 100 microcuries, 1 percent; and 150 microcuries, 0.5 percent. It is surprising to note such a considerable degree of radio-iodine uptake in tissues which evidence such marked injury. The radioautographs show concentration in occasional follicles which have been spared destruction. This is evident in all three of the dose levels presented here. However, considerable concentration occurs in regions in which there is no tissue identifiable as arising from the thyroid. Under high power magnification these cells are small, possess pyknotic nuclei and scanty cytoplasm. Occasionally they are arranged in rosettes, but without presence of colloid. In many instances they appear in groups without any recognizable attempt to form patterns suggestive of thyroidal acini. Finally, they have been seen to occur in strands. Another observation is that not all cells of this peculiar morphology will accumulate iodine. It will be noted that the radioautographs differ in the amount of blackening. The 150 microcurie specimen presented in Fig. 1 shows the greatest darkening of the photographic emulsion. This arose from the fact that a much longer exposure was employed in an attempt to indicate that region totally devoid tissue resembling that of the thyroid could accumulate radio-iodine. Quite deliberately no quantitative comments concerning dosimetry are presented in this account. Recently we have succeeded in successfully preparing astatine radioautographs and find that the accumulation is extremely irregular within the gland. Some acini would appear to contain from 10 to 20 times more astatine than other of comparable size and morphology. Thus to state the amount of ionizing radiation



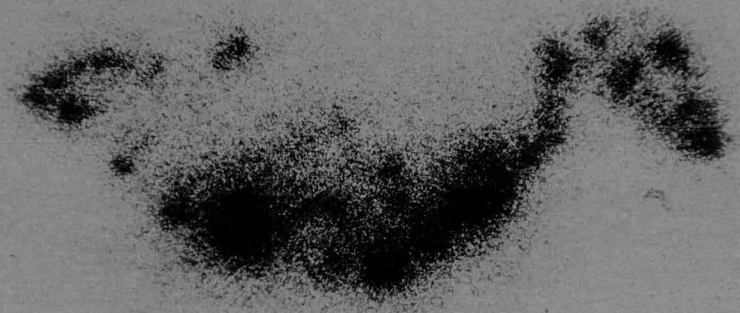
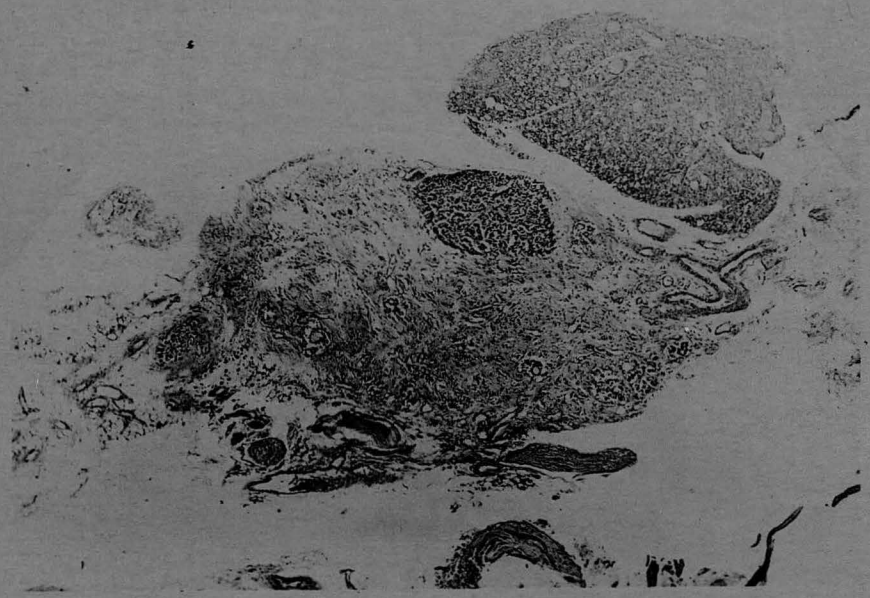


Figure 1: Photomicrograph of rat thyroid and corresponding radio-iodine radioautograph. The animal received 150 µg of At^{211}, 40 days later given 5 µc of carrier-free radio-iodine, sacrificed 24 hours later, thyroid removed, paraffin section prepared and contact radioautograph made using no-screen x-ray film. The section was stained with hematoxylin and eosin. It will be noted that the recognizable architecture of the thyroid is gone. One solitary follicle is seen towards the left and periphery of the thyroid tissue. From the radioautograph it is evident that accumulation occurs in regions where the cellular structure does not resemble thyroid tissue. The parathyroid appeared under high magnification to be unchanged.



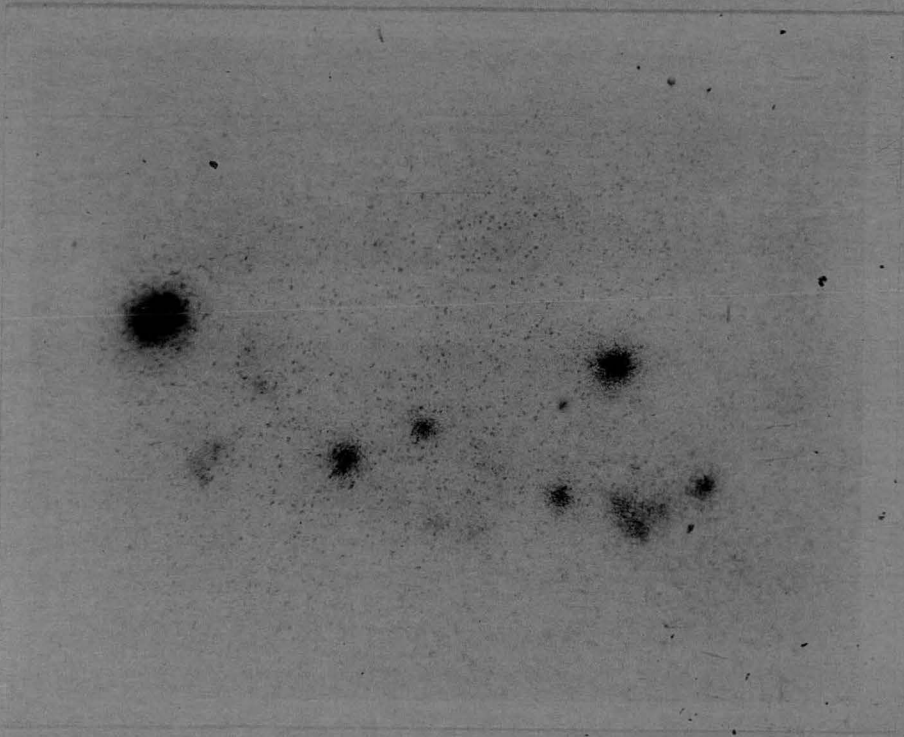


Figure 2: All procedures relating to the preparation of these specimens are the same as in Figure 1 except that this animal received 100 μc of At^{211}. The histopathological appearance is quite similar. Several rosettes of cells may be noted, a number of which contain colloid-like material and their position is demonstrated by the corresponding radioautograph.

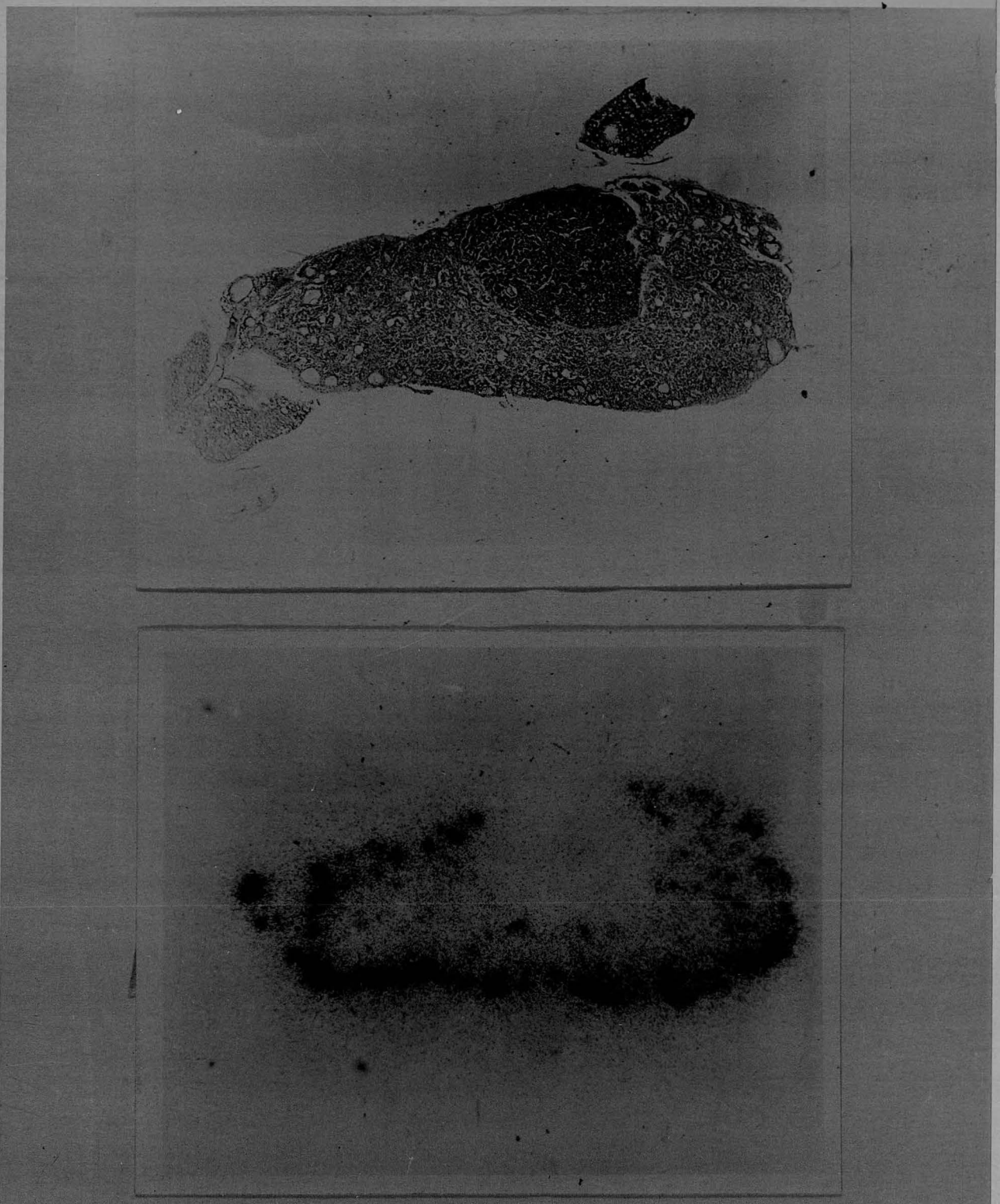


Figure 3: Experimental conditions the same as in the preceding two figures except that only 50 μc of At^{211} were given. It will be noted that the activity as evidenced by the dark spots of the radioautograph tends to be peripherally located and it can be seen from the section that most of the acini are in the corresponding positions.

delivered to the thyroid as a whole is both meaningless and misleading. An interesting characteristic which is commonly encountered in these radioautographic and histopathological studies is that the larger acini and those about the periphery of the gland generally accumulate less astatine and radio-iodine. This probably explains the rather marked peripheral deposition of radio-iodine in Fig. 3.

Currently, with the cooperation of the Division of Pathology of the Medical School, we are going over in detail not only the thyroid but other target tissues; notably stomach, digestive tract, lymph gland, spleen and lymph node, for a more precise evaluation of the degree of radiation injury at the various dosage levels which ranged from 0.5 to 150 microcuries to the 150 gram rats employed in our studies.

Very recently an interesting development in our radioautographic techniques has occurred in that we now have found it possible to prepare simultaneous iodine and astatine radioautographs upon the same thyroid sections. Carrier-free radio-iodine and astatine are administered 18 hours before the animals are sacrificed and the thyroids removed. The period for fixation, dehydration, and embedding of the tissue has been cut to 4 hours to avoid excessive loss of the astatine by radioactive decay. The sections are mounted with 10 micron NTA stripping film, developed 24 hours later, and stained by the routine hematoxylin and eosin procedure. By careful adjustment of dosages of these two radioelements, the accumulated iodine demonstrates its presence as small, rather dark granules and the astatine by the heavy characteristic alpha particle tracks. This new procedure opens up a number of interesting possibilities, particularly in a correlation between the uptake of iodine and astatine by individual acini. The results to date are of too preliminary a character for us to make any conclusive statements. Furthermore, it permits a correlation of astatine uptake and radio-iodine uptake in the same thyroid tissue which has been damaged either by astatine or radio-iodine. Finally, a program is being initiated to attempt to isolate the compounds to which astatine may be bound in the thyroid cells and thyroglobulin.

The effect of At^{211} when injected into the anterior chamber of the eyes of monkeys in relatively large doses has been investigated. The At^{211} was placed in the anterior chamber by hypodermic injection after the removal of sufficient volume from the anterior chamber to permit the injection of a similar volume of isotonic saline containing At^{211}. The At^{211} dosage in microcuries and the accompanying effects are summarized in Table II.

It can be seen that alpha particles from At^{211} can effectively damage the anterior chamber of the eye in doses greater than 1000 rep. The rate of disappearance of At^{211} from the eye was measured with a Geiger counter placed over the eye to detect the K x-ray associated with the decay of this radioelement. Astatine does not remain in the anterior chamber for relatively long periods of time. The mean biological half-time was found to be 1.3 hours in the monkey for astatine in At^{0} and At^{-} chemical states. Owing to the decay of the At^{211} the net half-life in the anterior chamber was calculated to be 1.1 hours. Thus one microcurie of At^{211} decaying by alpha disintegration is calculated to deliver 24 rep per microcurie per gram of tissue. The volume of the anterior chamber of the monkeys used in these studies was very

TABLE II

	Monkey No.1		Monkey No.2		Monkey No.3	
	Rt. eye	Lt. eye	Rt. eye	Lt. eye	Rt. eye	Lt. eye
Dose At^{211} 7/20/50	77 µc	22 µc	143 µc	55 µc	220 µc	55 µc
7/27/50	Severe iritis deep ant. chamber hazy vit. humor	Same as rt. eye to lesser degree	Conjunctivitis edema, same as monkey No.1 rt. eye, only worse	Infiltrated posterior cornea conjunctivitis iritis	Cornea hazy rough epithelium conjunctivitis edema	Normal
8/3/50	Hazy cornea wrinkled Descemet's membrane	Essentially normal	Hazy cornea	Hazy cornea hemorrhage in anterior chamber	Hazy cornea rough surface grey patch in posterior cornea	Normal
10/26/50	Cone shaped cornea split by edema fluid vascularized	Normal pupil enlarged reacts sluggishly to light.	Eyes enlarged, vascular, cornea enlarged, deep anterior chamber epithelium irregularly stippled cornea thin at apex of cone.		Completely grey cornea, sheaf of blood vessels temporal superior	Essentially normal
Calculated dose in rep	1860	530	3450	1320 (there was evidence to suggest infection)	5300	1320

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close to 0.1 cc.

The histo-pathological data is not yet available, but will be described in the next report.

As a correlated part of the experiment, the monkey which received 275 microcuries of astatine also was given 100 microcuries of carrier-free radio-iodine 24 hours before it was sacrificed. A search for the thyroid revealed no tissue grossly identifiable as thyroid gland. The trachea was removed, and by means of a counter an area was found which contained a detectable amount of radio-iodine indicating an uptake of the order of a few tenths of a percent. This radioactive tissue was sectioned and radioautographs prepared, a typical example of which is presented in Fig. 4. A careful examination of the sections revealed no recognizable thyroid tissue, as such. Clusters of cells were noted to take up sufficient radio-iodine to produce significant darkening of the photographic emulsion. However, these cells were quite unlike the normal follicular cells of the thyroid acinus. Unfortunately, it was not feasible to determine the amount of uptake of astatine by the thyroid in these animals at the same time the disappearance rate from the eyes was being studied. Since this rather small amount of astatine produced such a remarkable degree of destruction to the thyroid, additional monkeys have been procured for a more quantitative determination of the uptake of astatine by the thyroid and its destructive action. All of this work is a prelude to human studies with this most interesting radioelement with a view in mind of its possible therapeutic application to hyperthyroidism. It will be recalled from earlier reports that at dosage values well below the lethal level, marked changes were noted in the lacrimal glands and the hemopoietic system. For this reason, it is understandable that much caution must be exercised before this material can be used in humans.

Carrier-Free Radio-bismuth.

Carrier-free Bi^{206} was prepared on the cyclotron by the (d,2n) reaction on lead. The radiochemical procedures for its isolation have been previously reported. It was administered to 200-gram rats by intravenous injection and each animal received 7 microcuries. The animals were divided into groups of three and sacrificed at 2 hours, 4 hours, 1 day, 4 days, and 7 days. One group of animals had lymphosarcomatous tumors. The reason for doing these studies on a tumor bearing group of animals was that in the literature there has been reported selective accumulation of bismuth in neoplasms. The classical literature dealing with the metabolic behavior of bismuth in man and animals indicates that approximately 50 percent is excreted within a period of 3 weeks but that the remainder is most tenaciously retained, the kidney and liver being the principal organs of retention. In such studies the bismuth was administered usually by intramuscular injection. Various compounds were employed but regardless of the bismuth compound used, the metabolic behavior seemed to be quite similar. The principle organs of accumulation, both in animals and man, were the kidney and liver. Bone, while retaining an appreciable fraction, did not apparently indicate a high level of concentration on a per gram basis.

It will be seen in Table III that the carrier-free studies bear out certain of the reported information concerning the metabolism of this element

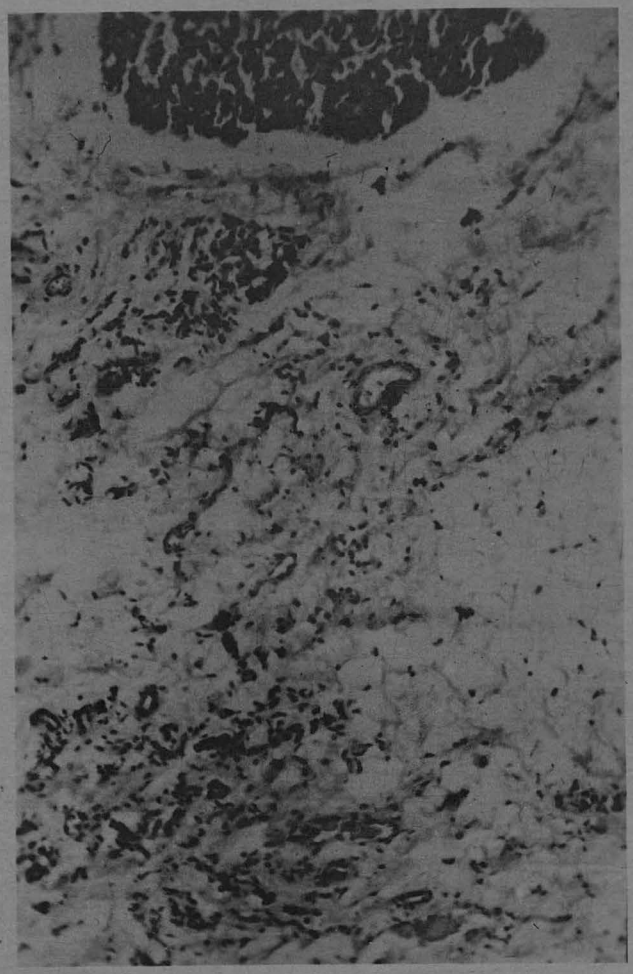

FIGURE 4

Photomicrograph of paratracheal tissue of monkey after administration of 275 microcuries of astatine (parathyroid at top of picture; thyroid aplastic)

TABLE III

DEPOSITION OF CARRIER-FREE Bi^{206} IN NORMAL RATS 2 HOURS, 4 HOURS, 1, 4, and 7 DAYS AFTER INTRAVENOUS INJECTION AND IN 3 RATS BEARING LYMPHOSARCOMAS 1 DAY AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 7 MICROCURIES OF Bi^{206}.

Organ	2 hour		4 hour		1 day		1 day tumor		4 day		7 day	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.11	.14	.08	.09	.04	.04	.02	.02	.01	.01	.01	.01
Lung	2.44	1.12	1.86	.99	.32	.15	.26	.17	.25	.10	.36	.11
Spleen	.46	.54	.52	.45	.88	.47	.72	.59	.22	.21	.27	.31
Cells	.75	.09	.39	.04	.15	.01	.10	.01	.03	.01	.04	<.01
Plasma	1.63	.27	.74	.12							<.01	<.01
Liver	19.9	2.17	24.1	2.67	11.3	1.16	13.6	1.31	6.56	.66	5.80	.63
Kidney	34.4	22.7	33.4	19.8	29.6	13.8	34.3	19.8	14.4	7.38	3.76	2.33
Stomach	.25	.17	.18	.12	.07	.05	.07	.05	.01	<.01	.02	.02
Sm. Int.	2.04	.51	1.11	.27	.40	.11	.57	.11	.04	<.01	.06	.02
Lg. Int.	1.65	.53	3.54	.81	1.46	.47	1.24	.52	.58	.14	.49	.16
Stom. Cont.	.13	.09	.10	.12	.08	.21	.02	.11	.01	<.01	<.01	<.01
Sm. Int. Cont.	5.22	1.13	2.70	.94	.80	.32	.68	.47	.06	.01	.05	.01
Lg. Int. Cont.	1.39	.50	4.21	.95	3.20	1.58	7.38	5.25	.18	.04	.19	.03
Pancreas	.22	.14	.28	.15	.14	.08	.07	.07	.06	.02	.05	.03
Skeleton	2.84	.18	2.16	.12	2.97	.15	2.32	.15	1.50	.09	1.11	.06
Muscle	3.89	.04	3.37	.03	1.37	.01	1.52	.01	.59	.006	.41	.004
Skin	6.53	.19	6.43	.18	3.76	.11	2.29	.09	.28	.01	.56	.02
Fat	-	.02	-	-	-	.01	-	-	-	.02	-	.01
Brain	.02	.02	.01	<.01	<.01	<.01	<.01	<.01	.01	<.01	.01	<.01
Eyes	.03	.11	-	-	<.01	<.01	<.01	<.01	<.01	-	<.01	<.01
Pituitary	-	-	-	-	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.08	.04	.06	.04	.02	<.01	.03	.01	.02	.01	.02	<.01
Thyroid	-	-	-	-	<.01	-	<.01	-	.01	-	<.01	-
Adrenal	.02	-	.02	-	<.01	-	<.01	-	.01	-	<.01	-
Lymph Gl.	-	.40	-	.32	-	.15	-	.26	-	.18	-	.06
Urine	16.5	-	14.7	-	35.3	-	18.0	-	56.3	-	57.3	-
Feces	.02	-	.06	-	8.15	-	4.36	-	18.9	-	29.5	-
Tumor	-	-	-	-	-	-	12.4	.29	-	-	-	-

when it was administered at levels of the order of one milligram or more per kilogram of body weight. The liver and kidney show the highest concentration per gram, and as has been previously reported, the kidneys are the principle channel of excretion. However, the rate of elimination is far more rapid than is indicated in studies in which the metabolism of stable bismuth was being studied by classical chemical procedures. At the end of 7 days over 85 percent of the administered carrier-free radio-bismuth had been eliminated, the urinary excretion being approximately twice that of the fecal elimination.

Carrier-Free Radio-Manganese.

A continuation of the preliminary studies of the metabolic pathways of carrier-free manganese has been done. In the preceding Quarterly Report, preliminary data were presented for the metabolism of this radioelement in rats following its intravenous administration. The animals were sacrificed in groups of 3, at 2 and 24 hours. Subsequently, 5 and 48 hour studies have been conducted. The outstanding observations are that this radioelement under the conditions of the experiment shows a high concentration in the liver, kidney and pancreas. The latter is of interest in that there is the possibility that it might be accumulated in the islet tissue. It is planned to undertake radioautographic studies to see if this should be the case. Excretion is almost exclusively by way of the digestive tract and it is surprising to find such a high concentration in the kidney which is not a major route of excretion. It will also be noted that there is considerable concentration in the stomach which suggests that this organ may be responsible in part for the elimination of the carrier-free radio-manganese. It would appear that the deposition in the liver is not primarily due to colloid-like behavior of this radioelement as the values for the spleen on a per gram basis are much less than the corresponding figures for the liver. The results are summarized in Table IV.

Carrier-Free Radio-Molybdenum.

A preliminary 4-hour study of the metabolism of carrier-free radio-molybdenum in the rat following intravenous administration has been done. A group of three animals received this material as $MoCl_5$ by intravenous injection and were sacrificed at the time interval indicated above. The activity measured was primarily Mo^{99} though there were traces of the shorter-lived Mo^{93} in preparation. In this very preliminary study it will be noted that excretion would appear to be fairly rapid, there being over 30 percent eliminated in the urine within the 4 hour time interval. Technical difficulties have retarded more extensive studies at this time. For the longer time intervals the 67 hour Mo^{99} is the only radioisotope of this element available. For the preparation of carrier-free Mo^{99} the only means as yet for producing it is the alpha particle bombardment of Zr^{96}. The yields obtained are quite low due to the fact that the abundance of Zr^{96} is 2.8 percent. An attempt will be made to enhance this yield by using enriched material though at present the amount available is only of the order of a few milligrams. The radio-chemical procedures used have been reported elsewhere. The results are summarized in Table V.

TABLE IV

DEPOSITION OF CARRIER-FREE Mn^{52} IN THE RAT 5 and 48 HOURS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 2.5 MICROCURIES OF Mn^{52}.

	5 hour		48 hour	
Organ	% per organ	% per gram	% per organ	% per gram
Heart	.78	.74	.25	.31
Lung	.98	.42	.82	.42
Spleen	.55	.47	.55	.55
Blood	.08	<.01	.06	<.01
Liver	26.2	2.36	18.3	1.76
Kidney	7.00	3.33	4.70	2.56
Adrenal	.06	-	.14	-
Thyroid	.02	-	.01	-
Lymph Gland	-	.45	-	.54
Pancreas	1.90	1.16	2.34	.91
Brain	.07	.05	.16	.10
Stomach	1.74	.99	1.28	.90
Stomach Content	.16	.10	.07	.02
Small Int.	4.41	.91	1.83	.37
Small Int. Cont.	5.04	1.03	1.81	.47
Large Int.	2.70	.74	1.96	.51
Large Int. Cont.	19.7	4.08	2.73	.58
Skeleton	7.10	.38	3.84	.21
Muscle	9.79	.08	10.8	.10
Skin	9.83	.21	9.49	.21
Eyes	.04	-	.04	-
Pituitary	<.01	-	<.01	-
Gonads	.91	.35	.88	.39
Urine	.02	-	.14	-
Feces	.14	-	38.4	-

TABLE V

DEPOSITION OF CARRIER-FREE MIXTURE OF Mo^{93} and Mo^{99} IN THE RAT 4 HOURS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 2.6 MICROCURIES OF $Mo^{93,99}$.

Organ	% per organ	% per gram
Heart	.19	.20
Lung	1.18	.65
Blood	2.51	.19
Liver	30.3	3.86
Kidney	2.47	1.52
Stomach	.57	.51
Stomach Content	.19	.15
Small Int.	2.62	.67
Small Int. Cont.	4.87	1.43
Lg. Int.	1.84	.39
Lg. Int. Cont.	.71	.16
Pancreas	.99	.81
Skeleton	3.58	.23
Muscle	7.20	.08
Skin	7.51	.21
Fat	-	.13
Brain	.08	.05
Gonads	.27	.13
Urine	32.9	-
Feces	.07	-

Neptunium^{237}.

A 64-day tracer study using Np^{237} has been done with a group of three rats. Each animal received 1.3 milligrams of this long-lived isotope of neptunium in solution as NpO_2^{++} with 85 milligrams of ammonium citrate and 20 milligrams of ammonium chloride. The neptunium was given by intramuscular injection. This is a group which is part of a series of studies extending to 256 days. Only 5 percent of the neptunium was retained at the injection site at the 64 day time interval. Its metabolic behavior may be noted to differ significantly from that of plutonium. The skeletal retantion is about half of what was observed with plutonium at this time interval and in this respect it resembles a little more the behavior of carrier-free uranium. Here again, the fact that this material contained a weighable amount of neptunium may have influenced its behavior as compared to being in the carrier-free state. However, shorter-term studies with the carrier-free Np^{237} suggest, but do not conclusively prove, that its deposition in the skeleton is appreciably less than that of plutonium. An interesting point is that the content in the kidney is rather high and in this respect more nearly resembles uranium than plutonium. To summarize, at the longer time intervals, the skeleton is definitely the target organ in that it shows the higher per gram retention of any of the tissues taken. It is interesting to note that the urinary excretion is much greater than the fecal elimination which shows a characteristic more like uranium than plutonium. The results are summarized in Table VI.

Radio-tantalum.

The fate of Ta^{182} has been studied in the rat. The information given here has been obtained from animals which received 10 microcuries of radio-tantalum in 200 micrograms of tantalum as Ta_2O_3 in solution. There were three animals to each group and the material was administered uncomplexed and complexed by the intramuscular and intravenous routes. The animals were sacrificed at 256 days and the data are presented in Tables VII and VIII. The intramuscular data have been corrected for the fraction remaining unabsorbed at the injection site. When given uncomplexed, 81 percent was found to be still remaining at the injection site at the end of the 256 day interval. Complexing with citrate reduced the degree of retention at the injection site to 36 percent of the administered dose. There does not appear to be any striking difference in the distribution in the body following intramuscular injection, whether or not the tantalum was complexed. Corresponding data at 64 days showed the liver and skeleton retention at that time interval to be doubled. The most striking variation is the relatively higher fecal excretion noted when the material was administered in the uncomplexed state. Some other variations in concentration in the tissues were observed, notably skin and spleen. Significantly high concentration may be noted in the skeleton. Following intravenous administration, it may be seen that there is a very high concentration in the liver and spleen. Interestingly, it may be noted that it was greater when the tantalum solution had citrate added to it. This would suggest that the tantalum was behaving as a colloid in both instances and that its true metabolic characteristics were altered under the conditions of the experiment. The degree of reliability for the intramuscular data is probably somewhat better, though the rather low specific activity of the material probably altered what would be the actual metabolic properties of radioactive

TABLE VI

DEPOSITION OF Np^{237} IN THE RAT 64 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 1.3 MILLIGRAMS OF Np^{237} AND A MIXTURE OF 85 MILLIGRAMS OF AMMONIUM CITRATE AND 20 MILLIGRAMS OF AMMONIUM CHLORIDE.

Organ	% per organ	% per gram
Heart	.33	.35
Lung	.22	.11
Spleen	.50	.58
Blood	<.01	<.01
Liver	2.78	.24
Kidney	2.01	.98
Adrenal	.03	-
Thyroid	<.01	-
Lymph Gl.	-	.18
Pancreas	.37	.27
Brain	<.01	<.01
Fat	-	.01
Stomach	1.02	.26
Sm. Int.	1.16	.11
Lg. Int.	1.25	.14
Skeleton	27.5	1.63
Muscle	3.80	.03
Skin	1.73	.04
Eyes	.01	.04
Pituitary	<.01	-
Gonads	.07	.03
Urine	37.1	-
Feces	20.1	-

TABLE VII

DEPOSITION OF TANTALUM IN THE RAT USING Ta^{182} AS A TRACER 256 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 0.20 MILLIGRAMS OF TANTALUM AS Ta_2O_5 AND 10 MICROCURIES OF Ta^{182}. THREE RATS EACH RECEIVED 4.8 MILLIGRAMS OF SODIUM CITRATE.

	256 day		256 day + citrate	
Organ	% per organ	% per gram	% per organ	% per gram
Heart	.04	.03	.12	.12
Lung	.13	.04	.30	.12
Spleen	.34	.27	.58	.56
Blood	.10	<.01	<.01	<.01
Liver	3.50	.21	4.53	.28
Kidney	.24	.08	.44	.14
Adrenal	<.01	-	.02	-
Thyroid	<.01	-	<.01	-
Lymph Gl.	-	.03	-	.51
Pancreas	.30	.05	.40	.14
Brain	<.01	<.01	<.01	<.01
Fat	-	<.01	-	.02
Stomach	.05	.01	.11	.02
Sm. Int.	.18	.01	.48	.03
Lg. Int.	.11	.01	.19	.02
Skeleton	4.52	.17	6.77	.26
Muscle	3.56	.02	5.87	.04
Skin	2.56	.04	6.40	.09
Eyes	.01	.03	.03	.09
Pituitary	<.01	-	<.01	-
Gonads	.52	.16	.77	.26
Urine	41.7	-	45.6	-
Feces	42.2	-	27.4	-

TABLE VIII

DEPOSITION OF TANTALUM IN RATS USING Ta^{182} AS A TRACER 256 DAYS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND ARE EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 0.17 MILLIGRAMS OF TANTALUM AS Ta_2O_5 AND 17 MICROCURIES OF Ta^{182}. THREE RATS EACH RECEIVED 2.4 MILLIGRAMS OF SODIUM CITRATE.

	256 day		256 day + citrate	
Organ	% per organ	% per gram	% per organ	% per gram
Heart	.13	.12	.08	.06
Lung	.29	.15	.32	.15
Spleen	.52	.53	2.89	2.37
Blood	.02	<.01	<.01	<.01
Liver	20.4	1.37	45.4	2.79
Kidney	.27	.08	.82	.27
Adrenal	.01	-	.07	-
Thyroid	<.01	-	<.01	-
Lymph Gl.	-	.80	-	.46
Pancreas	.59	.27	.27	.24
Brain	<.01	<.01	<.01	<.01
Fat	-	.04	-	.02
Stomach	.05	.01	.22	.04
Sm. Int.	.39	.02	2.43	.18
Lg. Int.	.27	.02	.64	.05
Skeleton	8.07	.31	6.05	.23
Muscle	6.37	.05	1.21	.008
Skin	11.6	.17	1.85	.02
Eyes	.02	.05	<.01	<.01
Pituitary	<.01	-	<.01	-
Gonads	.67	.27	.08	.02
Urine	32.8	-	12.0	-
Feces	17.5	-	26.2	-

tantalum in the carrier-free state, or at a level of very high specific activity. One thing which arouses suspicion is that its behavior is somewhat different from both protoactinium and columbium whose chemical properties are quite similar to those of tantalum. It is desirable that adequate studies be done using carrier-free material prepared by cyclotron bombardment. Preliminary studies using carrier-free Ta^{178} were reported earlier but their reliability is under question for reasons cited below. As will be recalled, we have been besieged with considerable difficulties to prepare carrier-free tantalum from either the deuteron or alpha particle bombardment of hafnium.

Two obstacles have retarded seriously our work in this direction. In the first place, the yields of long-lived isotopes of tantalum by the transmutation of hafnium have been discouragingly small. The radiochemical procedures employed have been described in earlier reports. The second difficulty arises from the fact that all hafnium which has as yet been available to us has contained of the order of 0.5 percent of zirconium. The yields of long-lived radioisotopes of columbium from zirconium are very high with the results that there have been present a sufficient amount of radio-columbium concomitantly produced with bombardment of the hafnium targets to make all experimental data we have secured unreliable. An attempt is being made now to secure hafnium metal in a purity of the order of 99.9 percent to avoid formation of troublesome amounts of radio-columbium, and this is to be attached to an internal cyclotron target which should enable us to increase our yield by a factor of nearly 100.

However, these data do suggest that the skeleton is a major organ of concentration of tantalum, but not to a degree that has been noted with protoactinium.

Carrier-Free Radio-scandium.

This radioisotope was prepared in carrier-free state by the (d,α) reaction on titanium. The radiochemical procedures employed have been previously reported as have the 1 day tracer experiments. Three rats were employed for each time interval and the radio-scandium was complexed with sodium citrate. It was administered to rats in groups of 3 both by muscular injection and by the intravenous route and the animals sacrificed at 1 and 15 days. In the case of the intramuscular data, the values given are corrected for the portion remaining unabsorbed at the intramuscular site of administration and the data are given in Tables IX and X. Over 70 percent was absorbed from the injection site by 24 hours and thereafter little of the remaining 30 percent apparently was absorbed. The intramuscular and intravenous data show very little differences both at the 1 day and 15 day intervals.

In the 1-day Sc^{46} studies recently reported in which citrate complexing was not employed differences are to be noted. The uncomplexed Sc^{46} following intramuscular injection showed more accumulation in the liver, but not the spleen. Excretion was more rapid and less in skin and muscle. The studies with the citrate complexed Sc^{46} are probably more reliable. The uncomplexed Sc^{46} intravenous experiments showed a striking degree of uptake by the liver and spleen which suggests colloidal behavior of the injected material.

TABLE IX

DEPOSITION OF CARRIER-FREE Sc^{46} IN THE RAT 1 and 15 DAYS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 2 MICROCURIES OF Sc^{46} AND 9.6 MILLIGRAMS OF SODIUM CITRATE.

	1 day		15 day	
Organ	% per organ	% per gram	% per organ	% per gram
Heart	.22	.26	.22	.20
Lung	.92	.45	.51	.28
Spleen	1.82	1.58	2.39	2.02
Blood	3.33	.24	.15	.01
Liver	15.0	1.49	9.32	.73
Kidney	1.61	.97	1.00	.39
Adrenal	.01	-	.04	-
Thyroid	.01	-	.02	-
Lymph Gl.	-	.68	-	.66
Pancreas	.81	.36	.27	.30
Brain	.05	.04	.07	.04
Stomach	.71	.34	.50	.15
Sm. Int.	8.06	.86	1.80	.12
Lg. Int.	4.02	.45	1.08	.10
Skeleton	17.1	1.07	13.4	.65
Muscle	14.6	.15	11.5	.10
Skin	13.4	.44	14.9	.30
Eyes	.22	.66	.02	.06
Pituitary	<.01	-	<.01	-
Gonads	.70	.34	1.00	.33
Urine	4.94	-	10.5	-
Feces	12.6	-	31.2	-

TABLE X

DEPOSITION OF CARRIER-FREE Sc^{46} IN THE RAT 1 and 15 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 2 MICROCURIES OF Sc^{46} AND 9.6 MILLIGRAMS OF SODIUM CITRATE.

	1 day		15 days	
Organ	% per organ	% per gram	% per organ	% per gram
Heart	.31	.35	.16	.14
Lung	1.15	.64	.78	.29
Spleen	3.25	2.27	1.58	1.18
Blood	5.81	.39	.17	.01
Liver	15.0	1.46	9.47	.84
Kidney	2.53	1.34	.97	.48
Adrenal	.07	-	.05	-
Thyroid	.03	-	.03	-
Lymph Gl.	-	.94	-	.76
Pancreas	.80	.48	.49	.29
Brain	.09	.05	.05	.03
Fat	-	.11	-	.08
Stomach	.86	.31	.32	.07
Sm. Int.	8.13	.80	1.41	.12
Lg. Int.	2.90	.33	1.18	.14
Skeleton	18.7	1.14	12.1	.60
Muscle	16.7	.16	15.1	.17
Skin	11.9	.35	12.7	.44
Eyes	.05	.15	.04	.12
Pituitary	.01	-	<.01	-
Gonads	.67	.32	.89	.48
Urine	4.36	-	10.0	-
Feces	6.62	-	32.4	-

As would be predicted from the behavior of yttrium and the rare earths, scandium, whose chemical properties resemble those of yttrium, shows a predilection of selective deposition in the skeleton. However it does evidence an interesting deviation from the metabolic behavior of yttrium in that there is a quite high and rather prolonged retention by both the spleen and the liver. At first thought, it might be considered that this was due to the fact that the carrier-free radio-scandium behaved in a colloid fashion, being adsorbed onto impurities in the solution and thus metabolically evidencing metabolic characteristics associated with colloids and independent of the chemical properties of the element itself. For example, for a given particle size the metabolic behavior of colloids of gold, manganese, chromic phosphate and yttrium are essentially indistinguishable when given by vein. In view of the fact that the behavior of carrier-free scandium, which was complexed with sodium citrate, was the same whether given intramuscularly or by vein. It is felt that these results are characteristic of scandium ion itself rather than a colloid-like material. Another point of interest is the fact that carrier-free scandium is shown to disappear from the skeleton more rapidly than has been noted with either yttrium or the rare earths. Rather large concentrations were noted in both the kidney and lymph glands. In the case of kidney, this is not too surprising as a considerable fraction was eliminated in the urine. In the case of lymph gland, this finding is rather surprising and one for which no ready explanation is available. It may be that scandium has a peculiar affinity for the reticulo-endothelial system as the spleen values are likewise high. At any event, it would appear that this radioelement, should it gain entry into the body, would have a relatively high degree of radiotoxicity in that it is selectively localized in organs sensitive to ionizing radiation and is apparently retained with a considerable degree of tenacity.

Radio-Thulium.

A series of tracer studies in rats with Tm^{170} have been completed. There were 3 animals in each group and 4 sets of parallel experiments set up for time intervals 1, 4, 15, and 32 days respectively. Each animal received 10 microcuries of Tm^{170} which contained 2.5 micrograms of stable thulium, this being the highest specific activity available. In the first series, the radio-thulium was administered without any complexing agent by the intramuscular route. The next group was given the radio-thulium in the presence of sodium citrate as a complexing agent. The third and fourth groups received the Tm^{170} with and without citrate, by intravenous injection.

Briefly, there are no very impressive differences in either the distribution or excretion rates at the four indicated time levels as is seen in Tables XI, XII, XIII and XIV. The content in the liver and spleen with the uncomplexed material given by intramuscular injection is somewhat higher than in the other groups and this might be due to some minor degree of colloid-like behavior following its absorption. It will be recalled that thulium, element 69, is almost at the end of the lanthanide earths whose last member is lutecium. The chemical properties of the last members of the lanthanide group resemble in many respects those of yttrium. Notably, they can be made to form stable solutions in the presence of high concentration of carbonate and there are other indications of their relatively acidic properties which is shared by yttrium. On the other hand, lanthanum hydroxide, though quite insoluble, is

TABLE XI

DEPOSITION OF THULIUM IN THE RAT USING Tm^{170} AS A TRACER 1, 4, 15 AND 32 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND ARE EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 2.5 MICROGRAMS OF THULIUM AND 10 MICROCURIES OF Tm^{170}.

	1 day		4 day		15 day		32 day	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.13	.13	.06	.06	.05	.05	.03	.03
Lung	.85	.16	.25	.12	.20	.10	.15	.06
Spleen	.50	.47	.60	.31	.36	.34	.22	.19
Blood	1.89	.13	.40	.02	.11	<.02	.07	<.01
Liver	8.92	.79	4.00	.35	2.33	.21	1.07	.10
Kidney	2.21	.91	2.04	.87	.78	.36	.46	.23
Adrenal	<.03	-	<.02	-	<.02	-	<.01	-
Thyroid	<.03	-	<.02	-	<.02	-	<.01	-
Lymph. Gl.	-	.35	-	.21	-	.23	-	-
Pancreas	.19	.09	.10	.04	.05	.03	.06	.03
Brain	<.03	<.03	.08	.06	.02	<.02	<.01	<.01
Fat	-	-	-	-	-	<.02	-	.03
Stomach	.69	.25	.25	.06	.16	.05	.10	.03
Sm. Int.	2.33	.25	.75	.06	.36	.03	.17	.01
Lg. Int.	1.80	.22	.79	.08	.29	.03	.17	.01
Skeleton	49.1	2.43	56.6	3.14	55.8	3.19	57.7	2.62
Muscle	7.91	.06	2.66	.02	1.99	.02	1.74	.01
Skin	5.23	.13	3.41	.08	3.60	.08	1.58	.04
Eyes	<.03	<.03	<.02	<.02	<.02	<.02	<.01	<.01
Pituitary	<.03	-	<.02	-	<.02	-	<.01	-
Gonads	.16	.06	.17	.06	.13	.07	.13	.06
Urine	11.7	-	19.0	-	20.8	-	19.3	-
Feces	6.30	-	8.66	-	12.9	-	17.0	-

TABLE XII

EFFECT OF A COMPLEXING AGENT ON THE DEPOSITION OF THULIUM IN THE RAT USING Tm^{170} AS A TRACER 1, 4, 15 and 32 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 2.5 MICROGRAMS OF THULIUM, 10 MICROCURIES OF Tm^{170}, and 4.8 MILLIGRAMS OF SODIUM CITRATE.

	1 day		4 days		15 days		32 days	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.07	.09	.04	.06	.04	.04	.03	.04
Lung	.35	.19	.25	.12	.13	.08	.15	.06
Spleen	.30	.36	.35	.40	.46	.39	.40	.40
Blood	.32	.02	.09	<.01	.04	<.01	.03	<.01
Liver	3.42	.45	.243	.28	1.23	.11	1.72	.18
Kidney	1.56	1.03	1.12	.72	.58	.27	.94	.46
Adrenal	<.01	-	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.20	-	.20	-	.09	-	.12
Pancreas	.11	.08	.14	.07	.03	.04	.06	.03
Brain	.02	.01	.01	<.01	.02	.01	.01	<.01
Fat	-	-	-	-	-	<.01	-	<.01
Stomach	.37	.28	.25	.08	.09	.02	.09	.02
Sm. Int.	1.24	.20	.43	.05	.29	.03	.44	.04
Lg. Int.	1.31	.22	.43	.06	.15	.02	.16	.02
Skeleton	55.0	4.20	51.2	3.75	61.2	3.34	59.3	3.16
Muscle	3.68	.04	3.75	.04	2.55	.02	2.41	.02
Skin	3.02	.11	2.71	.10	2.71	.05	2.95	.07
Eyes	<.01	<.01	<.01	.02	<.01	<.01	<.01	.02
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.13	.05	.09	.04	.13	.05	.13	.05
Urine	14.9	-	19.0	-	21.6	-	21.3	-
Feces	14.2	-	17.7	-	8.81	-	9.83	-

TABLE XIII

DEPOSITION OF THULIUM IN THE RAT USING Tm^{170} AS A TRACER 1, 4, 15 and 32 DAYS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 1.5 MICROGRAMS OF THULIUM AND 5 MICROCURIES OF Tm^{170}.

	1 day		4 day		15 day		32 day	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.08	.09	.06	.07	.04	.05	.02	.04
Lung	.49	.29	.37	.18	.26	.13	.36	.09
Spleen	.57	.64	.28	.31	.86	.73	.28	.24
Blood	.44	.03	.12	<.01	.06	<.01	.06	<.01
Liver	4.07	.59	1.98	.22	1.49	.15	.70	.07
Kidney	3.38	2.49	1.65	.93	.78	.42	.49	.26
Adrenal	.01	-	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.20	-	.15	-	.21	-	.07
Pancreas	.07	.10	.05	.05	.03	.04	.02	.02
Brain	.02	.01	.01	<.01	.03	.02	.02	.02
Fat	-	.01	-	-	-	<.01	-	-
Stomach	1.03	.49	.26	.04	.12	.04	.08	.04
Sm. Int.	2.07	.37	.50	.06	.39	.03	.17	.02
Lg. Int.	1.12	.32	.40	.09	.32	.04	.13	.02
Skeleton	63.0	4.15	67.1	4.02	60.3	4.03	68.9	4.33
Muscle	3.77	.05	2.33	.02	4.21	.04	1.92	.02
Skin	4.53	.13	3.56	.07	1.77	.05	1.49	.04
Eyes	<.01	.01	<.01	<.01	<.01	.01	<.01	.01
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.20	.09	.15	.07	.20	.07	.16	.06
Urine	13.9	-	13.7	-	13.9	-	15.5	-
Feces	1.30	-	7.41	-	15.3	-	9.78	-

TABLE XIV

EFFECT OF COMPLEXING AGENT ON THE DEPOSITION OF THULIUM IN THE RAT USING Tm^{170} AS A TRACER 1, 4, 15 and 32 DAYS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF ABSORBED DOSE. EACH RAT RECEIVED 1.6 MICROGRAMS OF THULIUM, 5 MICROCURIES OF Tm^{170} and 4.8 MILLIGRAMS OF SODIUM CITRATE.

	1 day		4 day		15 day		32 day	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.07	.08	.06	.07	.04	.04	.03	.03
Lung	.55	.22	.30	.16	.25	.13	.16	.09
Spleen	.23	.29	.31	.34	.44	.26	.23	.23
Blood	.23	.02	.12	.01	.06	<.01	.04	<.01
Liver	2.93	.43	1.88	.23	1.12	.11	.62	.05
Kidney	1.57	1.16	1.29	.76	.72	.38	.51	.21
Adrenal	<.01	-	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.16	-	.16	-	.14	-	.06
Pancreas	.07	.07	.08	.06	.03	.04	.03	.02
Brain	.02	.01	.02	.01	<.01	<.01	.01	<.01
Fat	-	.01	-	.01	-	.01	-	<.01
Stomach	.45	.25	.29	.10	.15	.07	.10	.01
Sm. Int.	1.48	.27	.51	.05	.32	.03	.21	.02
Lg. Int.	3.35	.64	.49	.09	.27	.06	.13	.01
Skeleton	61.2	3.93	59.9	3.87	62.3	3.85	58.2	3.35
Muscle	2.11	.03	2.75	.03	2.01	.02	1.29	.01
Skin	3.56	.10	3.03	.08	1.64	.04	2.12	.05
Eyes	.01	.03	.01	.03	<.01	.02	<.01	<.01
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.13	.10	.21	.10	.17	.08	.13	.06
Urine	21.4	-	20.3	-	20.6	-	18.4	-
Feces	.65	-	8.50	-	9.88	-	17.9	-

a relatively strong base. The reason for this effect is in part related to the gradual change in ionic radius as one proceeds down the list of the lanthanide group of rare earths. The apparent paradox of the observation that the ionic radius of lanthanum, element 57, is significantly greater than that of lutecium, element 71, may be explained in the following manner. Throughout the entire lanthanide group of elements, the configuration of the p electron shell remains the same and the O shell shows but minor variations. The n shell is the one into which additional electrons fill in as one passes down the series of this group of elements. This, of course, is an explanation of the remarkable chemical similarity of the entire group. The decrease in ionic radius is produced by the ever increasing nuclear charge in the series which tends to draw in the electron shells, thus reducing the ionic radius of the group which terminates with lutecium.

The occasion for discussing this arises from the observation that the metabolic behavior of yttrium and lanthanum are strikingly different in that carrier-free yttrium when given by intramuscular injection shows a relatively small concentration by the liver and of the order of 60 percent is taken up by the skeleton and retained there with an extreme degree of tenacity, considerably longer than is encountered with calcium which is a normal component of the skeleton. Lanthanum has been demonstrated to accumulate of the order of 70 percent in the liver under comparable conditions and is eliminated by it rather rapidly. The skeletal uptake is much lower than with yttrium but is firmly retained in that organ. The effect is identical whether the material be administered with or without complexing agents which is one of a number of considerations that serve to rule out the likelihood that carrier-free radio lanthanum is behaving in a colloid-like manner in the body, whereas yttrium does not. It was predicted that progressing down the series of rare earths one should therefore note a lower uptake by the liver and a higher uptake by the skeleton. These data in our estimation demonstrate this effect. It will be seen that the skeletal uptake averages close to 60 percent of the administered material and that in the course of the 32 day period no statistically significant amounts have been released from that organ.

The Movement of Sodium and Potassium in the Tissues of the Rat Following Acute Radiation Injury Using Na^{22} and $K^{42,43}$ as Tracers.

John Z. Bowers and Kenneth G. Scott.

Ionizing radiations cause chemical changes in cells which are poorly understood. This includes direct effects upon the nuclear and cytoplasmic constituents of cells, as well as indirect effects which are caused by the formation of active radicals in water present in living tissue. The sum of these effects results in the response of biological systems to radiation and is most evident in tissues which are sensitive to radiation injury. Radioactive tracers have been used in these studies in order to estimate the relative change in electrolytes of the tissues of the rat following x-ray irradiation.

Methods. Slonaker rats weighing approximately 250 grams were fed a synthetic diet, which is complete for rats, containing 24 percent purified casein, 64 percent sucrose, 8 percent hydrogenated vegetable oil, 4 percent salt mixture, and added vitamin concentrates. Potassium content was 6.9 mgms per gram and sodium 3.45 mgms per gram as determined with the flame photometer, and by estimation from the dietary ingredients.

Radioactive sodium (Na^{22}) with a half-life of 2.6 years, prepared on the 60-inch cyclotron of the Crocker Laboratory was kindly supplied for these experiments by Dr. Joseph G. Hamilton. Two microcuries of the radioisotope, a "tracer" dose, was injected subcutaneously into the experimental animals at least twenty-four hours before the start of each experiment. The radio-potassium used in these studies was prepared by bombarding argon with alpha particles from the cyclotron resulting in K^{42} and K^{43}. In order to use radio-potassium as a tracer, it was necessary to give from 50 to 175 rep to the control group as well as to the x-irradiated animals. When desired, urine and feces were separated in a modification of a rat holder suggested to us by Professor W. O. Reinhardt. This device permits accurate separation of urine and feces in the face of diarrhea. A complete separation and collection of feces in a diarrheal rat is difficult, but we believe that the figures that we have accumulated are, in general, reliable. The animal holders used gave precise separation of excreta and the only losses were from the drying of the liquid stools on the holder. Following collection and measurement of volume, the excretions were dried at 100°C for 24 hours and then ashed in the muffle at 500-600°C for a similar period. At the time of sacrifice, the animals were anesthetized with ether and heart's blood withdrawn into a syringe containing heparin. The animals were then sacrificed with additional ether and the various tissues cleanly removed. The contents of the gastro-intestinal tract were separated and the tissues washed carefully in Tyrode's solution after which they were blotted dry on filter paper. All tissues and organs were weighed wet, dried at 104°C, re-weighed, and ashed in the muffle. Ashed specimens were assayed for radioactivity by conventional G.M. counting procedures and calculated as percent of the administered dose per cc of urine, per gram of feces, or per gram of tissue. The specimens were then re-dissolved in N/10 HCl and determinations for potassium were carried out on the flame photometer (Beckman) using external standards of potassium. We are indebted to Miss Helen Johnson for the determinations on the flame photometer.

Irradiation dosage was verified with a Victoreen r meter placed in a paraffin phantom. Control animals were placed under the x-ray machine for a time period similar to that for the experimental animals and in the same holder. The dose rate and amount of filtration varied with the experiments.

Experiments 1 and 2 were designed to determine the effects of total body irradiation at approximately an $L.D._{50}$ and an $L.D._{100}$ level on the excretion of sodium and potassium in urine and feces. Dose was 710 r, 215 kv, 15 m.a. 1 m.m. Cu filter and 0.5 m.m. Al filter, and rate 77.4 r per minute in Experiment 1. In Experiment 2 the dose was 1370 r, 210 kv, 15 m.a., 1 m.m. Al and 0.5 m.m. Cu filter, with a rate of 100 r per minute.

Experiment 3 was designed to determine the effects of total body irradiation at approximately an $L.D._{50}$ level on the sodium space and the sodium and potassium content of various organs and tissues. The animals received 880 r, 215 kv, 15 m.a., with 1.2 m.m. Al and 0.5 m.m. Cu filter and were then serially sacrificed at 0 time (9 rats), 24 hours (8 rats), 48 hours (9 rats), 72 hours (8 rats), 96 hours (5 rats), 120 hours (5 rats), and 9 days (6 rats). Three rats were retained as control animals and sacrificed on the fifteenth day. Sodium space was determined for the various organs and tissues by a modification of equations proposed by Manery and Bale, and Painter.

$$\frac{\%\text{ of dose/gram tissue}}{\%\text{ of dose/ml plasma}} \times \frac{0.93}{0.95} \times 100 = \text{sodium space for organ or tissue}$$

In experiment 4, 15 control, and 15 irradiated rats were used to study the fate of potassium following x-ray. The animals were given 880 r at the same rate and filtration as in Experiment 3. The animals were divided into 3 groups and sacrificed at 24, 48, and 72 hours after irradiation. The radio-potassium was administed 24 hours before the animals were sacrificed.

Results. In Experiment 1 after receiving 710 r, the rats showed a fall of food and water intake within 24 hours. (See Table XV.) Diarrhea occurred on the third day and persisted until the seventh day. The stools were tarry on the fourth and fifth days. After the seventh day, the stools became quite bulky and were semiformed containing large amounts of mucus. One of the six animals in this experiment died on the ninth day after irradiation. Fig. 5 shows the urinary and fecal excretion of sodium plotted as the percent of the dose of the radio-sodium administered per gram of feces or per ml of urine. It can be seen that beginning with the third day after irradiation, the excretion of sodium from the rats via the feces per gram was many times greater than the control group. This effect was observed to continue until the ninth day following irradiation. The loss of sodium in the urine was depressed below the normal level during the period of high fecal output. As the apparent irradiation damage to the intestinal tract subsided, the urinary excretion increased to values greater than normal until the 15th day after irradiation at which time they returned to normal values. The apparent high fecal output of sodium appears to be related more to a reduction in stool weight rather than to an excessive loss of sodium.

Fig. 6 shows the total fecal and urinary excretion of sodium and potassium as determined with the flame photometer. A reduction of urinary sodium and potassium output was observed which reached a maximum at 4 days after irradiation and then gradually returned to the levels initially observed prior to irradiation. It must be pointed out, however, that the reduction of sodium and potassium output is in part related to the reduced intake of these electrolytes since during this time period the animals ate less food than they normally would. Even with the diarrhea observed, the total fecal output of sodium and potassium remained relatively constant. Any large variation in sodium and potassium output from normal after irradiation was accomplished by the kidneys.

In Experiment 2, the diarrhea appeared within 48 hours after irradiation. The stools were tarry. Food and water intake were promptly reduced. Urine volume fell slightly. The ratio of Na/K in the urine and feces was estimated from flame photometer analyses of sodium and potassium. The major change was observed in the urine where the ratio dropped from 0.74 at 0 days to 0.28, 0.18, 0.37 at 1, 2, and 3 days after irradiation, respectively. The ratio was reversed on the 4th day after irradiation and was 2.50. It must be pointed out that the animals were moribund at this time. Na/K ratios on normal animals were observed for similar time periods and experimental conditions. They were observed to be 0.78, 0.67, 0.50, 0.65, and 0.81 on 0 to 4 days, respectively. Similar measurements carried out on feces were less striking.

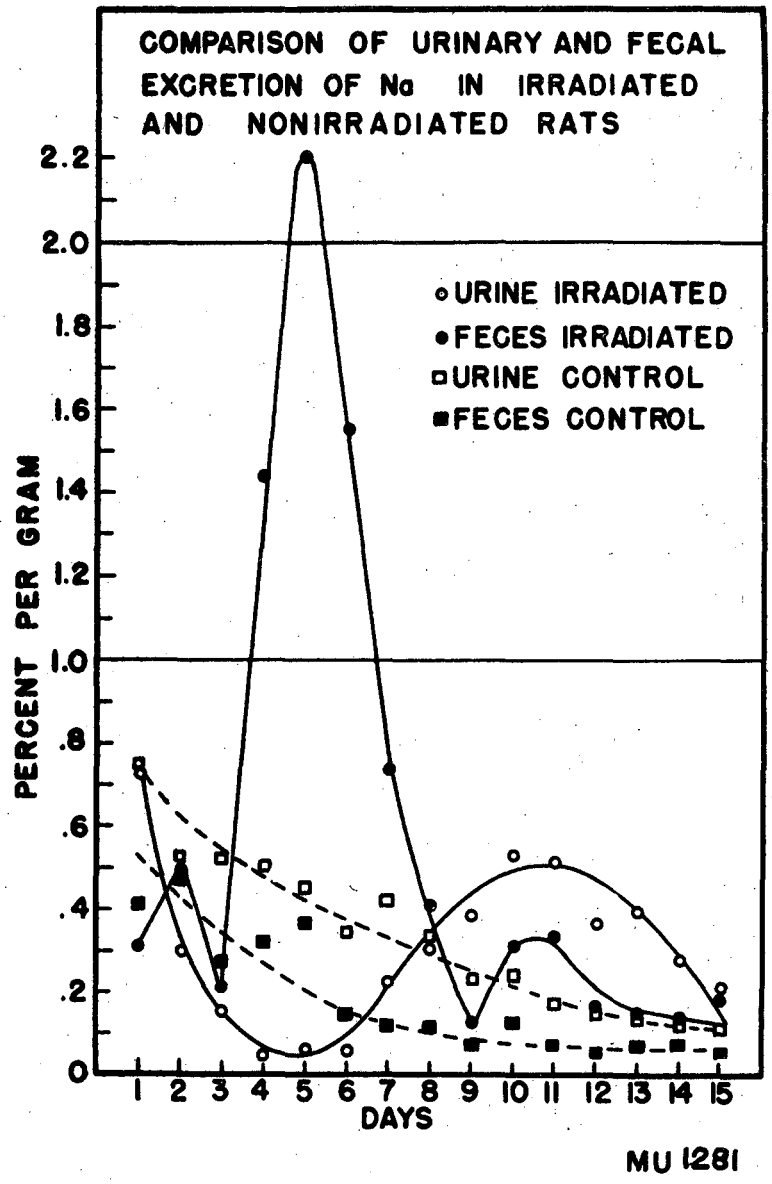
COMPARISON OF URINARY AND FECAL EXCRETION OF Na IN IRRADIATED AND NONIRRADIATED RATS
URINE IRRADIATED
FECES IRRADIATED
URINE CONTROL
FECES CONTROL
PERCENT PER GRAM
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DAYS
MU 1281

Fig. 5

FIG. 11

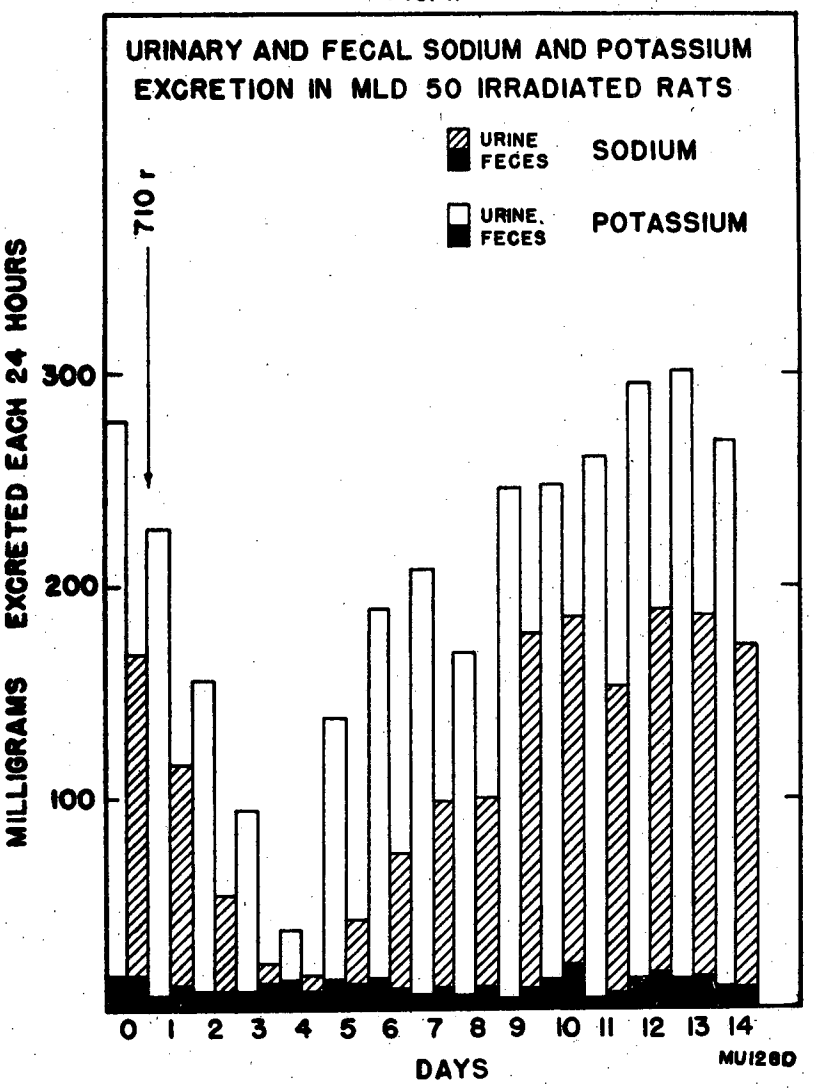
URINARY AND FECAL SODIUM AND POTASSIUM
EXCRETION IN MLD 50 IRRADIATED RATS
URINE
FECES
SODIUM
URINE.
FECES
POTASSIUM
710 r
MILLIGRAMS EXCRETED EACH 24 HOURS
300
200
100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
DAYS
MU1280

Fig. 6

TABLE XV

AVERAGE DAILY FOOD AND WATER INTAKE AND URINE OUTPUT IN RATS RECEIVING 710 r TOTAL BODY IRRADIATION

Days	Water In (ml)		Food In (gms)		Urine (ml)	
	Irradiated	Control	Irradiated	Control	Irradiated	Control
Control	22.8	16.6	22.1	21.0	8.8	7.5
Control	19.5	23.0	18.7	17.2	13.0	10.7
1	18.0	22.2	7.8	17.0	16.0	12.3
2	10.5	23.5	3.1	18.0	12.3	14.8
3	5.84	27.8	1.6	20.7	11.2	16.6
4	5.02	16.5	1.0	19.0	10.1	14.1
5	4.0	22.7	5.0	17.0	7.8	19.8
6	7.5	19.2	5.6	16.0	7.1	12.5
7	12.5	24.6	11.3	17.0	8.9	13.5
8	11.65	19.6	11.3	19.9	8.6	15.0
9	14.5	19.8	16.0	18.7	11.9	13.2
10	16.4	20.7	17.0	16.2	10.9	12.1
11	18.15	16.6	17.4	15.5	11.5	11.08
12	12.6	13.8	13.4	18.7	9.75	7.8
13	17.1	22.4	16.2	18.4	11.9	12.4
14	11.1	14.4	18.0	17.0	10.65	13.7

When approximately the L. D.$_{50}$ level of x-ray was administered to rats and in the case of this 880 r, alteration of sodium space as studied with Na^{22} was observed in tissues which were radio-sensitive. In general, the change in sodium space was composed of two components following irradiation. The first was a reduction in sodium space which occurred in the first 48 hours following irradiation. This was followed by an expansion of sodium space beginning generally at the third day following irradiation and reaching a maximum between the 4th and 9th day. For example, the reduction of the sodium space in lymph gland was 22 percent of normal on the second day following irradiation, and on the fifth day post irradiation was observed to be three times greater than normal. Similar, but less pronounced effects, were observed in the gastro-intestinal tract, spleen, and gonads following x-ray irradiation. These data are summarized in Table XVI.

Other organs of the same rats showing relatively little change of sodium space are listed in Table XVII, which includes kidney, heart, lung, liver, brain, skin, skeleton, muscle, and eyes. The plasma values for 0, 1, 2, 3, 4, 5, and 9 days after irradiation were observed to be 1.2, 1.3, 1.2, 1.3, 1.3, 1.2, and 1.5 percent of the dose of Na^{22} administered prior to irradiation per gram of plasma. No significant alteration of plasma sodium level was observed following irradiation. This may be explained in part by the ability of the kidney to maintain equilibrium, and by the fact that the radiation insensitive tissues such as muscle contain the bulk of the total sodium in the body and because of this, sodium variations were limited to tissues which represent less than 20 percent of the total body weight. In addition to the above, an expansion or retraction of sodium space could be accomplished by a change in the water content, or of the total organ weight. Measurements of the water content of several organs and tissues are given in Table XVIII. Very little variation in water content was observed. The Na^{22} per gram wet weight tissue was used to calculate the sodium space of the organs listed in Tables XVI and XVII. For this reason, any change in total organ weight would not enter into the calculation. However, the effect of irradiation upon total organ weight was determined and these data are presented in Table XIX. Some reduction of organ weight was observed and in general was consistent with the loss of weight of the animals following irradiation, and is undoubtedly mostly related to a reduction of food and water intake.

Similar studies to the ones just described were carried out for 1, 2, and 3 days after x-ray irradiation using radio-potassium instead of radio-sodium. Owing to the relatively short half-life of the isotope available, it was necessary to administer the posassium tracer 24 hours prior to the time the animals were sacrificed. This time period was considered to be the point at which almost complete equilibrium could be attained between the tracer and the other potassium in the body. Owing to the short half-life, doses of radiopotassium had to be administered which delivered appreciable radiation to the control animals. The animals sacrificed at 1, 2, and 3 days in the control group received a calculated dose of 50, 85, and 175 rep, respectively. The animals composing the irradiated groups received a total radiation of 882, 901, and 991 combined r and rep's for the same time periods.

Tissues which were shown to be radiosensitive using Na^{22} as an indicator suffered a reduction in their potassium content and/or uptake and/or exchange

TABLE XVI

DEVIATION OF SODIUM CONTENT IN PERCENT OF NORMAL IN TISSUES OF RATS ON A PER GRAM WET WEIGHT BASIS USING Na^{22} AS A TRACER AND ADMINISTERED 1 DAY PRIOR TO IRRADIATION WITH 880 r X-RAY

Organs Showing Relatively Large Alterations in Sodium Space

	Days after Irradiation							Controls
Organ	0 day	1 day	2 day	3 day	4 day	5 day	9 day	15 day
Lymph nodes	-42.	58.	9.3	70.	100.	323.	176.	41
Small Intestine	36.	33.	22.	62.	76.	67.	27.	44.
Large Intestine	50.	28.	24.	58.	76.	50.	24.	
Stomach	50.	28.	26.	33.	79.	77.	37.	54.
Spleen	-37.	35.	46.	37.	61.	54.	18.	27.
Gonads	51.	48.	39.	21.	50.	36.	43.	45.

TABLE XVII

Organs Showing Relatively Small Alterations in Sodium Space

	Days after Irradiation							Controls
Organ	0 day	1 day	2 day	3 day	4 day	5 day	9 day	15 day
Kidney	52.	63.	62.	56.	60.	45.	68.	62.
Heart	45.	49.	37.	35.	37.	47.	49.	40.
Lung	53.	35.	55.	60.	52.	64.	68.	59.
Liver	40.	38.	44.	35.	39.	40.	36.	37.
Brain	42.	49.	42.	42.	64.	63.	54.	44.
Skin	55.	33.	42.	46.	44.	47.	36.	52.
Skeleton	96.	120.	114.	96.	120.	112.	95.	104.
Muscle	25.	24.	27.	25.	23.	23.	27.	25.
Eyes	20.	86.	86.	72.	75.	91.	90.	

TABLE XVIII

PERCENTAGE WATER CONTENT OF VARIOUS ORGANS AND TISSUES OF RATS FOLLOWING ACUTE WHOLE BODY IRRADIATION OF 880 r.

Organ	0 day	1 day	2 day	3 day	4 day	9 day
Spleen	76.5	70.5	73.7	71.7	70.2	77.5
Lymph Nodes	59.1	53.5	62.7	59.5	-	-
Sm. Intestine	78.6	76.7	83.1	77.4	79.6	84.1
Lg. Intestine	71.7	75.0	79.0	77.9	77.6	84.8
Stomach	73.9	75.4	79.5	80.6	80.4	81.6
Gonads	83.1	85.1	84.8	84.7	82.3	90.3
Liver	70.0	72.9	73.4	71.0	69.9	76.1
Kidney	77.5	75.0	77.3	75.0	71.8	80.3
Brain	77.2	77.1	78.4	77.3	77.7	80.8
Lungs	71.5	76.2	75.7	73.1	72.7	84.6
Heart	73.7	69.4	79.8	76.9	73.8	80.1

TABLE XIX

VARIATIONS IN THE WHOLE ORGAN WEIGHT OF THE RAT AT VARIOUS TIME PERIODS FOLLOWING WHOLE BODY X-RAY IRRADIATION OF 880 r.

Organ	0 day	1 day	2 day	3 day	4 day	5 day	9 day
Aver.Init.Wt.	214.1	210.0	222.75	216.7	204.1	209.5	213.6
Aver.Final Wt.	214.1	210.0	211.5	188.2	172.0	172.0	150.1
Aver.Wt.Loss	-	-	11.25	28.5	32.1	37.5	63.5
Spleen	.522	.466	.422	.331	.344	.177	.304
Sm. Intestine	4.74	4.53	4.06	3.08	3.42	3.49	4.18
Lg. Intestine	2.39	2.69	2.46	2.05	1.62	1.73	2.08
Stomach	1.34	1.475	1.33	1.36	1.45	1.24	1.09
Gonad	2.17	2.28	2.25	2.01	1.92	1.99	1.80
Liver	8.12	8.68	8.59	7.59	5.64	5.32	7.33
Lungs	1.64	1.84	1.78	1.475	1.282		1.27
Kidney	2.01	1.875	1.95	1.67	1.58	1.53	1.58

when compared to relatively non-irradiated normal tissues. Tissues shown to be relatively non-radiosensitive maintained potassium levels which were normal or almost normal. These data are summarized in Table XX.

Discussion. Tissue Changes. It is interesting to compare our results with existing concepts as to the sensitivity of lymphatic tissue, spleen, germinal epithelium, and gastro-intestinal mucosa to radiation injury as compared with other tissues and organs in the body. The rapid and pronounced loss of potassium from the organs containing these tissues, with the exception of the gonad and germinal epithelium, is obvious. However, quantitative interpretations of this loss on the basis of the relative sensitivity of these tissues are made difficult by the fact that several of these organs are composed of insensitive, as well as sensitive tissues. The early loss of sodium from these sensitive tissues is difficult to explain, except as an effort to maintain osmotic equilibrium in the face of extensive potassium loss and the formation of osmotically active chemical fragments within injured cells as would accompany the breakdown of large protein moieties. Probably this loss of sodium from the tissues accounts for the swelling of cells which is a characteristic manifestation of radiation injury. The subsequent expansion of sodium space in these tissues should represent the penetration of sodium into cells which have been severely damaged. Probably the potassium levels in lymph nodes and spleen would have fallen even lower had there not been extensive hemorrhage in these organs.

Further inspection of the results reveals that alteration in electrolytes are not restricted to sensitive tissues, but that less pronounced deviations appear in lungs, kidney, and heart. In general, these organs show a loss of potassium which is most pronounced 48 to 72 hours after the radiation injury occurs. Since these losses were evident before diarrhea ensued, it might be assumed that this is a manifestation of radiation injury.

Perhaps the injurious effects of radiation are not localized more or less specifically to so-called sensitive tissues, but while the changes are more pronounced and are "irreversible" in these tissues; other tissues show a less pronounced and "reversible" radiation injury.

In recent years, there has been increased emphasis on the role of bone in sodium metabolism since large stores are present there and it has been suggested that sodium in the bone reservoir is not easily available in circumstances of sodium depletion. Our data suggest that sodium can move into bone for "stockpiling".

Urinary and Fecal Loss. Loss of diarrheal stools on the animal holders affects the accuracy of the figures on quantitative loss of electrolyte, but several facts are obvious and interesting. In the diarrhea of acute radiation injury there is a sharp rise in the concentration of sodium and potassium in the stool, which is generally in proportion to the severity of the injury. This is not surprising in view of the extensive cellular destruction in the gastro-intestinal mucosa with loss of intracellular potassium into the lumen, as well as the movement of potassium out of cells in more remote segments of the body. In addition, large amounts of extracellular fluid with a high sodium content appear in the bowel.

TABLE XX

DEVIATION OF POTASSIUM CONTENT IN PERCENT OF NORMAL IN TISSUES OF RATS ON A PER GRAM WET WEIGHT BASIS USING RADIO-POTASSIUM AS A TRACER ADMINISTERED 24 HOURS PRIOR TO SACRIFICE OF ANIMALS AND FOLLOWING X-RAY IRRADIATION EQUAL TO 880 r.

Relatively Radiosensitive Tissues

Tissue	Days Following Radiation 1	2	3
Lymph nodes	38.	66.	62.
Small Intestine	83.	59.	65.
Large Intestine	98.	77.	82.
Stomach	94.	81.	84.
Spleen	91.	84.	90.
Gonads	N*	93.	93.
Thymus	-	37.	70.

Relatively Radiosensitive Tissues or Fluids

Kidney	N	91.	N
Heart	N	90.	94.
Lung	N	82.	85.
Liver	N	N	111.
Brain	N	N	87.
Skin	N	87.	92.
Skeleton	94.	66.	78.
Muscle	N	N	N
Red Cells	115.	92.	94.
Plasma	133.	N	133.

Percent or Potassium Excreted

	Normal	Irrad.	Normal	Irrad.	Normal	Irrad.
Urine	9.7	10.1	6.7	9.8	3.4	7.9
Feces	0.5	0.5	0.8	0.8	0.5	1.8

*NOTE: A deviation of less than $\pm$ 5 percent is given as normal.

Data on the urine indicate the ability of the kidney to conserve sodium in the face of impaired intake and excessive fecal loss. In the case of potassium, however, renal defensive ability is not so apparent. The ability of the kidney to retain sodium so promptly and significantly suggests that adrenal cortical function was not depressed at these dosage levels.

Summary. Acute radiation injury is characterized by heavy and early losses of potassium from sensitive tissues (irreversible injury), and less pronounced but significant losses from a number of other tissues (reversible injury). In sensitive tissues, there is an early loss of sodium, but subsequently a penetration of sodium into damaged cells, as indicated by an expansion of sodium space. There are no characteristic or significant changes in the water content of the various organs demonstrated in these experiments. The data indicate that potassium may move out of radiosensitive tissues following irradiation.

Chelating Experiments

Harry Foreman

In the last Quarterly Progress Report, UCRL-960, data was presented which showed that the administration of certain chelating agents, namely calcium ethylene diamine tetracetic acid (Ca EDTA) and Fe-3, to rats carrying a body burden of Pu^{239} resulted in marked increases in the urinary excretion of the radioelement over that in similar animals which received no treatment. As a follow-up to these observations, a new series of *in vivo* chelating experiments are now being planned and set up. The primary aim of these experiments is to determine how much of plutonium which has become well fixed in bone can be removed from the body by the use of these chelating agents.

Pu^{238} instead of Pu^{239} is to be employed in this experiment because of the 200 fold increase in specific activity. This is deemed important as the plutonium concentration in the tissues and body fluids will approach levels that may be encountered in man.

A series of preliminary experiments are now in progress in order to determine the optimum conditions for running the key experiment indicated above. Previous work has shown that these agents are effective by mouth since they are readily absorbed through the G.I. tract. These preliminary experiments are being run to learn the effects of prolonged day-to-day administration of these drugs and to determine the maximum amount of these chelating agents that can be incorporated into a stock feed and still have a diet which is tolerable to rats. So far, four groups of animals have been set up. The first group has been fed a stock diet containing 10 percent Ca EDTA. A second group received 5 percent Ca EDTA in the food. The third group was fed 10 percent Fe-3 and the fourth group, 5 percent Fe-3. After ten days the animals receiving 10 percent Ca EDTA in their food died. It was noted that they ate an average of 5 grams each daily of this diet as compared to control animals which took in an average of 11-12 grams daily. The animals developed diarrhea on the second day of the diet. Diarrhea was very marked and continued throughout the experiment. On the fourth day the animals were noticeably lethargic and the condition of the fur was very poor. By the time of death, the animals had lost approximately one-third of their body weight in the time period of the ten days. Autopsy revealed markedly distended and thinned out cecum with evidence of hemorrhage in the region of the rectum. The remainder of the gut was also somewhat dilated. There were no other visible changes grossly manifest in any of the other organs except in the fur as indicated above. Sections of liver, kidney, large intestine and small intestine were taken for histological study. Reports on this will be forthcoming later.

On the 27th day of the experiment the animals receiving the other diets are still alive. All of the animals developed diarrhea on the second day of the experiment. The animals receiving 5 percent Ca EDTA still have diarrhea. The other animals, namely the animals fed 10 percent Fe-3 and 5 percent Fe-3, began to have semi-formed soft stools on the 14th day of the experiment. It is interesting to note that after a diminished intake for the first 3 or 4 days, all of the animals are now taking the same amount of food as the control animals, namely 11-12 grams each daily. It is planned to

continue this experiment for at least a month more, or until the animals die.

Animals are being set up which will receive 3 percent and 1 percent of each of the chelating agents in their food. It is in this level of feeding that the key experiment will probably be set up.

Radiochemistry

W. M. Garrison, H. R. Haymond, J. D. Gile and D. Morrison

Carrier-Free Pd^{103} from Rhodium.

The 17-day Pd^{103} was prepared by (d,2n) reaction on rhodium. The bombarded rhodium metal was fused with $KHSO_4$ and the melt was leached with water. After centrifugation, the solution was adjusted to 6N with HCl and the solution was saturated with SO_2 after the addition of 20 mg of selenious acid. Ninety-eight percent of the carrier-free Pd^{103} co-precipitated with the Se metal. Rhodium was retained in the supernatant. After two reprecipitations to remove traces of rhodium, the Se precipitate containing the Pd^{103} was transferred to a distilling flask and Se was separated by distillation with the addition of HBr. The H_2SO_4 residue containg the Pd^{103} was evaporated to dryness. HCl was added and the resultant solution was evaporated down on NaCl.

Carrier-Free $Mo^{93,99}$ from Zirconium.

The $Mo^{93,99}$ was prepared by (α,xn) reaction on zirconium. The ZrO_2 target material was dissolved in HF and the resultant solution was evaporated to incipient dryness. HNO_3 was added and the ZrF_4 precipitate was removed by centrifugation. The carrier-free $Mo^{93,99}$ was quantitatively retained in the supernatant. HCl was added in excess to destroy HNO_3 and the solution was adjusted to 6N HCl. The Mo activity was extracted into ether and back-extracted with H_2O.

Carrier-Free W^{181} from Tantalum.

The 180-day W^{181} was prepared by (d,2n) reaction on tantalum. The Ta target was dissolved in HF-HNO_3 and the solution was slowly added to NH_4OH with stirring. The tantalum hydroxide precipitate was centrifuged off; the carrier-free W^{181} was recovered in the supernatant. Several reprecipitations were required to separate the W^{181} quantitatively. The supernatant solutions were combined and treated with excess HNO_3 to remove HF and ammonium salts. Previous studies indicate that further purification of the W^{181} can be obtained by ether extraction from HCl solution.

Carrier-Free $Ta^{177,178,182}$ from Hafnium.

The carrier-free radio-tantalum was prepared by (d,xn) reaction on hafnium. The HfO_2 was dissolved in HF and the resultant solution was evaporated to incipient dryness. Ten normal HNO_3 was added. HfF_4 was separated by centrifugation. The tantalum activity remained in the HNO_3. Ten milligrams of $KMnO_4$ were added and activity was quantitatively co-precipitated with the MnO_2. Separation of the MnO_2 and the carrier-free tantalum activity was effected by use of a previously reported procedure.

Other Activities.

The following carrier-free radioactivities were separated from cyclotron targets using previously reported procedures: Cr^{51}, $K^{42,43}$, $Bi^{204,206}$, Mn^{52}, and At^{211}.

II BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge

Project 48 A-1

The Effect of Specific Liver Irradiation on the Chromic Phosphate Disappearance Constant

Ernest L. Dobson

Introduction.

The rate constant for the disappearance of intravenously injected colloidal chromic phosphate from the blood stream has been used as an index of liver blood flow[1].

In order to study the effects of radiation on the liver circulation large doses of radiation were given to both rabbits and mice. In short term experiments possible complications in the measurement of the chronic phosphate disappearance rate shortly after the administration of an irradiating dose due to the presence of residual traces of chromic phosphate in the blood stream were avoided by using an isotope with a much shorter half life than P^{32} for administering the irradiation. For this purpose the yttrium isotope of mass 90 was incorporated into an yttrium-hydroxy-citrate colloid, the preparation of which is described elsewhere[1].

The Calculation of Irradiation Dosages.

To calculate the irradiation dose, the amount of energy delivered and the mass of the tissue receiving this energy must be known. One microcurie represents 3.7×10^4 disintegrations per second. The two isotopes used in these irradiation experiments are P^{32} and Y^{90}. They are pure beta emitters and their beta rays have a maximum energy of 1.71 and 2.35 million electron volts respectively. The average energy of the P^{32} betas has been measured[2] and found to be 0.695 Mev. The average energy of the Y^{90} betas may be approximated by the rule that the average energy is equal to one third of the maximum.

Using the above data and the factor 1 Mev = 1.6×10^{-6} ergs, it can be shown that one microcurie of P^{32} will deliver energy at the rate of 3560 ergs per day. If it is allowed to decay completely it will deliver a total of 7.4×10^4 ergs. One microcurie of Y^{90} will deliver energy at the rate of 4000 ergs per day; and if it is allowed to decay completely it will deliver a total of 1.56×10^4 ergs.

P^{32} has a half-life of 14.3 days and nearly two months are required for 95 percent decay, while Y^{90} has a half-life of 65 hours and eleven days are required for 95 percent decay. In order to give a total of 830,000 ergs per gram of tissue (10,000 r.e.p*), 11.2 uc/gm of P^{32} and 53.2 uc/gm of Y^{90} must be given.

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* r.e.p. stands for roentgen equivalent physical and corresponds to an energy dissipation of 83 ergs per gram of tissue.

The Effect of Specific Liver Irradiation on the Chromic Phosphate Disappearance Constant in the Rabbit.

The rate of disappearance of chromic phosphate from the blood stream of a rabbit has been studied before and after doses of irradiation amounting to 2,300 and 16,000 r.e.p. The irradiation was administered by injecting chromic phosphate containing the radioisotope, P^{32}. The specific localization of this material in the liver and spleen makes it an ideal agent for giving beta radiation to these organs.

The rabbit is different from the dog, rat, and mouse in that about five percent of the injected dose localizes in the bone marrow. This is from three to five times as high an uptake as is exhibited by the bone marrow of the mouse.

The chromic phosphate disappearance constant was measured on a 2.4 kilogram rabbit with a tracer dose of the suspension. The disappearance constant was found to be 0.97 $min.^{-1}$ Following this measurement, 440 microcuries of chromic phsophate were given for the purpose of irradiating the liver. After two months, when 95 percent of the available energy from this dose had been exhausted, the disappearance constant was measured again, employing another tracer dose of chromic phosphate. In this two months period, the rabbit had increased in weight to 4.1 kilograms, and the disappearance constant had fallen to 0.57 $min.^{-1}$ The total energy dissipated in the liver amounted to 1.9×10^5 ergs per gram of liver tissue (2,300 r.e.p.). The probable liver weight was estimated from a scatter diagram of liver weight vs. body weight and it was estimated that about 80 percent of the injected chromic phosphate was localized in the liver.

After the completion of this measurement of the diaappearance constant, the rabbit was given a second irradiation dose of 2.35 millicuries of chromic phosphate. This, in addition to the previous dose, gave a total of 1.3×10^6 ergs per gram of liver tissue or 16,000 r.e.p. Six months later the rabbit weighed 4.9 kilograms, a gain of 20 percent in body weight; but the constant for the disappearance rate of chromic phosphate had fallen to 0.092, a value equal to one tenth of the original pre-irradiation rate constant. The above data are summarized in Table I.

The rabbit died four months after the final measurement. The body weight at the time of death was 5 kilograms, and the animal was very fat.

The liver weighed 1.25 grams which is well within normal limits. Grossly it had a somewhat mottled appearance suggesting either fatty or necrotic areas. Microscopically, the cells seemed abnormally vacuolated, and a large portion of the nuclei were pyknotic.

The central portions of the lobules were apparently harder hit than the more peripheral parts. The cells directly adjacent to the central veins showed considerable hyaline degeneration. This was not in evidence elsewhere in the liver parenchyme. There also seemed to be a subcapsular hyperemia.

TABLE I

THE EFFECT OF IRRADIATION ON THE CHROMIC PHOSPHATE

DISAPPEARANCE CONSTANT

Time Months	Rabbit Weight Kgm.	$CrPO_4$ given for Irradiation.	Energy Dissipation		$CrPO_4$ Disappearance Constant as Calculated from the Fast Component.
			Ergs per gram of Liver Tissue.	r.e.p.	
0	2.4	440 µc	None	None	0.97
2	4.1	2.35 mc	1.9×10^5	2,300	0.57
8	4.9		1.3×10^6	16,000	0.092
12	5.0		Rabbit died		

This rabbit died during the night and was not discovered until the following morning so that the tissues may have been considerably autolysed. This of course throws some doubt on any interpretation of the histological findings.

Any general parenchymal damage may have been due to autolysis and the subcapsular hyperemia could be caused by the settling of the orythrocytes, however, the hyaline degeneration which was found at the center of the lobule and which was not found elsewhere may possibly be attributed to causes other than autolysis.

Unfortunately the phagocytic efficiency of the liver was not determined, so that the relative effect of the efficiency and the liver blood flow could not be ascertained. However, it is quite clear that irradiation with a liver localizing colloid such as chromic phsophate produces a marked effect on one of the following: the efficiency of the liver phagocytes, the liver blood flow, or both of these entities simultaneously.

The Disappearance Curves in the Irradiated Rabbit

The three chromic phosphate disappearance curves which were obtained on the rabbit of the previous section are shown together in Fig. 1. These curves have been normalized to made the zero time intercepts coincide.

The change in the curve with irradiation is very pronounced. The second curve shows a relatively large fraction, approximately 50 percent, of a second component with a half time of about five minutes. In the normal animal, there is usually a second component present, but it amounts to only about 5 or 10 percent of the total. It has been suggested elsewhere[1] that the second component may be due to the presence of small particles which are less efficiently phogocytized, and it may be that owing to irradiation the individual Kupfer cells have become damaged so that they are able to handle efficiently only the very largest of the particles. This would in essence amount to raising the particle size threshold and increasing the number of functionally small particles in the suspension, thus increasing the contribution of the slow component. Another possibility is that the individual Kupfer cells are affected by the irradiation so that they are saturated more quickly than usual, which would amount to lowering the particle number threshold, with resulting lowered efficiency of the liver phagocytic system as a whole and a lowered rate of disappearance for the chromic phosphate. However it is the first or most rapidly disappearing component which is a measure of the liver circulation.

The Effect of Specific Liver Irradiation on the Chromic Phosphate Disappearance Constant in the Mouse.

Irradiation with Yttrium-Hydroxy-Citrate Colloid

Fifteen Swiss mice (11 males and 4 females) were given approximately 700 microcuries of a colloid containing yttrium 90. Three of these mice were

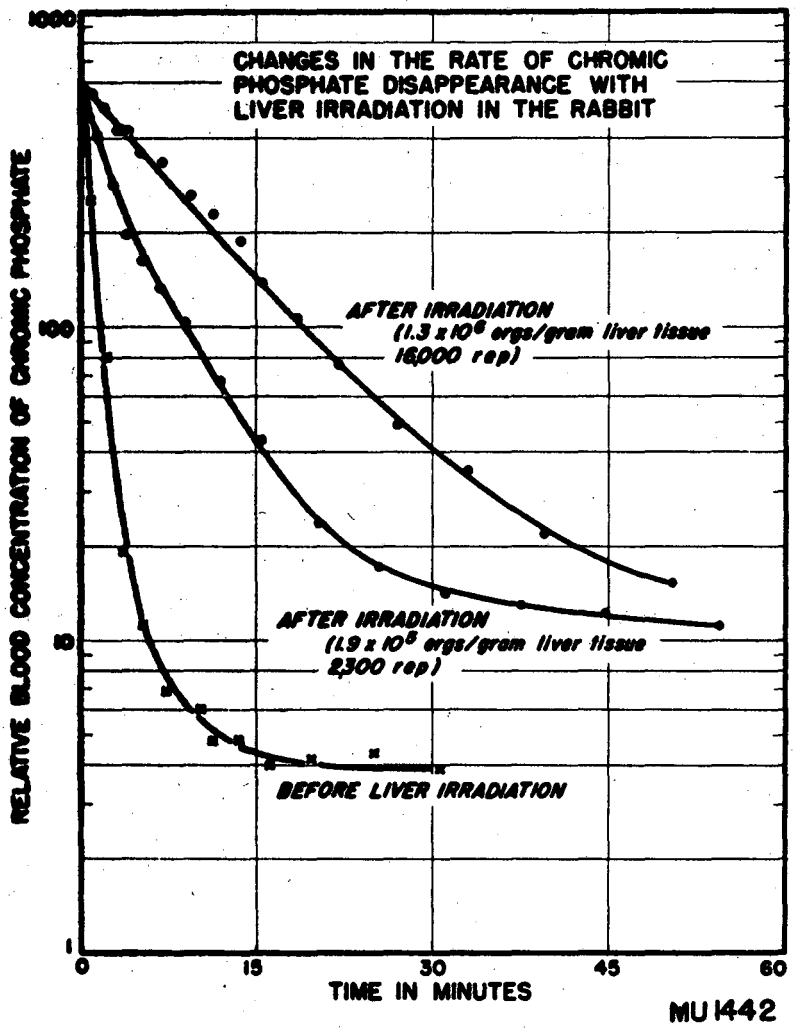

Fig. 1

The graded slowing of the chromic phsophate removal rate following graded doses of irradiation is illustrated above. The fast components obtained by subtracting the slow components from the complex curves are: before irradiation $T_{1/2}$ = 43 seconds; after 1.9×10^5 ergs per gram of liver tissue $T_{1/2}$ 73 seconds; and after 1.3×10^6 ergs per gram of liver tissue $T_{1/2}$ = 7.5 minutes.

killed after two days. The tissue analysis showed about two-thirds of the injected material in the liver (range 55-78 percent). The uptake by the spleen was even more varied. One showed 4 percent, one 20 percent and one 30 percent of the injected material localized in the spleen. The combined liver plus spleen uptake was considerably more constant. The values for the three mice were 82, 88, and 87 percent uptake by these two organs.

Although the spleen uptake of chromic phosphate is somewhat variable, no such wide variation has ever been observed as that with the yttrium-hydroxy-citrate colloid described here.

One microcurie of yttrium 90 will emit about 166 ergs per hour. Jones, Wrobel and Lyons[3] have calculated that for beta particles whose half thickness for tissue absorption is one millimeter, which is just the calculated half thickness for yttrium 90, the mouse liver retains 75 percent of the radiant energy arising from a source homogeneously distributed within the liver. Thus each microcurie of yttrium 90 which is homogeneously distributed throughout the liver will deliver energy to the liver tissue at the average rate of 125 ergs per hour. It is to be noted, however, that the surface and the thin edges of the liver will receive less radiation than the central portions due to geometrical factors.

The livers of these animals apparently took up only about two thirds of the 700 microcuries injected so that the total rate of energy absorption averaged about 5.8×10^4 ergs per hour at the time of injection.

The mouse liver averages about 6 percent of the body weight so that the average liver weight for this group of mice is 1.7 grams. This gives an initial tissue dose rate of 3.4×10^4 ergs per gram of tissue per hour (410 r.e.p. per hour).

The total dose delivered in any time is the product of the dose rate and the time interval; but since the dose rate is continually changing due to radioactive decay of the yttrium, this product must be obtained through integration.

$$D = \int Idt = \int_0^t I_0 e^{-\lambda t} dt$$

Here D is the total dose, I the dose rate at any time and I_0 the dose rate at the time of injection, t the time, e the base of the natural logarithms and λ the decay constant for Y^{90}.

After the injection of the Y^{90} colloid, the mice were weighed and the chromic phosphate disappearance constant was determined at frequent intervals. The data obtained have been summarized in Table II and in Fig. 2.

Table II represents a protocol of the experiment. The estimated initial irradiation rate for each mouse is given, followed by the body weight at approximately daily intervals. Also included is the time of death for each mouse and certain other information such as tissue distribution.

TABLE II

DAILY RECORD OF THE MOUSE LIVER IRRADIATION EXPERIMENT
(Irradiation with Y^{90} Colloid)

Mouse No.	I_0 ergs/gm per hour	Body Weight Days After Injection 1	2	3	4	5	6	8	9
1	3.4×10^4	28.3	27.7		25.4	22.9	died		
2	3.3×10^4	29.3	28.0		26.3	25.4		22.4	died
3	3.0×10^4	32.3	29.8		28.6	27.6		25.3 Killed for histology	
4	3.4×10^4	28.6	26.8		23.9	22.5		died	
5	3.7×10^4	26.9	25.6	Injected $CrPO_4$ in portal system					
6	4.1×10^4	24.1	21.8		20.2	Injected $CrPO_4$ in portal system. 50% went through liver.			
7	2.7×10^4	28.1	26.5		23.7	21.8	died		
8	3.1×10^4	30.5	28.7		25.4	24.8 Killed for histology			
9	4.5×10^4	21.5	19.7	Killed for distribution study (Liver 68%, Spleen 20%)					
10	3.3×10^4	29.3	28.5		26.8	25.5		died	
11	2.8×10^4	33.8	32.9	Killed for distribution study (Liver 78%, Spleen 4%)					
12	3.1×10^4	30.7	29.1		27.0	died			
13	3.9×10^4	24.6	22.6	Killed for distribution study (Liver 55%, Spleen 31%)					
14	3.2×10^4	29.7	27.1		24.8	23.3		20.6 died	
15	3.8×10^4	25.0	23.3		20.6	19.6		died	
Average	3.4×10^4	28.2		(3.4×10^4 ergs/gm/hr corresponds to 410 r.e.p./hr)					

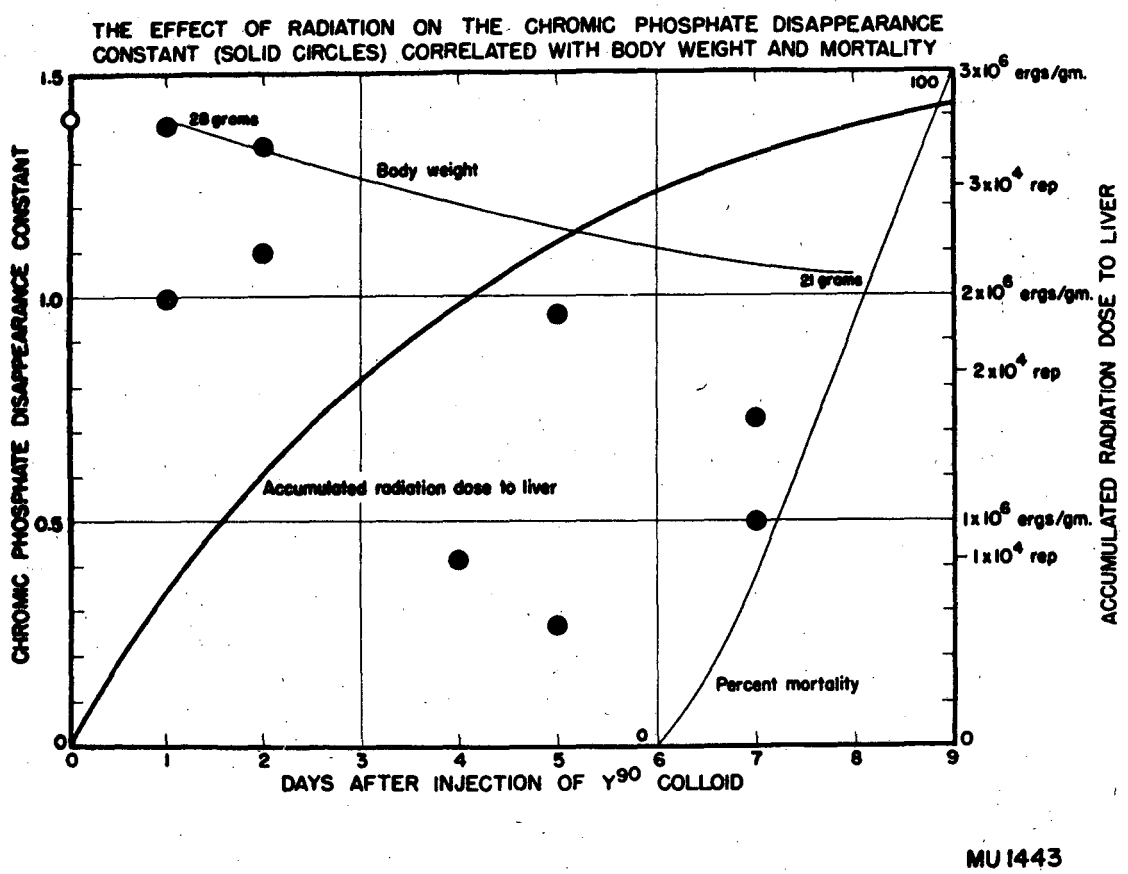

Fig. 2

The circles represent the chromic phosphate disappearance constant (obtained in mice) plotted as a function of time after the injection of a liver localizing colloid containing Y^{90}. The open circle at zero time represents the average disappearance constant as measured on normal non-anesthetized mice. Also included on the graph are the body weight, mortality, and accumulated irradiation dose to the liver. The ordinate at the right represents the radiation dose in two sets of units, ergs/gram of liver tissue and roentgens equivalent physical. The units for the body weight curve and for the percent mortality curve are given at the beginning and end of the curves.

Fig. 2 is an attempt to correlate the changes in the disappearance constant (solid circles) with changes in body weight, mortality and irradiation dosage. The open circle at zero time represents the average normal value for the disappearance constant. Although there is considerable variation in the disappearance constant, it is quite obvious that there is a very marked depression of this rate constant with irradiation.

The curve representing body weight was calculated by averaging the weight of the surviving mice after each weight had been normalized to the initial average weight of 28 grams. None of the mice had died by the sixth day after accumulating 2.5×10^6 ergs per gram of liver tissue (30,000 r.e.p.), and all mice were dead on the ninth day following the injection of the 700 microcuries of Y^{90} colloid.

Macroscopic examination at autopsy showed complete lack of body fat. The large fat depots present around the kidneys and in the mesentery of normal animals were completely absent, and the mice had a general emaciated appearance.

Histological examination of the livers of two mice showed no pronounced changes which could be directly attributed to irradiation damage. The spleen and bone marrow however, were very severly damaged. There were no lymphocytes present in the spleen at all, only the supporting reticular cells and macrophages remained. The bone marrow was completely wiped out; only a very small amount of cellular debris was left in the cavity. Adjacent organs which may have received irradiation escaping from the surface of the liver and spleen were not examined histologically.

The Effect of Irradiation on the Efficiency of the Liver Phagocytes

An attempt was made to evaluate the efficiency of the liver phagocytes in one of these Y^{90} irradiated mice (mouse No. 5). Chromic phosphate was injected into the portal stream three days after the administration of the yttrium. By this time the mice had received approximately 1.6×10^6 ergs per gram of liver tissue (20,000 r.e.p.).

The blood level following the portal injection of chromic phosphate indicated a clearance of 50 percent. The average clearance in normal mice evaluated elsewhere[1] was 79 percent. The standard deviation from this average value obtained on 36 mice is 12 percent. This indicates that such a low value as 50 percent clearance would occur only once in fifty times as a matter of chance. It appears therefore, that irradiation has probably lowered the efficiency somewhat.

In making efficiency measurements by following the blood level, it is also possible to determine the rate of disappearance of that portion of the chromic phosphate which was not removed in the first passage. The average disappearance constant for the transmitted chromic phosphate in 35 non-irradiated mice was 1.07 ± 0.07 ($\sigma = 0.41$)*. The disappearance constant for

* σ = standard deviation.

the fifty percent of the chromic phosphate which passed through the liver of the irradiated mouse 0.42. Since the disappearance constant includes the efficiency factor it should be divided out so that the liver blood flow constant* may be compared.

The average liver blood flow constant for the thirty five non-irradiated mice is 1.36 min^{-1} while the constant for the irradiated mouse is 0.83 min^{-1}. Statistically this means that the chances are about two to one that there is a real lowering of the liver blood flow in addition to the probable lowering of the phagocytic ability of the Kupfer cells mentioned above.

Conclusions.

The chromic phosphate disappearance constant in the mouse is definitely lowered by irradiation. An average of five mice whose livers received from 1.9×10^6 ergs per gram of liver tissue up to 2.6×10^6 ergs per gram of liver tissue (23,000-31,000 r.e.p.) showed an average disappearance constant of 0.57 which is lower than the average normal by a factor of two and a half. The lowest value obtained for the disappearance constant is only one fifth of the normal.

The efficiency measurement which was carried out indicates that the depression of the disappearance constant is due to two approximately equal factors. The efficiency of the liver phagocytes is lower than normal while the blood flow to the liver is also reduced. The lack of histological evidence of liver damage accompanied by the general emaciation and debility of the animals indicates that the diminution of blood flow may be due to a general circulatory depression rather than to a local hepatic effect. It should be noted that considerable difficulty was encountered in getting blood samples from the tails of these sick animals.

The fact that only two thirds of the irradiating colloid localized in the liver along with histological evidence of spleen and bone marrow destruction points toward the possibility of irradiation damage to other tissues especially the bone marrow as the cause of debility and death.

The organs adjacent to the liver and spleen (parts of the gastro-intestinal tract) may have received doses amounting to as much as half the dose at the center of the liver. However this dose would be obtained only at the point of contact and would fall off quite rapidly with distance.

The beta ray dose at a distance from a thick flat source is a logarithmic function of the distance from the surface of the source. For P^{32} beta particles in tissue the half value distance is 0.65 millimeters[4]. While the Y^{90} beta particles would have a somewhat greater penetrating power neither the Y^{90} nor the P^{32} would irradiate an appreciable fraction of the gut. Furthermore no gross abnormalities of the gastro-intestinal tract such as ulceration were observed at autopsy.

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* The disappearance constant (k) is in reality the product of two constants the efficiency (η) and the fraction of the blood volume passing through the liver per unit time (K)

$$k = \eta K$$

From the above considerations it seems that the cause of death in these Y^{90} irradiated animals was probably due to the observed bone marrow damage resulting from the uptake of the colloid by this organ rather than to possible gastro-intestinal damage resulting from radiation "leakage" from the liver and spleen.

The next section describes an irradiation experiment in which the animals survived much longer with higher total doses of irradiation. This was probably due to more specific limitation of the irradiation to the liver and spleen by using chromic phosphate, which localizes 97 percent in these organs, but the possibility that it might be due to slower irradiation rates achieved by using P^{32} rather than the shorter half-lived Y^{90} has not been refuted at this point.

Irradiation with Chromic Phosphate

Two groups of mice were injected with chromic phosphate to irrdiate their livers and spleens. The first group received an injection equivalent to 106 microcuries of P^{32} per gram of liver based on the average value of liver weight equal to six percent of body weight. About 95 percent of the chromic phosphate localizes in the liver. One microcurie of P^{32} will liberate 7.4×10^4 ergs of which about 80 percent will be absorbed within the liver tissue while 20 percent will escape from the surface. Thus these mice received a total of 6.2×10^6 ergs per gram of liver tissue or 75,000 r.e.p. The second group received just half of the above dose.

Approximately three and one half months after the injection of these irradiation doses, the chromic phosphate disappearance constant was measured employing a second injection of the suspension. Two animals which had received the higher dose had half times for disappearance of one minute and six minutes which correspond to values for the disappearance constant of 0.66 min^{-1} and 0.12 min^{-1} respectively. The animal showing the extremely low value, about ten percent of normal, died within twelve hours of the time of measurement. Two mice which received the lower dose of approximately three million ergs per gram of liver tissue each showed disappearance constants of 0.5 min^{-1}. This is just a little more than one third the normal value.

The disappearance constant was measured on one mouse, which had received the lower irradiation dose, nine months after the start of the irradiation. The value obtained for the disappearance constant was 0.83 min^{-1} which is about six tenths of the normal value. This mouse was apparently healthy except that a large tumor had developed in the abdomen.

At autopsy the liver of this animal looked like a coiled string of brown beads. This peculiar structure was in an anatomical position that indicated regeneration at the thin edge of the liver where the irradiation was at a minimum due to geometrical factors. The original liver tissue was apparently completely gone, only a fibrosed pedicle remaining. Indeed it was difficult to find the liver because it had more the appearance of a loop of intestine than of liver. Histologic examination showed apparently healthy liver tissue in the regenerated portions, with large numbers of bile ducts, which are thought by

some investigators to give rise to new hepatic cells. Mitotic figures were not observed. This was probably due to the lapse of about eight months between the administration of the radiation and the sacrifice of the animal. The amount of regenerated liver tissue could not be determined, but appeared to be considerably less than the amount of liver tissue present in the normal mouse.

The examination of other livers at autopsy showed abnormalities which were similar to but less pronounced than those of the liver described above. The irradiated livers which had time to regenerate generally exhibited a knobby structure with a more pronounced knobbyness at the edges. If the irradiation was sufficiently severe and the time for regeneration sufficiently long, the liver looked like a string of beads as described above or like a bunch of grapes with a fibrosed pedicle.

One of the mice receiving the higher irradiation dose had a great deal of ascitic fluid present in the abdomen and an almost complete lack of normal depot fat. The liver of this animal, including all of the fibrosed portion, weighed fifty percent more than the normal mouse liver. Although the general picture with the high irradiation dose was slow loss of weight followed by death within four months, this particular mouse gained about 10 percent in body weight in spite of the loss of body fat.

While the mortality of the group receiving 6.2×10^6 ergs per gram of liver tissue (75,000 r.e.p.) was 100 percent at the end of four months, the mice which received half this dose were all alive, but had lost an average of about 10 percent in weight. Most of this second group died between four and nine months, although one lived for a year following the start of the irradiation.

Summary of the Work on Irradiation.

Changes in the chromic phosphate disappearance constant have been observed with radiation in the rabbit and in the mouse. The observed lowering of the disappearance constant is apparently due in part to a decrease in the efficiency of the liver phagocytes and in part to a depression of the liver blood flow.

In regard to survival, either the rate at which the irradiation is given or more probably, the degree of localization in the liver and spleen seems to be important. When an irradiation dose of three million ergs per gram of liver tissue is given slowly by means of chromic phosphate, the mice die between four and nine months following the start of the irradiation. However, if this same dose of liver irradiation is given rapidly with a colloidal yttrium 90 -hydroxy-citrate complex, which shows less specific liver-spleen localization, the mice die within nine days.

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III HEALTH CHEMISTRY AND PHYSICS

Health Chemistry

N. B. Garden

Monitoring.

A new instrument is being used for taking samples in sewers giving broader information on their condition. A revised program has been initiated for servicing vacuum pumps. Alpha foot counters have been installed in the Chemistry Building. Facilities in ORL for general radioactive chemistry work have been extended. A glove-ported cupola has been added through which samples from the plutonium column of the dissolver solution processing equipment will be taken from the outside of the building, effecting a safer method.

Transportation, Decontamination and Storage.

With the change in the ship employed for waste disposal at sea, more efficient handling of the fifty-gallon drums filled with radioactive waste in cement was necessary. Cable ends are being inserted in cement in the bottom of the drums which creates a loop for drum pickup. This process has greatly facilitated drum loading. Last month and for the next two months the Laboratory's waste, in cement-filled drums, is being stored on Bikini ship "Independence" which itself will ultimately be disposed of.

The use of paint spray bombs inside contaminated gloved boxes at time of their removal for disposal or decontamination has been adopted.

Experiments with agar, soap jells and standard powdered cement to solidify liquid waste continue to indicate that the cement is still the best agent.

Modifications are being made in the initial model of the decontamination chamber. The compound Versene appears to be the best decontaminating agent used here so far; the new compound Radiowash has proved satisfactory but is more costly than other equally satisfactory materials. Oakite 33 has been found to be a good decontaminant for metals. The decontamination Group has taken over the strip coat testing during this period.

Berkeley Boxes.

To further standardize the Berkeley Boxes they are now being lined with a polyethylene film over the inside painted surface; this film is secured by stripping and by overlapping with the walls of the box. A single panel now contains all inlet-outlet fixtures, eliminating the need for holes on various sides of the box. A new wooden frame has been introduced, which holds the shelves and ringstands, secures the tray on the floor of the box and aids in holding the polyethylene lining. The boxes are being made now in section-like compartments, this will be of value in decontamination. All new boxes will have sliding doors rather than hinged ones.

Research and Development.

Equipment for processing highly active proton bombardments of uranium was completed and successfully used. Redesign of the equipment for processing the Hanford dissolver solution was completed. A furnace with auxiliary equipment for transuranic metal production was put in to operation. The box in the two-inch lead cave and a new lead box for cutting and dissolving the slug has been readied for processing a Chalk River pile-bombarded sample. This latter box has a laminated lead glass window 18 by 12 by 4 inches thick. Various small pieces of equipment such as a new power supply for electric stirrers, a swivel-arm pipettor and an improved overhead fluorescent light for use in the two-inch lead cave have been completed or designed.

General.

New members of the Health Chemistry group are being given a training course in functions of the Department. They spend two or more weeks with the monitoring group and a month in the decontamination area, followed by a study of the filter program.

Health Physics

B. J. Moyer

Portable Fast Neutron Counter.

A fast neutron counter with a battery supply has been put into operation. The basic elements are a recoil proportional counter and a two stage amplifier triggering a one-shot multivibrator. A pulse of current is put into a meter-integrating circuit each time the multivibrator triggers.

The counter is lined with polyethylene and filled to one atmosphere with 96 percent argon and 4 percent CO_2. The necessary voltage to operate in the proportional region is supplied by batteries with 5 voltage taps of 67-1/2 volts each above 2100 volts.

The gamma ray electron pulse is discriminated out by choosing the amount of output from the amplifier and by adjusting the collector voltage.

Three ranges are provided on the meter covering a neutron flux of 5 to 10,000 neutrons /cm^2/sec ($\sim$.1 to 40 Mev energy). Earphones are provided for lesser neutron fluxes. Gamma intensities of one r/hr can be discriminated out.

Statistical Summary of Monitoring Program

Survey instruments maintained:

1. B-γ ionization chamber	30
2. Victoreen 263 meters	19
3. I.D.L. portable Survey Meters	20
4. Cutie pies	3
5. Recording γ-intensity meters	15
6. Victoreen proteximeters	3
7. Fast neutron proportional counters	5
8. Slow neutron proportional counters	10
9. Balanced chamber (slow neutron survey instrument)	2
10. Balanced chamber (fast neutron survey instrument)	1
11. Special tissue wall survey instrument	1

Personnel Meters in Use:

1. Total people covered with film badges	1800
2. Total man days coverage with pocket chambers	2177
3. Total man days coverage with pocket dosimeters	4234
4. Total man days coverage with pocket chambers (SN)	3609

Cases of Weekly Exposures Above 0.3r:

Weekly film exposure above	184" area	60" area	Linear Accelerator	Synchrotron	Chemistry	Total
0.3r	18	18	0	0	11	47
0.5r	3	6	0	0	4	13
1.0r	0	2	0	0	2	4
1.5r	0	2	0	0	1	3
+5.0r	0	2*	0	0	0	2

* In the past three months we have had two exposures exceeding 5.r, one of which was received while undergoing chest fluoroscopy. The other was received while undergoing a dental x-ray examination.
These exposures were in no way project connected.

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Information Division