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MEDICAL AND HEALTH PHYSICS

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April, May and June 1950

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INFORMATION DIVISION
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I THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

J. G. Hamilton

Project 48 A-I

Radioautography and Histology

C. W. Asling and Berniece Jue

Studies on the histopathology of astatine have continued following two lines:

1. The toxicity of the element to body tissues in general.
2. The points of localization and destruction of thyroid tissue.

Fourteen rats received At^{211}, 5 at the 50 microcurie level, 5 at the 100 microcurie level and 4 at the 150 microcurie level. After 41 days they were sacrificed and the following specimens taken: stomach, ovary, lymph node, spleen, pituitary, salivary gland, kidney, small intestine, lacrimal gland, thymous, suprarenal, liver and vertebra. These structures are still under histologic study. At present, it appears that significant damage is very restricted. The lacrimal glands showed some damage at all three dose levels, most severe at the highest. The spleen, lymph nodes and kidney showed some damage at the higher levels. Ovarian changes were seen but have not been completely evaluated.

Radioautographic studies were also done on thyroid glands. After dosages of At^{211} varying from 0.5 microcuries to 150 microcuries, allowing 41 days post-injection interval for any damage to develop, 5 microcuries of I^{131} were administered and contact film radioautographs made to determine the capacity of the residual glandular tissue to concentrate iodine. In addition, stripping film autographs were made using various valence states of astatine - negative, zero, and positive, with short post-injection intervals (4 and 18 hours) and medium dosages (25 and 50 microcuries). Definitive statement of the results will be made when all radioautographs are complete. It may be said at this time that the thyroid takes up astatine in any of the valence states administered.

Tracer Studies in Rats with Radioactive Materials

Kenneth G. Scott

Tantalum (Ta^{182}). Studies upon the deposition of tantalum in rats using Ta^{182} as a radioactive tracer have been continued. This data is now complete up to 64 days after tantalum administration by intramuscular and intravenous routes. The tantalum was administered both in the uncomplexed and citrate complexed states. In general, these studies show that tantalum is rather readily eliminated from the body regardless of its mode of administration and/or whether it is complexed or not. That which remains deposited in the body 64 days after administration is primarily found in liver and kidney, skeleton, skin and the musculature. When one milligram of uncomplexed tantalum is given intramuscularly, approximately 10 percent is absorbed from the injection site. Of the material absorbed, the highest tissue concentration of any organ in the body was liver. Large amounts were retained likewise by the reticuloendothelial elements of body such as spleen and lymph glands. The concentration of tantalum in the skeleton was approximately 10 percent of the absorbed dose when administered in this manner. The tantalum was eliminated from the body and found in urine and feces in almost equal amounts, and was approximately 60 percent of the total amount absorbed. These data are summarized in Table I.

When a similar group of animals were given one milligram of tantalum, but complexed with citrate, the absorption from the injection site was increased seven fold as compared to uncomplexed tantalum. After its absorption into the body, the fate of tantalum was not appreciably different with respect to its deposition in the various tissues or its excretion whether complexed or not. These data are summarized in Table II.

Intravenous administration to rats of milligram amounts of tantalum using Ta^{182} as a tracer, showed relatively greater concentrations in liver than was found in the animals which received tantalum by intramuscular injection. For example, 64 days after intravenous administration, the liver organ contained 28 percent of the total amount of tantalum administered. This is six times greater on a per gram basis than the liver concentrations observed following intramuscular administration. The other organs studied including skeleton did not show appreciably different depositions of tantalum when given via the intravenous route as compared to intramuscular administration. These data are summarized in Table III.

Complexing tantalum with citrate prior to its intravenous administration did not change the distribution in the body appreciably and resulted in an even higher deposition in the liver than was observed in the experiments mentioned previously. These data are summarized in Table IV.

Tantalum aerosols have been prepared by burning milligram amounts of tantalum using radioactive Ta^{182} as a carrier in a carbon arc. These aerosols were given to rats and the fate of these particles in the lungs has been followed for a period of 64 days after inhalation. After this time period 99 percent of the tantalum inhaled has been excreted via the bronchial tree, having less than 1 percent of the material remaining in the lung. The penetration of tantalum oxides administered in this manner through the alveolar membranes and into the body was very small. Less than 1 percent of the total amount deposited in the lungs was absorbed by this

TABLE I

DEPOSITION OF TANTALUM IN THE RAT USING Ta^{182} AS A TRACER, 64 DAYS FOLLOWING ITS INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. ONE MILLIGRAM ADMINISTERED TO EACH RAT.

Tissue	% per organ	% per gram
Heart	.19	.19
Lungs	.29	.19
Spleen	.38	.48
Blood	.19	.01
Liver	10.2	.86
Kidney	1.15	.48
Adrenals	<.10	-
Thyroid	<.10	-
Lymph Glands	-	.57
Pancreas	.19	.10
Brain	<.10	<.10
Fat	-	<.10
Stomach	<.10	<.10
Sm. Int.	.76	.06
Lg. Int.	.29	.03
Skeleton	9.93	.57
Muscle	7.55	.07
Skin	7.07	.19
Eyes	<.10	<.10
Pituitary	<.10	-
Gonads	.67	.29
Urine	35.2	-
Feces	25.9	-

TABLE II

DEPOSITION OF TANTALUM COMPLEXED WITH CITRATE IN THE RAT USING Ta^{182} AS A TRACER, 64 DAYS FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. ONE MILLIGRAM ADMINISTERED TO EACH RAT.

Tissue	% per organ	% per gram
Heart	.18	.20
Lungs	.32	.21
Spleen	.52	.55
Blood	.03	.003
Liver	4.47	.61
Kidney	.93	.52
Adrenals	.02	-
Thyroid	<.02	-
Lymph Gl.	-	1.76
Pancreas	.39	.35
Brain	<.02	<.02
Fat	-	.09
Stomach	.20	.12
Sm. Int.	.90	.14
Lg. Int.	.35	.06
Skeleton	9.22	.49
Muscle	7.25	.07
Skin	6.79	.18
Eyes	<.02	.05
Pituitary	<.02	-
Gonads	.70	.27
Urine	44.5	-
Feces	23.2	-

TABLE III

DEPOSITION OF TANTALUM IN THE RAT USING Ta^{182} AS A TRACER, 64 DAYS FOLLOWING INTRAVENOUS ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. 0.1 MILLIGRAM GIVEN TO EACH RAT.

Tissue	% per organ	% per gram
Heart	.11	.15
Lungs	.45	.24
Spleen	.49	.62
Blood	.03	.002
Liver	28.4	3.82
Kidney	.70	.41
Adrenals	.01	-
Thyroid	<.01	-
Lymph Gl.	-	.45
Pancreas	.10	.17
Brain	<.01	<.01
Fat	-	.13
Stomach	.53	.24
Sm. Int.	.98	.13
Lg. Int.	.58	.09
Skeleton	5.84	.33
Muscle	8.56	.09
Balance	1.83	-
Skin	9.39	.26
Eyes	.02	.07
Pituitary	<.01	-
Gonads	.68	.47
Urine	26.2	-
Feces	15.1	-

TABLE IV

DEPOSITION OF TANTALUM COMPLEXED WITH CITRATE IN THE RAT USING Ta^{182} AS A TRACER, 64 DAYS FOLLOWING INTRAVENOUS ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND PERCENT OF DOSE. 0.1 MILLIGRAM GIVEN TO EACH RAT.

Tissue	% per organ	% per gram
Heart	.06	.06
Lungs	.62	.25
Spleen	2.83	3.29
Blood	.04	.002
Liver	45.1	4.37
Kidney	1.23	.54
Adrenals	.06	-
Thyroid	.02	-
Lymph Gl.	-	.58
Pancreas	.18	.21
Brain	<.01	<.01
Fat	-	.07
Stomach	.24	.11
Sm. Int.	4.12	.37
Lg. Int.	1.09	.16
Skeleton	6.11	.29
Muscle	2.15	.015
Balance	8.65	-
Skin	3.03	.06
Eyes	.01	.03
Pituitary	<.01	-
Gonads	.15	.06
Urine	8.32	-
Feces	16.0	-

process and even this amount probably reflects the sensitivity of the method rather than the actual amount absorbed. These data are summarized in Table V.

Carrier-Free Rhenium^{183}. Carrier-free rhenium^{183} has been administered into rats intravenously and its fate studied for 1, 4, 24 and 48 hours after. With the exception of a relatively large accumulation of this isotope by the thyroid, rhenium was not deposited to any great degree in any of the tissues studied. The thyroid concentrations were highest one hour after intravenous administration and continued to drop as the study progressed so that at 48 hours thyroid concentration was only 1/20th of that which was observed initially. At one hour after injection large amounts of rhenium were found in the contents of the G.I. tract. Rhenium, like iodine, was presumably secreted by the stomach and reabsorbed in the intestinal tract since it was not found to any great degree in the feces. The excretion, therefore, was primarily by the kidneys and at the 4 days, 94 percent of the material was eliminated in this manner and found in the urine. These data are summarized in Table VI.

The addition of carrier rhenium in the amounts of 50 micrograms per rat reduced the ability of the thyroid to accumulate rhenium by a factor of approximately ten. The distribution of excreta and other tissues is comparable to that observed with carrier-free rhenium. The data showing the distribution of rhenium^{183} with carrier is summarized in Table VII.

Carrier-Free Osmium^{185}. The fate of carrier-free osmium^{185} has been studied in rats following intramuscular administration. These animals were sacrificed one day following injection, in which time 75 percent of the material given was absorbed from the injection site. Of the material absorbed, 65 percent of it was excreted, primarily via the urine. At this time period following administration, relatively large amounts of osmium were found in kidney, and in the intestinal contents with lesser amounts being deposited in liver, blood and spleen. These data are summarized in Table VIII.

TABLE V

DEPOSITION OF TANTALUM IN THE RAT 64 DAYS FOLLOWING INHALATION USING Ta^{182} AS A TRACER. VALUES GIVEN AS PERCENT OF TOTAL FOUND IN ANIMAL.

Tissue	% per organ	% per gram
Heart	<.01	<.01
Lungs	.58	.28
Spleen	<.01	<.01
Blood	<.01	<.01
Liver	<.01	<.01
Kidney	<.01	<.01
G.I.	<.01	<.01
Skeleton	<.01	<.01
Muscle	<.01	<.01
Balance	.04	-
Skin	<.01	<.01
Head	<.01	<.01
Excreta	99.4	-

TABLE VI

DEPOSITION OF CARRIER-FREE Re^{183} IN THE RAT FOLLOWING INTRAVENOUS ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE.

Tissue	1 hour		4 hours		24 hours		4 days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.22	.36	.14	.18	.05	.06	<.01	<.01
Lungs	1.29	.67	.56	.32	.13	.07	<.01	<.01
Spleen	.26	.33	.14	.14	.02	.02	<.01	<.01
Blood	7.65	.75	3.65	.35	.70	.08	.01	.001
Liver	2.63	.43	1.50	.21	.23	.03	.01	.001
Kidney	1.05	.76	.55	.37	.09	.07	<.01	<.01
Adrenals	.04	-	.01	-	<.01	-	<.01	-
Thyroid	.25	~ 10.0	.16	~ 6.4	.06	~ 2.4	.001	~ .04
Trachea	.24	3.16	.10	.51	.03	.14	<.01	.03
Lymph Gl.	-	.51	-	.21	-	.05	-	.08
Pancreas	.26	.42	.11	.19	.02	.03	<.01	<.01
Brain	.06	.04	.03	.01	<.01	<.01	<.01	<.01
Fat	-	.16	-	.09	-	.02	-	<.01
Stomach	3.15	3.20	3.44	3.03	.61	.52	.01	.009
Stom. Cont.	6.93	13.9	4.45	8.05	.07	.33	.06	.01
Sm. Int.	2.58	.44	1.74	.29	.11	.02	<.01	<.01
Sm. Int. Cont.	.56	.46	.18	.23	.05	.02	.01	.002
Lg. Int.	.68	.32	.33	.17	.07	.02	<.01	<.01
Lg. Int. Cont.	.42	.23	.24	.10	.19	.18	.01	.002
Skeleton	4.70	.38	2.44	.18	.50	.03	.07	.005
Muscle	12.7	.17	5.93	.08	1.17	.02	.08	.001
Balance	7.07	-	3.57	-	1.80	-	.91	-
Skin	23.1	.87	17.4	.58	8.64	.38	4.92	.18
Eyes	.06	.19	.02	.09	<.01	.02	<.01	<.01
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.08	.49	.06	.39	<.01	.03	<.01	.03
Urine	23.5	-	52.5	-	85.0	-	93.2	-
Feces	.54	-	.74	-	.42	-	.67	-

Note: Gamma dose approx. 3000 c/s.

TABLE VII

DEPOSITION OF Re^{183} IN THE RAT FOLLOWING INTRAVENOUS ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. 50 MICROGRAMS CARRIER GIVEN ALONG WITH Re^{183}.

Tissue	4 hours		24 hours	
	% per organ	% per gram	% per organ	% per gram
Heart	.11	.17	.01	.02
Lungs	.28	.24	.03	.02
Spleen	.13	.13	.01	.01
Blood	2.96	.29	.27	.03
Liver	1.32	.20	.08	.01
Kidney	.38	.28	.02	.02
Adrenals	<.01	-	<.01	-
Thyroid	.02	~.80	.009	~.36
Trachea	.05	.27	<.01	.03
Lymph Gl.	-	.25	-	.09
Pancreas	.15	.15	.01	.03
Brain	.02	.01	<.01	<.01
Fat	-	.04	-	<.01
Stomach	3.55	3.23	.22	.20
Stom. Cont.	3.52	7.77	.11	.54
Sm. Int.	.94	.17	.04	.01
Sm. Int. Cont.	.25	.19	.02	.01
Lg. Int.	.28	.11	.04	.02
Lg. Int. Cont.	.23	.08	.13	.07
Skeleton	2.08	.16	.17	.01
Muscle	5.29	.07	.41	.006
Balance	4.96	-	1.25	-
Skin	8.44	.34	3.19	.14
Eyes	.02	.08	<.01	<.01
Pituitary	<.01	-	<.01	-
Gonads	.02	.20	<.01	<.01
Urine	64.7	-	93.1	-
Feces	.26	-	.88	-

Note: Gamma dose approx. 2000 c/s.

TABLE VIII

DEPOSITION OF CARRIER-FREE Os^{185} IN THE RAT 1 DAY FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE.

Tissue	% per organ	% per gram
Heart	.15	.18
Lungs	.30	.20
Spleen	.22	.30
Blood	2.94	.27
Liver	3.61	.61
Kidney	4.48	3.39
Adrenals	.01	-
Thyroid	.01	-
Trachea	.03	.12
Lymph Gl.	-	.41
Pancreas	.12	.09
Brain	.03	.01
Fat	-	.03
Stomach	.18	.16
Stom. Cont.	.19	.38
Sm. Int.	1.04	.16
Sm. Int. Cont.	1.93	1.26
Lg. Int.	1.36	.50
Lg. Int. Cont.	8.22	2.10
Skeleton	1.90	.11
Muscle	3.35	.04
Skin	4.08	.14
Eyes	.01	.05
Pituitary	<.01	-
Gonads	.04	.22
Urine	62.7	-
Feces	3.13	-

Chelating Experiments

Harry Foreman, AEC Postdoctoral Fellow

Studies on the employment of chelating agents for hastening excretion of radioactive material have continued.

In consideration of suitable chelating agents for use in forcing excretion of elements from the body, it has been found that certain characteristics are necessary. First of all, the stability constant of the chelating compound formed between the chelating agent and the element to be removed must be much greater than that formed between the agent and any essential element normally found in the body, i.e., ethylenediamine tetracetic acid (EDTA) cannot be used to remove strontium from the body because the chelate formed with calcium is more stable and consequently the calcium will be removed preferentially. On the other hand, yttrium is readily removed since it forms a very stable chelate and will displace calcium from complexes formed with the chelating agent. Secondly, the chelate must be non-toxic at effective dose levels. It must be soluble in serum, readily excreted, but not readily catabilized.

In view of the importance of the toxicology of beryllium, a number of chelating agents were screened in vivo for possible use for removing beryllium which has been deposited in the body. The compounds were tested for one of the characteristics noted above, namely the ability to form soluble beryllium chelates at pH 7. If one did not meet this requirement, it was not considered for further testing in the body. These tests were carried out as follows: 10 cc of approximately 10 percent water solution of a test agent was added to 5 cc of a solution containing approximately 500 mg of beryllium chloride at pH 3-4. One-tenth normal sodium hydroxide was added until the pH was brought to 7-8. If no precipitate was found, it was considered a soluble chelate was present, since untreated beryllium solutions under the same conditions begin to form precipitates at pH 5.5. The compounds tested and the results are presented in Table I.

As reported in previous progress reports EDTA was found to form stable complexes with rare earth and alkaline earth metals and could be used for removing at least one of these, yttrium, from the body. A screening experiment was carried out to determine what other cations would form soluble chelates with this compound under physiological conditions. The test was carried out in a manner similar to that described above for beryllium. Ten cubic centimeters of a 20 percent solution of EDTA at pH 7 was added to 5 cc of a solution containing approximately 500 mg of the test element at pH 3-4. One-tenth normal sodium hydroxide was added until pH 7-8. Only cations which formed precipitates in the region of pH 7 could be tested in this manner. The cations tested and results are indicated in Table II.

In vivo experiments were continued to show the actual effect of the chelating agents within the body. Two groups of 6 rats each were injected with a dose of Pu^{239} and Ce^{144}. One group was subjected to various dose time schedules of each of the following chelating agents; EDTA, citric acid, "Fe-3" (a commercial compound whose structure is not revealed), and zirconium combined with EDTA. The second group was used as controls. The animals were sacrificed at 64 days. The results and excreta are now being analyzed and the results and full details of the experiment will be reported later.

TABLE I

FORMATION OF BERYLLIUM CHELATES

Compound	Results (Soluble Chelates)
Oxalic Acid	+
Citric Acid	+
Tartaric Acid	+
Malonic Acid	+
Glycolic Acid	+
Ascorbic Acid	-
EDTA	-
Nicotinic Acid	-
Picolinic Acid	-
Mucic Acid	-
Ethylenediaminediacetic Acid	-

TABLE II

CATIONS FORMING SOLUBLE CHELATES WITH EDTA

Cation	Results
Ag^{+}	+
Zr	+
Sm^{++++}	+
Sn^{++}	+
Be	-
Hg^{+}	+
Hg^{++}	+
Mn^{++}	-
Pb	+
Mg	+
Co	+
Cr	+
Ni	+
Cu	+

A long-term experiment to determine the chronic effects of daily administration of small amounts of EDTA was carried out. The experiment was designed to give information as to the maximum amounts of the compound which could be administered to rats daily in the drinking water and food. In addition, it was attempted to determine whether animals so treated could be slowly decalcified. The procedure was as follows. Four pregnant rats were placed on a low calcium diet (0.1 percent calcium) early in their pregnancy. Two of these were used as test animals and were given water containing .1 percent EDTA. The other two were used as controls. The test animals gave birth to a total of 7 fetuses. The controls delivered 6. Shortly after delivery the drinking water content of EDTA was changed to 0.25 percent for the test animals. Three of the test fetuses died within two days after birth. One died two weeks later and the remaining three lived for six weeks, but died only after receiving large doses of EDTA. Two weeks after delivery the EDTA content of water was raised to 0.5 percent and at one month to 2 percent. The animals refused the 2 percent solution. After two days they were placed on distilled water and the EDTA was placed in the food to the extent of 1 percent by weight. All of the young animals died within three days but the adults appeared to do well on the diet. The young animals showed marked effects of treatment. At the time of death, they were two-thirds the size of the control animals and their fur was in very poor condition. Femurs, pituitaries and parathyroids were taken for histological examination. The two adults were continued on the above regimen for two weeks. At that time the EDTA content of the food was raised to 10 percent. After three days the animals died. Again tissues were taken for histological examination. It was estimated that at 0.1 percent EDTA the young animals received 10 mg and the adults received 30 mg of EDTA daily. The corresponding amounts for the higher doses received can be readily calculated from this.

A Preliminary Report on the Effect of Whole Body Radiation on Extra and Intracellular Electrolytes

John Z. Bowers

Several effects of total body radiation should induce significant changes in body water and body electrolytes since these have been shown to cause:

1. Decreased intake of food and water
2. Impaired absorption from the G.I. tract
3. Alterations in permeability of blood vessels
4. Damage to cells and their membranes
5. Biochemical consequences of diarrhea
6. Renal loss or conservation of electrolytes

The first experiments have been aimed at establishing the pattern of fecal and urinary excretion of electrolytes in acute radiation injury. To accomplish this, a modified animal holder has been made so that feces and urine would be separated without cross contamination and the entire 24 hour output was collected, weighed and analyzed separately. Twenty-four hour intake of food and water was also measured, using a synthetic diet in which the mineral content was known of casein and sucrose with added minerals and vitamins. Male Slonaker rats weighing approximately 250 grams were used throughout. Sodium^{22}, prepared in the Crocker Laboratory Cyclotron, was injected subcutaneously in an amount of 2.0 microcuries 36 hours before irradiation.

In Group I, six animals were exposed to 685 r at a dose rate of 81.6 r/min., 215 kv, 15 ma, 1 mm copper was used as a filter. Tube distance was twelve inches from the rats. The dosage was checked in a paraffin phantom. Six rats were set up in similar racks as controls.

After irradiation, the food intake was immediately depressed and the animals ate on an average less than 1 gram of food per 24 hour period during third, fourth and fifth days. Food intake returned to normal by the seventh day. Water intake showed a similar trend, but the decrease was not so pronounced, i.e., intake fell by 3-4 cc. Urine output fell only slightly on the fifth and sixth day.

Diarrhea began on the third day in the irradiated animals and lasted for 3-4 days. The stools were fluid and tarry. Fig. 1 shows the percent of dose of sodium per gram of feces and of urine through the fourteenth day post-radiation. The animals were irradiated after the first collection and it will be noted that accompanying the diarrhea there was a prompt and striking increase in fecal sodium concentration which paralleled the severity of the diarrhea and became normal as it subsided.

With the heavy fecal loss, there was in contrast a striking reduction in urine sodium excretion which approached zero on the days when the diarrhea was at its height. As fecal sodium excretion fell, urine sodium excretion rose. Since a functioning renal tubular epithelium and the presence of a salt resorbing hormone of the 17 desoxysteroid group are essential for such a prompt homeostatic

mechanism, it is apparent that the adrenal and kidney were functionally competent at the L.D. 50 level.

A second group of animals received 1370 r dose rate 100 r/min. 215 kv, 15 ma. Tube distance, 13 inches with 1 millimeter Al + .5 millimeter Cu filter. The animals showed an immediate depression of food intake and of water intake. Again urine output fell only slightly, and when the animals were terminal. The animals lost an average of 55 grams; deaths occurring on the third to fifth day.

In Group II, diarrhea developed in 24-48 hours and again there was a corresponding rise in fecal sodium concentration. Here the rise was more striking, but more irregular; indeed, in this group of animals there was surprising variation in electrolyte response.

The concentration of sodium in the urine of these animals fell to its lowest level at 48 hours post-irradiation, a time when fecal sodium concentration was rising. However, urinary sodium concentration then rose only slightly while fecal sodium continued to rise rapidly until there was a ten-fold increase.

In the course of these experiments, one of the control rats developed a spontaneous copious diarrhea which persisted for 6 days; stools were not bloody nor tarry. The electrolyte picture was similar to that of the irradiated rats; a prompt rise in fecal sodium and a concomitant sharp fall in urine sodium. With subsidence of the diarrhea, urine sodium concentrations rose rapidly.

The animals were sacrificed when moribund and samples of heart blood, as well as various organs were removed. The concentration of radio-sodium in these organs was determined as is shown in Table I. Classical chemical determinations are now being carried out and we expect to sacrifice animals at various time intervals after irradiation to determine precisely the effect on tissue electrolytes.

TABLE I

RELATIVE SODIUM CONCENTRATION IN VARIOUS ORGANS

$$\frac{\%\text{ per gram organ}}{\%\text{ per gram animal}} = Na^{22}$$

Organ	Group I Irradiated	Controls	Group II Irradiated
Spleen	.18	.91	.93
Blood	.80	1.20	.40
Liver	.45	.55	.53
Kidney	.73	1.23	.91
Lymph Gland		1.20	.64
Brain	.59	.80	1.03
Fat		.42	.24
Stomach	.83	.89	1.00
Sm. Int.	.67	.85	.95
Lg. Int.	.87	.82	.97
Skeleton	2.5	2.4	2.4
Muscle	.47	.46	.57
Skin		1.18	.95
Gonads		.96	.86

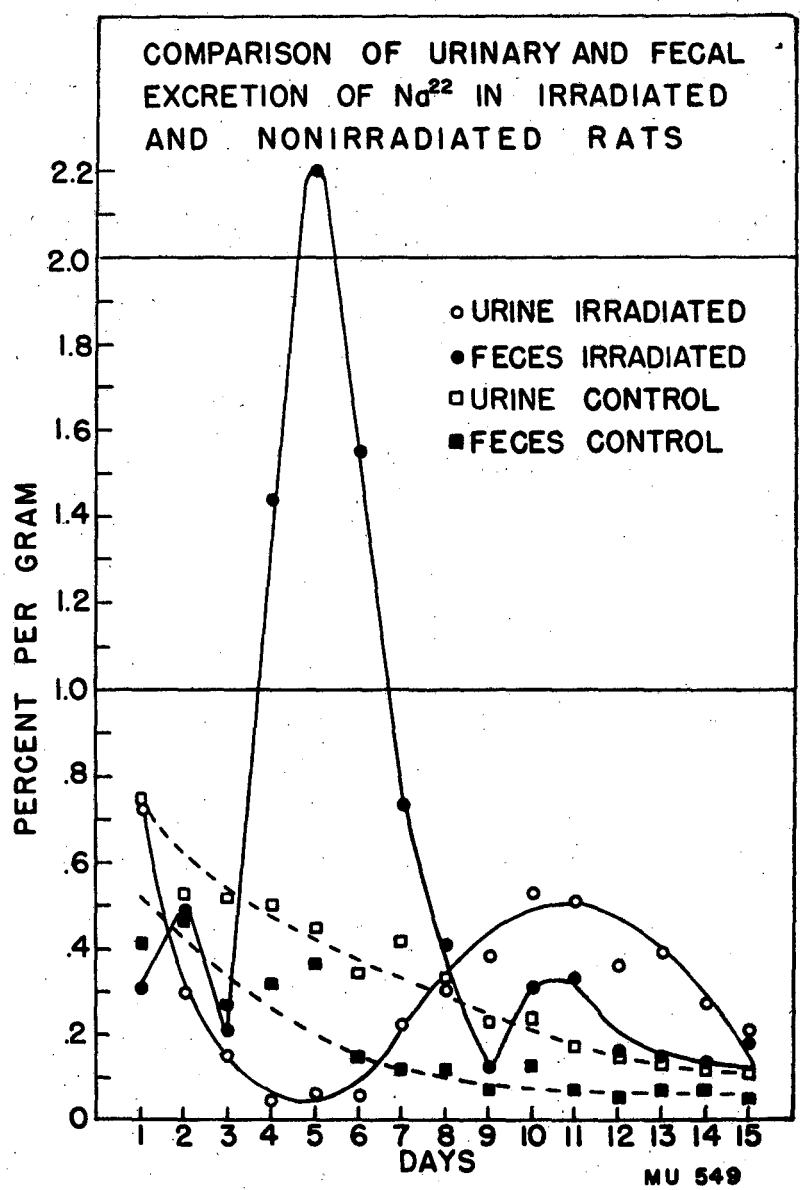
COMPARISON OF URINARY AND FECAL EXCRETION OF Na22 IN IRRADIATED AND NONIRRADIATED RATS
URINE IRRADIATED
FECES IRRADIATED
URINE CONTROL
FECES CONTROL
PERCENT PER GRAM
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DAYS
MU 549

Fig. 1

Decontamination and Bone Metabolism Studies

D. H. Copp, B. Kawin, R. Lerner, D. M. Thomson and F. Ulrich

Kinetic Studies of the Distribution and Excretion of Ce^{144}, Cb^{95}, Y^{90} and Pu^{239}, and of the Effects of Zirconium Citrate Treatment. In the following experiments, a study was made of the curves for distribution and excretion of Ce^{144}, Cb^{95}, Y^{90} and Pu^{239} with time, during the first hour following intravenous injection. The purpose was to obtain information concerning the metabolism of these elements during the critical first hour following administration, and to determine the effect of treatment with massive doses of zirconium citrate. Such treatment, when given promptly, has been found highly effective in increasing the urinary excretion and removal of these isotopes from the body

Procedures:

The following isotope preparations were used (individual dose per rat is given):

1. Ce^{144} - 5 microcuries, carrier-free, in equilibrium with Pr^{144}, made up in 0.25 cc of a 0.01 percent solution of sodium citrate, at pH 6.

2. Cb^{95} - 5 microcuries of Cb^{95}, carrier-free, and freshly separated from Zr^{95}, made up in 0.25 cc of a 0.01 percent solution of sodium citrate at pH 6.

3. Y^{90} - 40 microcuries of Y^{90} in a solution containing 0.5 micrograms of Y as nitrate, in 0.25 cc of a 0.01 percent solution of sodium citrate at pH 6.

4. Pu^{239} - 8 micrograms of Pu^{239} (VI) in 0.25 cc of a solution of 0.01 percent sodium citrate at pH 6.

Thirty adult female rats (weight range 225-275 grams) were used for each isotope. Each rat was given 0.25 cc of the solution of isotope by injection into the great sapenous vein, and was then placed in an individual metabolism cage. Half of the animals (15) in each group were immediately injected intraperitoneally with 1.6 cc of a solution of zirconium citrate containing 40 mg Zr. The balance served as controls. They were sacrificed in groups of 3 at 5, 10, 15, 30 and 60 minutes after administration of the isotope.

At the time of sacrifice, samples of cardiac blood were collected in heparin-rinsed syringes. The femur and liver were removed, cleaned of excess blood and extraneous tissue, and weighed. The total bladder urine was removed and added to any excreted urine.

The results of the analysis of the tissues and urine are shown in Figs. 1-14. In these figures tissue content and blood level have been plotted as percent of the radioisotope per gram tissue at various times following the administration of the isotope. Residue in the body has been determined by subtracting the amount excreted from total recovery.

Results:

The blood level, the excretion, and the tissue uptake varied with the radio-element and the time:

1. Blood Level. When injected intravenously, the blood level of all the radioisotopes fell very rapidly during the first ten minutes, generally with a rapid component of half-time of 2-5 minutes. These fast components may be related to distribution in the extracellular fluid space.

   The rapid component was followed by an intermediate component of 5-15 minutes half-time. This may represent urinary excretion.

   The blood isotope levels appeared to decrease slowly after the first thirty minutes. The exact half-times were generally not determinable due to the limitation of the experimental time period.

   Zirconium citrate treatment caused a more rapid fall in the blood levels in all cases, although the effect varied with the different radioisotopes.

2. Urinary Excretion. Excretion of the radioisotopes in the urine was initially rapid (component of less than five minutes half-time corresponding to the rapid fall in blood level). However, after the first five or ten minutes the excretion rate became much slower.

   The zirconium citrate treatment tended to extend the duration of the initial rapid rate of urinary excretion.

3. Femur. The deposition of columbium in the femurs of both control and untreated animals, after an initial rapid uptake during the first fifteen minutes, leveled off and decreased somewhat. Treatment with zirconium citrate appeared to actually increase the general level of uptake of this isotope.

   Intravenously injected cerium, plutonium and yttrium were taken up rapidly by the femur. Treatment with zirconium citrate appeared to decrease slightly the amount in the femur at the end of the hour, but the effect, if any, was very small.

4. Liver. The uptake of intravenously injected cerium by the liver was both rapid and high in both treated and untreated animals. Liver columbium reached a maximum attained at fifteen minutes in both treated and control animals, and then fell off to about half of this value at the end of an hour. The final level in the zirconium treated animals was lower than that in the controls.

   Liver plutonium uptake in the treated group was almost twice as great as in the control group at the end of the first five minutes. This was followed by a rapid fall. The plutonium level in the treated group approximated that in the controls by the end of the hour.

The uptake of radio-yttrium by the liver in the treated groups was almost as rapid as in the control groups, but did not reach the same magnitude. Whereas the control level continued to increase slowly throughout the hour, the liver Y^{90} in the treated group rose to a maximum by thirty minutes, and then fell slowly to the 5-10 minute level.

Discussion:

An initial rapid fall in blood level was observed with all metals. This may have been due to distribution in the extracellular fluid space, specific uptake in the tissues, and urinary excretion. Simple polyvalent cations rapidly leave the blood stream for the extracellular fluid space, or may be taken up by bone or other tissues. Small colloidal particles tend to be deposited in the bone marrow, and at a rather slow rate. Large colloidal particles are removed from the blood in a single passage through the liver. The rapid uptake and loss of plutonium and other metals from liver may be related to changes in colloidal size and to the fall in blood level.

Urinary excretion rates initially rapid corresponded to the changes in blood level. However, in the animals treated with zirconium citrate, the period of rapid urinary excretion was prolonged and this resulted in a continued fall in blood level. Previous experiments have shown that most of the injected zirconium citrate is excreted in the urine within a short time. It is possible that the radioactive metals in blood and soft tissues may become adsorbed on the colloidal zirconium citrate complexes and so be removed by excretion. There appeared to be very little effect of the zirconeate complex on the uptake of the radioactive metals by femur, suggesting that its principal action was on the soft tissue fraction. However, this removal of labile radioisotope from soft tissues will prevent ultimate deposition in bone, and so reduce permanent fixation. This also accounts for the marked effect of zirconium citrate when given immediately (while a large part of the dose of radioactive material is in the soft tissues) as compared to the very small effect when zirconium citrate is given several days later (when the material has become fixed largely in the skeleton).

Conclusions:

1. A study was made of the curves for distribution of Ce^{144}, Cb^{95}, Y^{90} and Pu^{239} during the first hour following intravenous injection.

2. An initial rapid fall in blood level during the first 10 minutes was followed by a much slower decline.

3. Treatment with massive doses of zirconium citrate prolonged the initial rapid rate of urinary excretion and fall in blood level.

4. Treatment with zirconium citrate appeared to have no direct effect on the uptake by bone, but did reduce the level in soft tissues.

5. It is suggested that these effects may be related to radio-colloidal behavior.

Removal of Radio-calcium from the Body by Feeding a Diet Low in Phosphorus. Following injection of radio-calcium or radio-strontium into young normal rats, much of the dose is taken up by the skeleton within the first hour and remains fixed there. The subsequent excretion is very slow, and this, combined with the long half-lives of the isotopes, presents a serious hazard from chronic irradiation of bone.

When young rats are reared on a diet dificient in phosphorus, a condition of severe rickets develops. Day and McCollum[1] have shown that such animals are in negative calcium balance, and there is extensive demineralization of bone.

The purpose of the following experiment was to determine whether the removal of radio-calcium from the skeleton might be accelerated by feeding animals, previously injected with the isotope, on a diet deficient in phosphorus. This preliminary experiment was carried out with calcium because of its significance in bone metabolism. It is planned to extend the work to radio-strontium because of the importance of the isotopes Sr^{89} and Sr^{90} in fission products.

Procedure:

Weanling rats 22 days of age (average weight 42 gms) were injected intraperitoneally with 5 microcuries of Ca^{45} in an isotonic solution containing approximately 1.5 mgm of carrier calcium. They were placed in individual metabolism cages which permitted separate collection of urine and feces.

The phosphorus deficient diet was that previously described in A.E.C.D report number 2483 modified by increasing the fibrin from 20 to 25 percent. The deficient animals were fed this diet ad libitum; the second group (pair-fed controls) were paired with the deficient animals, and were fed the same quantity of a complete diet as that consumed by the former; the third group (ad lib controls) received the complete diet ad libitum.

Bones and feces were dry ashed and a suitable aliquot was taken for measurement of Ca^{45}. The urine was diluted directly. Correction was made for self-absorption of the soft beta radiation from Ca^{45}.

Results:

The results are shown in Table I. There was no significant difference between ad lib and pair-fed control groups, so they are plotted together. Although the radio-calcium would already be largely deposited in the skeleton before the animals began to consume the experimental diets, the urinary excretion of Ca^{45} was much higher in the low phosphorus animals than in either control group from the very first day, and remained at a much higher level throughout the duration of the experiment. At the end of two weeks, these animals had excreted over 5 times as much Ca^{45} as had the controls. The residue of calcium in the body has been determined. The slope of the curves indicates a biological half-time of approximately 16 months for the control animals, and of only 43 days for the animals fed the phosphorus deficient diet. In a previous pilot experiment, the radio-calcium in the

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[1] Day, H. G., and McCollum, E. V.,: J. Biol. Chem. 130:269, 1939.

TABLE I

CUMULATIVE EXCRETION OF Ca^{45}

Day	Low Phosphorus Diet	Control Pair Fed	Control Ad Lib
1	3.75	1.19	0.64
2	8.06	1.59	1.19
3	10.17	1.80	1.53
4	11.75	2.07	1.71
5	13.44	2.36	1.92
6	14.82	2.97	2.16
8	17.42	3.45	2.45
12	22.00	4.25	3.24
17	25.16	4.63	3.72
26	39.67	5.46	4.53

bones of these experimental animals was found to be reduced almost 80 percent as compared to the controls.

Discussion:

Removal of radio-calcium from the body was greatly accelerated in the animals fed the low phosphorus diet. This may be due to the negative calcium balance and demineralization of the skeleton which is associated with developing phosphorus deficiency. Day and McCollum[1] have suggested that under such conditions resorption of bone takes place to provide essential phosphorus for the soft tissues, and that the excess calcium liberated is excreted in the urine. While this would account for the removal of the freshly deposited Ca^{45}, it is interesting that the increase in urinary excretion of radio-calcium was evident from the first day, and long before there was time for development of histological evidence of rickets and bone resorption. Apparently a very sensitive mechanism is involved which promptly reflects the effect of low phosphorus intake.

It is planned to extend these experiments to radio-strontium to determine the feasibility of such treatment for decontamination of radio-strontium in both young and adult animals.

Conclusions:

1. After injection of Ca^{45} into normal young rats, feeding a phosphorus deficient diet resulted in an immediate and marked increase in the urinary excretion of radio-calcium, with accelerated removal from the skeleton.

2. This procedure would appear to have possibilities for decontamination of radio-strontium.

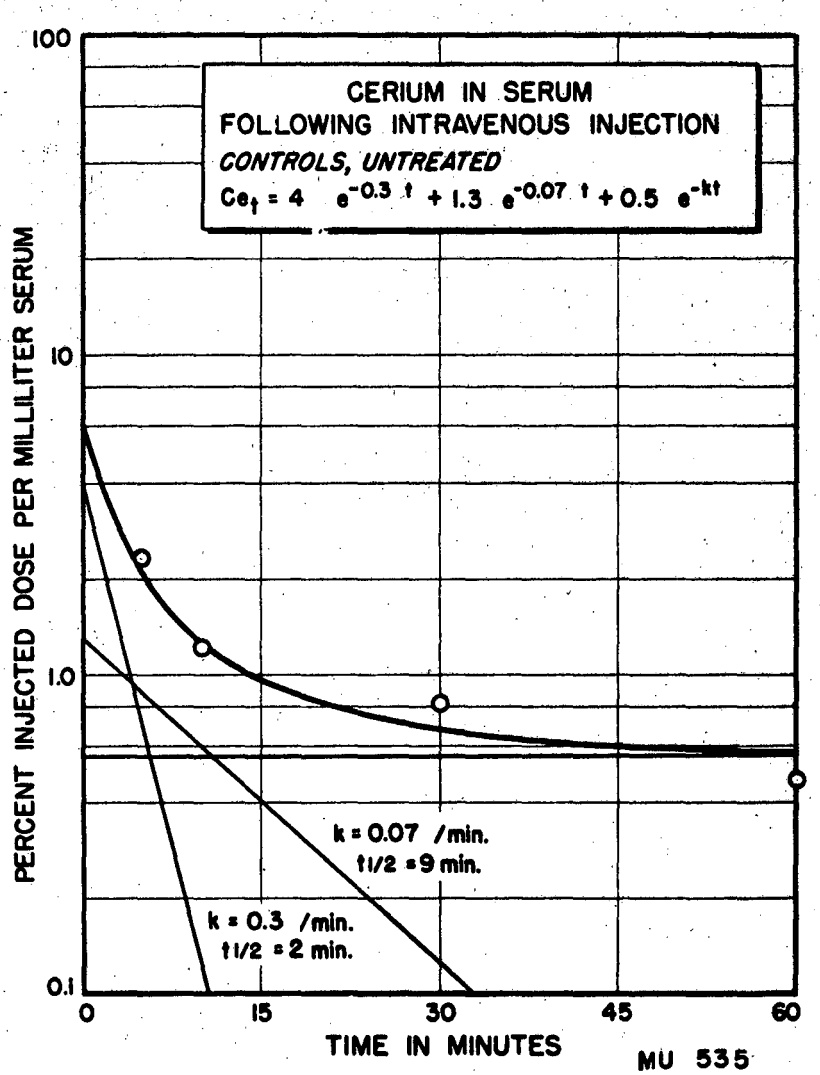
CERIUM IN SERUM
FOLLOWING INTRAVENOUS INJECTION
CONTROLS, UNTREATED
$Ce_t = 4\ e^{-0.3\ t} + 1.3\ e^{-0.07\ t} + 0.5\ e^{-kt}$
PERCENT INJECTED DOSE PER MILLILITER SERUM
100
10
1.0
0.1
k = 0.07 /min.
t1/2 = 9 min.
k = 0.3 /min.
t1/2 = 2 min.
0
15
30
45
60
TIME IN MINUTES
MU 535

Fig. 1

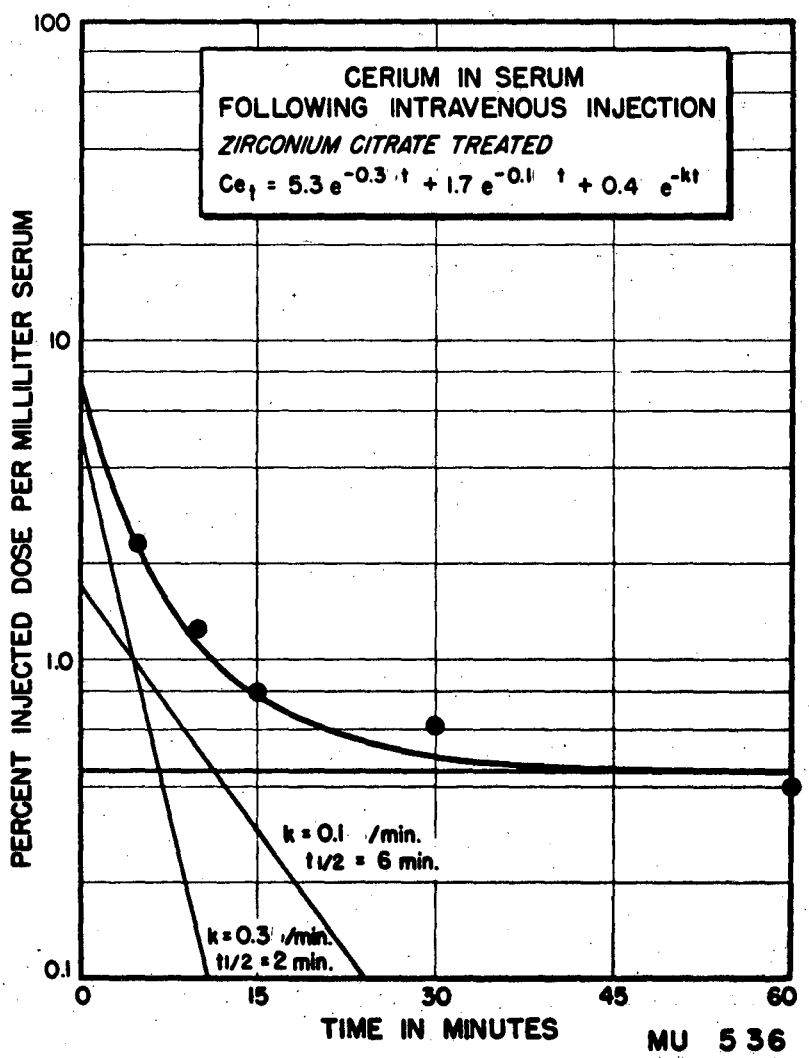
CERIUM IN SERUM
FOLLOWING INTRAVENOUS INJECTION
ZIRCONIUM CITRATE TREATED
Ce_t = 5.3 e^-0.3 t + 1.7 e^-0.1 t + 0.4 e^-kt
PERCENT INJECTED DOSE PER MILLILITER SERUM
100
10
1.0
0.1
k = 0.1 /min.
t1/2 = 6 min.
k = 0.3 /min.
t1/2 = 2 min.
0
15
30
45
60
TIME IN MINUTES
MU 536

Fig. 2

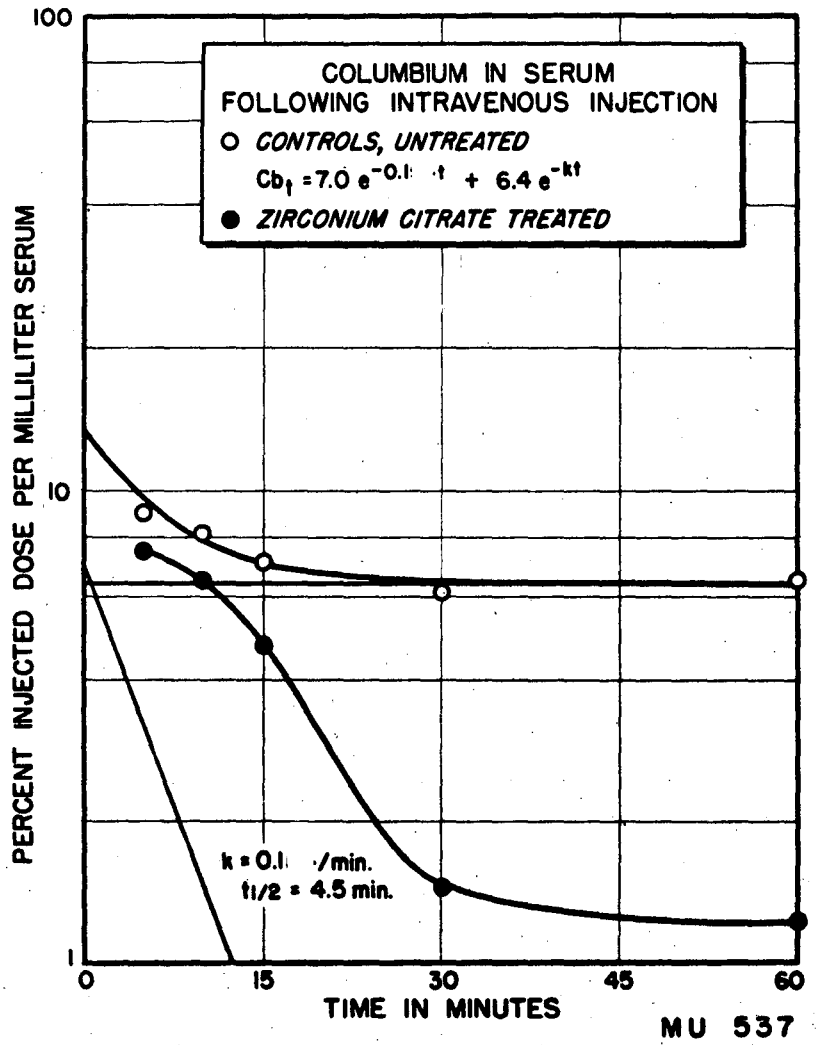
COLUMBIUM IN SERUM
FOLLOWING INTRAVENOUS INJECTION
CONTROLS, UNTREATED
ZIRCONIUM CITRATE TREATED
100
10
1
PERCENT INJECTED DOSE PER MILLILITER SERUM
0
15
30
45
60
TIME IN MINUTES
MU 537

Fig. 3

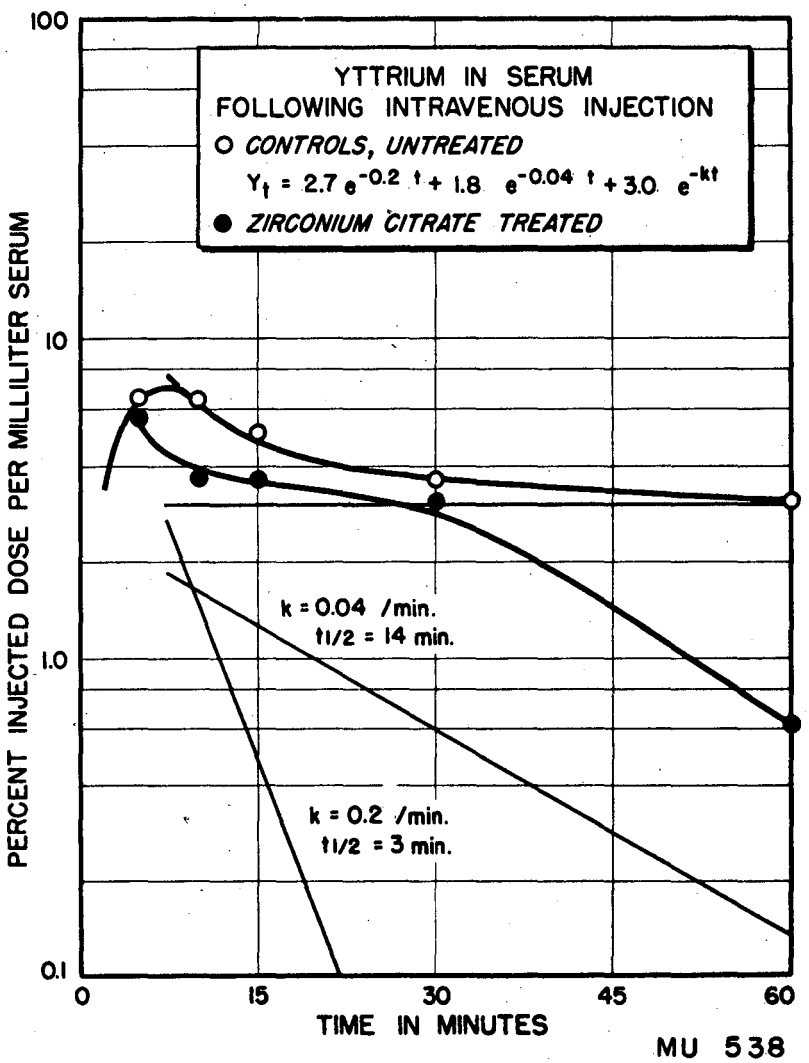
YTTRIUM IN SERUM
FOLLOWING INTRAVENOUS INJECTION
○ CONTROLS, UNTREATED
$Y_t = 2.7\,e^{-0.2\,t} + 1.8\,e^{-0.04\,t} + 3.0\,e^{-kt}$
● ZIRCONIUM CITRATE TREATED
k = 0.04 /min.
t1/2 = 14 min.
k = 0.2 /min.
t1/2 = 3 min.
PERCENT INJECTED DOSE PER MILLILITER SERUM
100
10
1.0
0.1
0
15
30
45
60
TIME IN MINUTES
MU 538

Fig. 4

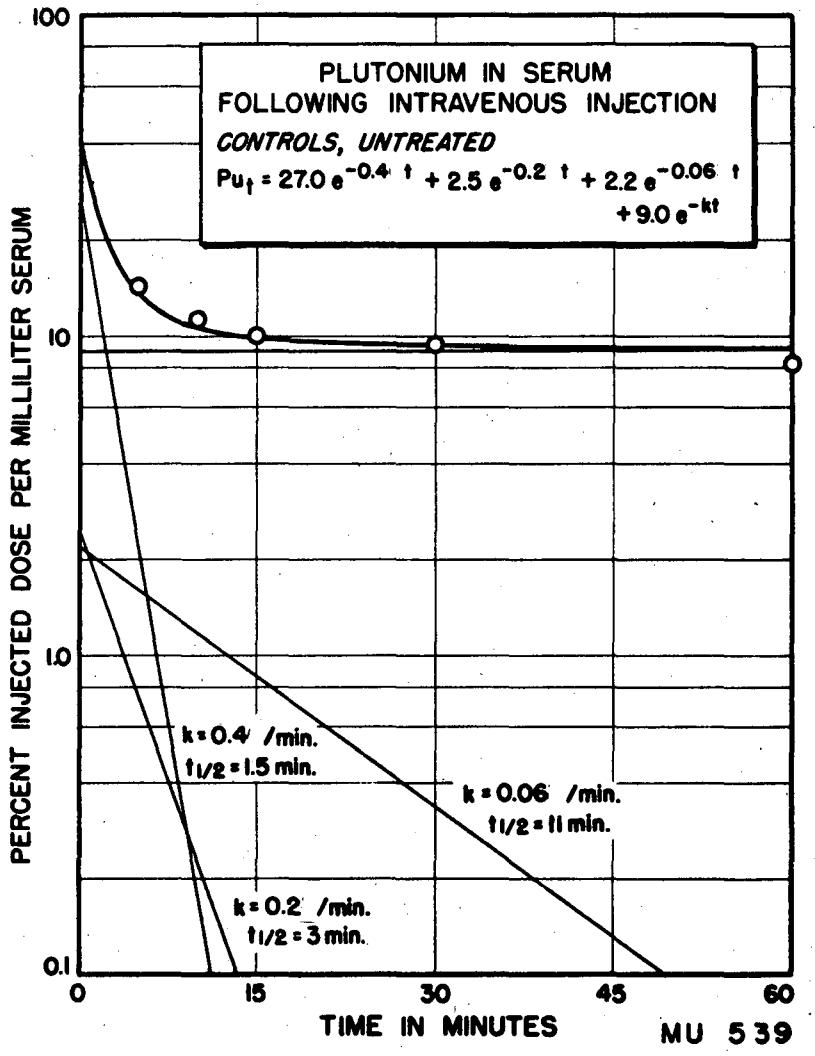
PLUTONIUM IN SERUM
FOLLOWING INTRAVENOUS INJECTION
CONTROLS, UNTREATED
$Pu_t = 27.0\,e^{-0.4\,t} + 2.5\,e^{-0.2\,t} + 2.2\,e^{-0.06\,t} + 9.0\,e^{-kt}$
PERCENT INJECTED DOSE PER MILLILITER SERUM
100
10
1.0
0.1
k = 0.4 /min.
t1/2 = 1.5 min.
k = 0.06 /min.
t1/2 = 11 min.
k = 0.2 /min.
t1/2 = 3 min.
0
15
30
45
60
TIME IN MINUTES
MU 539

Fig. 5

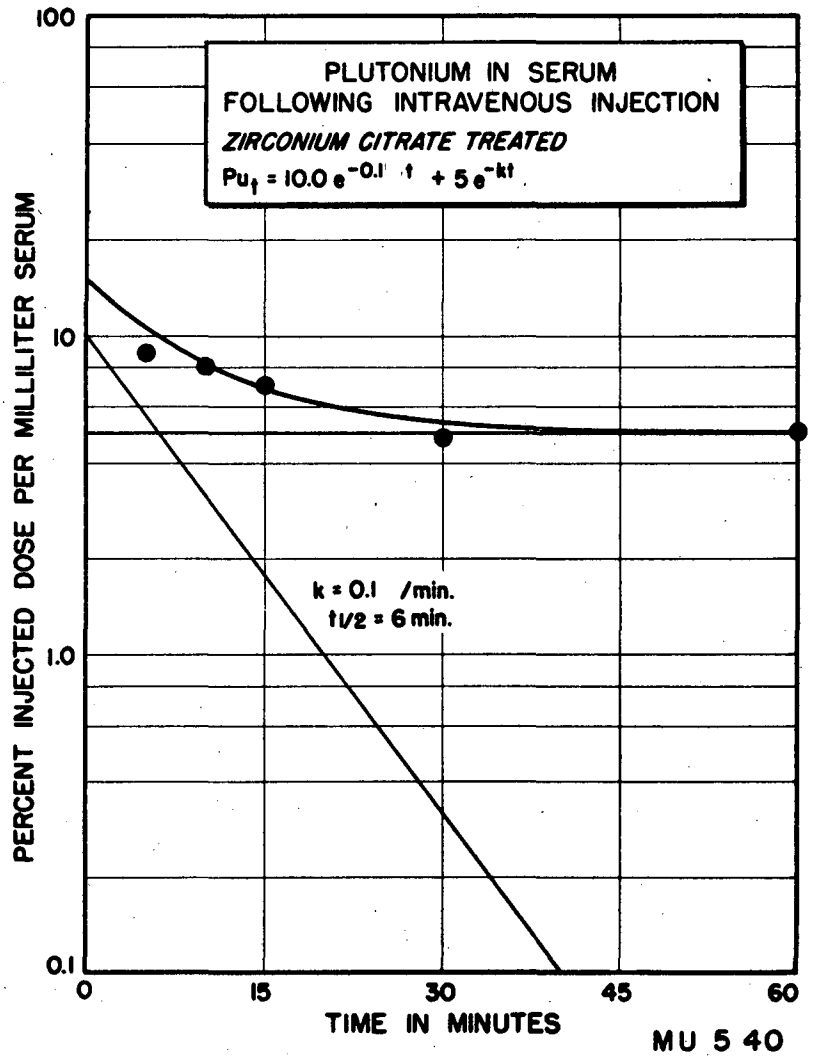
PLUTONIUM IN SERUM
FOLLOWING INTRAVENOUS INJECTION
ZIRCONIUM CITRATE TREATED
$Pu_t = 10.0\,e^{-0.1\,t} + 5\,e^{-kt}$
k = 0.1 /min.
t1/2 = 6 min.
PERCENT INJECTED DOSE PER MILLILITER SERUM
100
10
1.0
0.1
0
15
30
45
60
TIME IN MINUTES
MU 5 40

Fig. 6

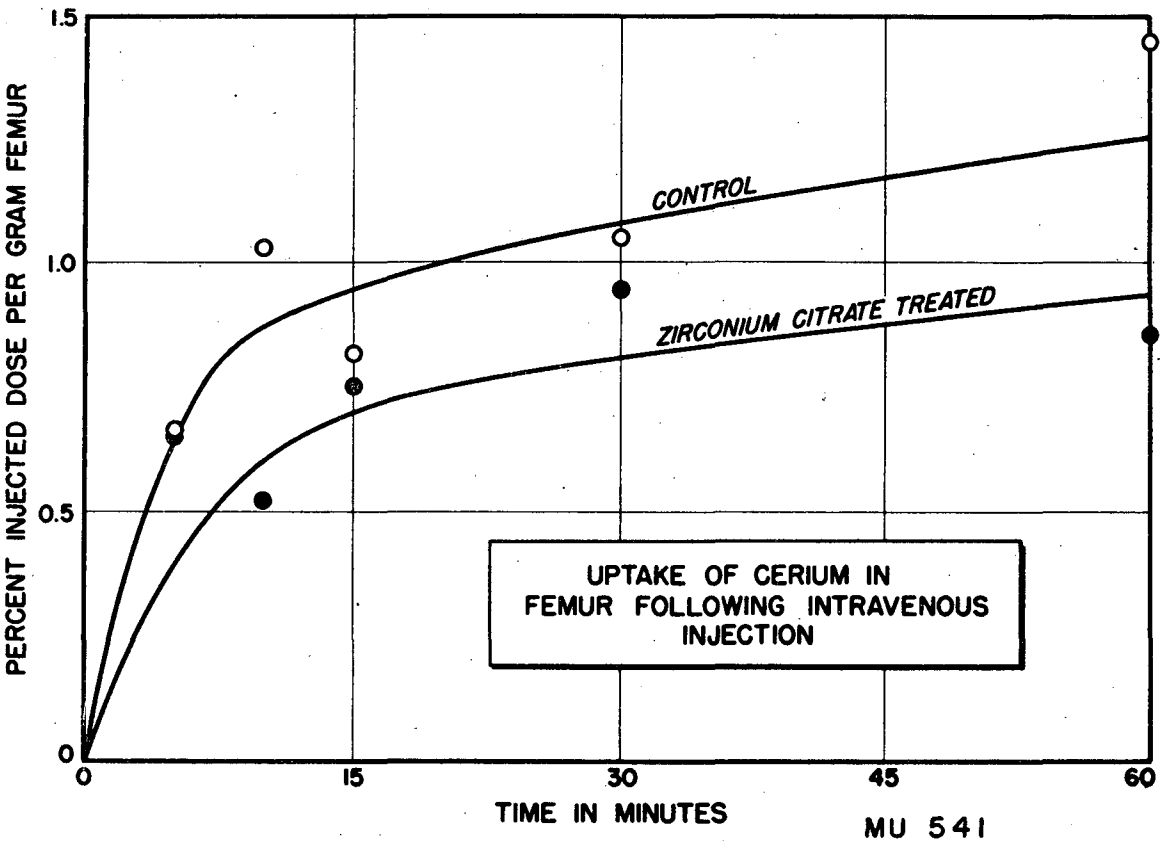
1.5
1.0
0.5
0
PERCENT INJECTED DOSE PER GRAM FEMUR
CONTROL
ZIRCONIUM CITRATE TREATED
UPTAKE OF CERIUM IN FEMUR FOLLOWING INTRAVENOUS INJECTION
0
15
30
45
60
TIME IN MINUTES
MU 541

Fig. 7

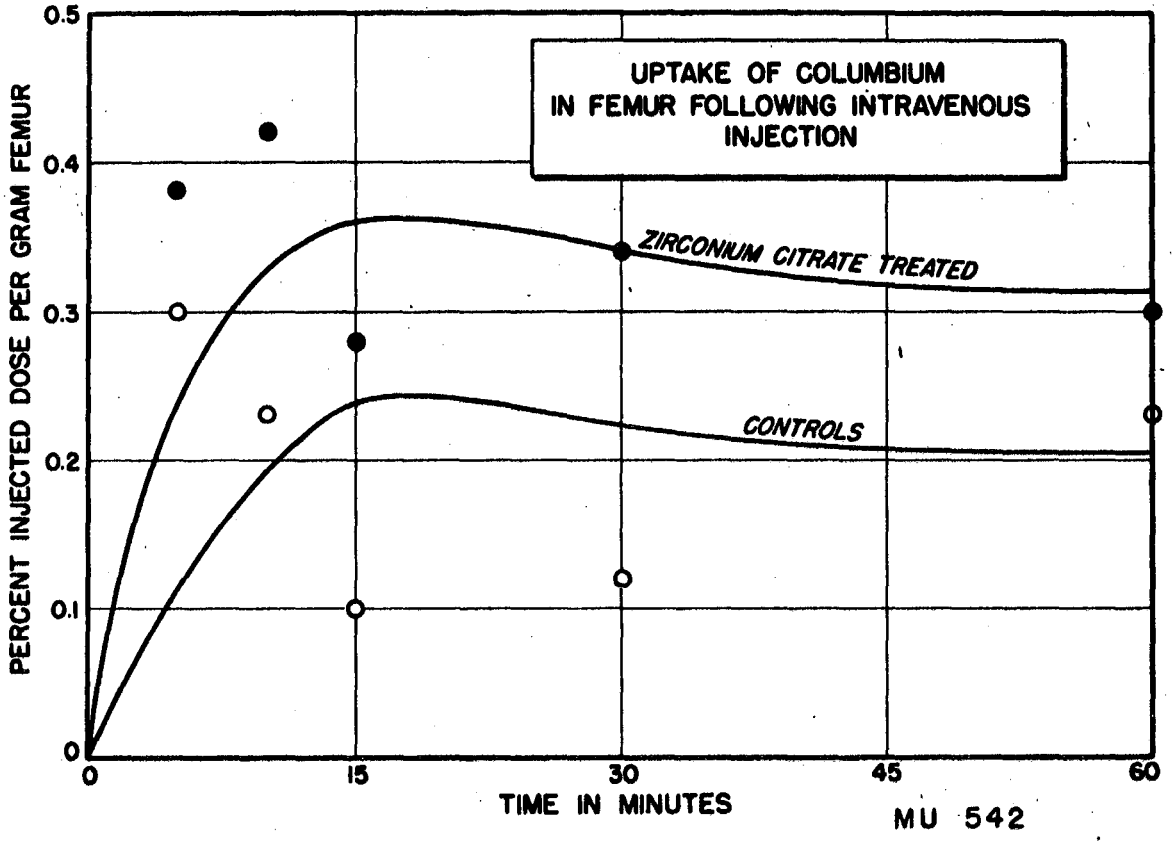
UPTAKE OF COLUMBIUM
IN FEMUR FOLLOWING INTRAVENOUS
INJECTION
ZIRCONIUM CITRATE TREATED
CONTROLS
PERCENT INJECTED DOSE PER GRAM FEMUR
0.5
0.4
0.3
0.2
0.1
0
0
15
30
45
60
TIME IN MINUTES
MU 542

Fig. 8

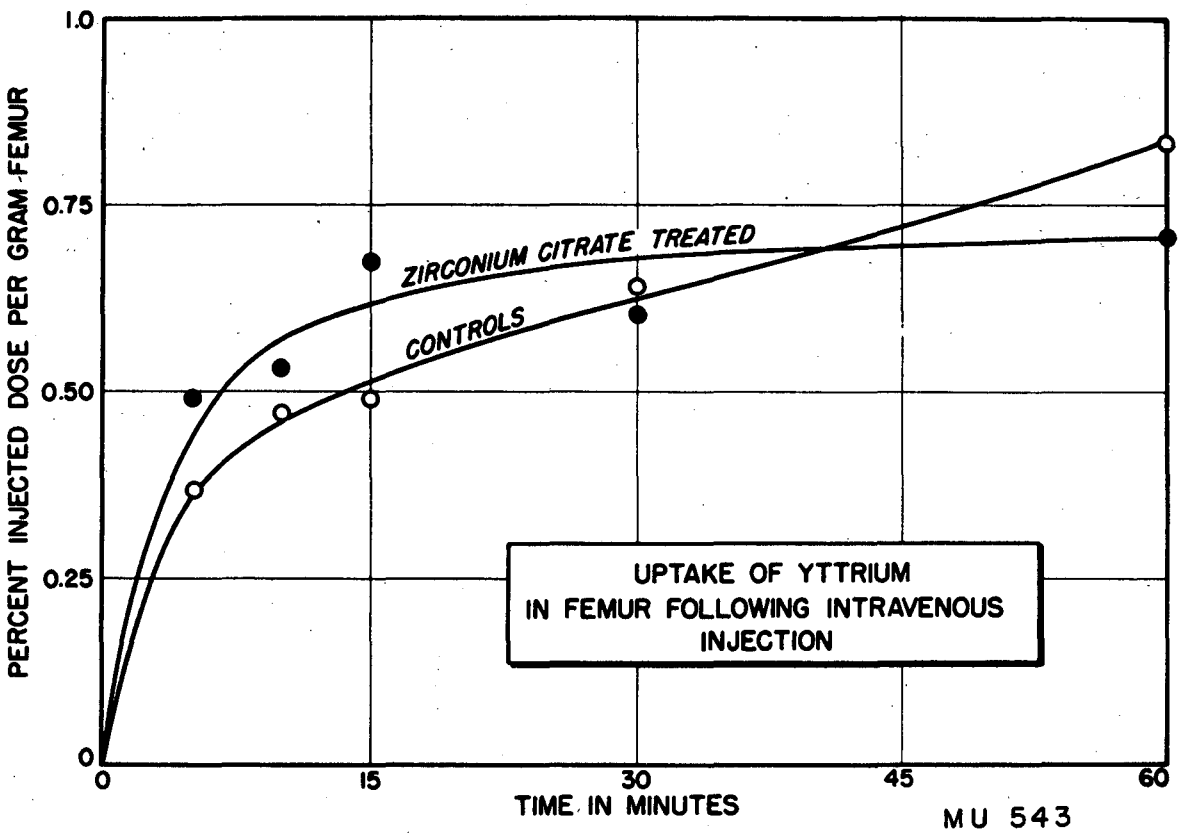
1.0
0.75
0.50
0.25
0
PERCENT INJECTED DOSE PER GRAM FEMUR
ZIRCONIUM CITRATE TREATED
CONTROLS
UPTAKE OF YTTRIUM
IN FEMUR FOLLOWING INTRAVENOUS
INJECTION
0
15
30
45
60
TIME IN MINUTES
MU 543

Fig. 9

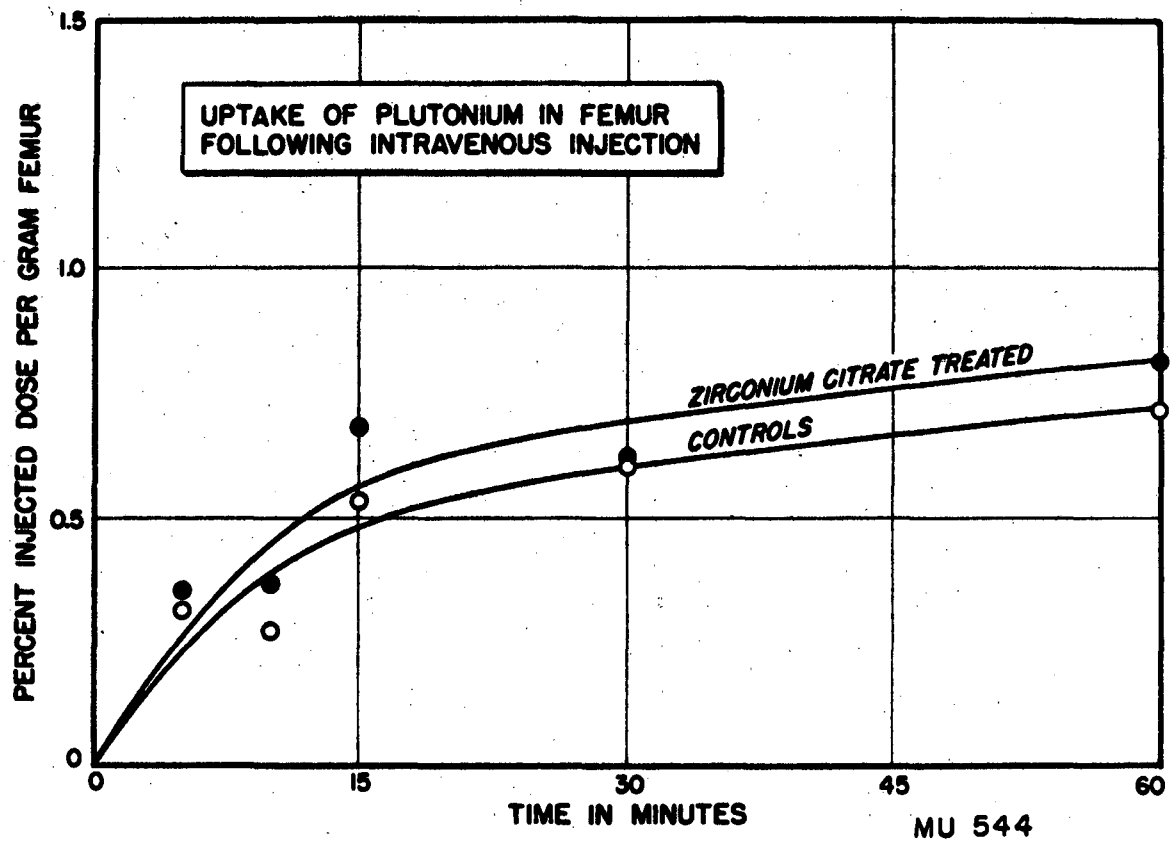
UPTAKE OF PLUTONIUM IN FEMUR
FOLLOWING INTRAVENOUS INJECTION
PERCENT INJECTED DOSE PER GRAM FEMUR
1.5
1.0
0.5
0
ZIRCONIUM CITRATE TREATED
CONTROLS
0
15
30
45
60
TIME IN MINUTES
MU 544

Fig. 10

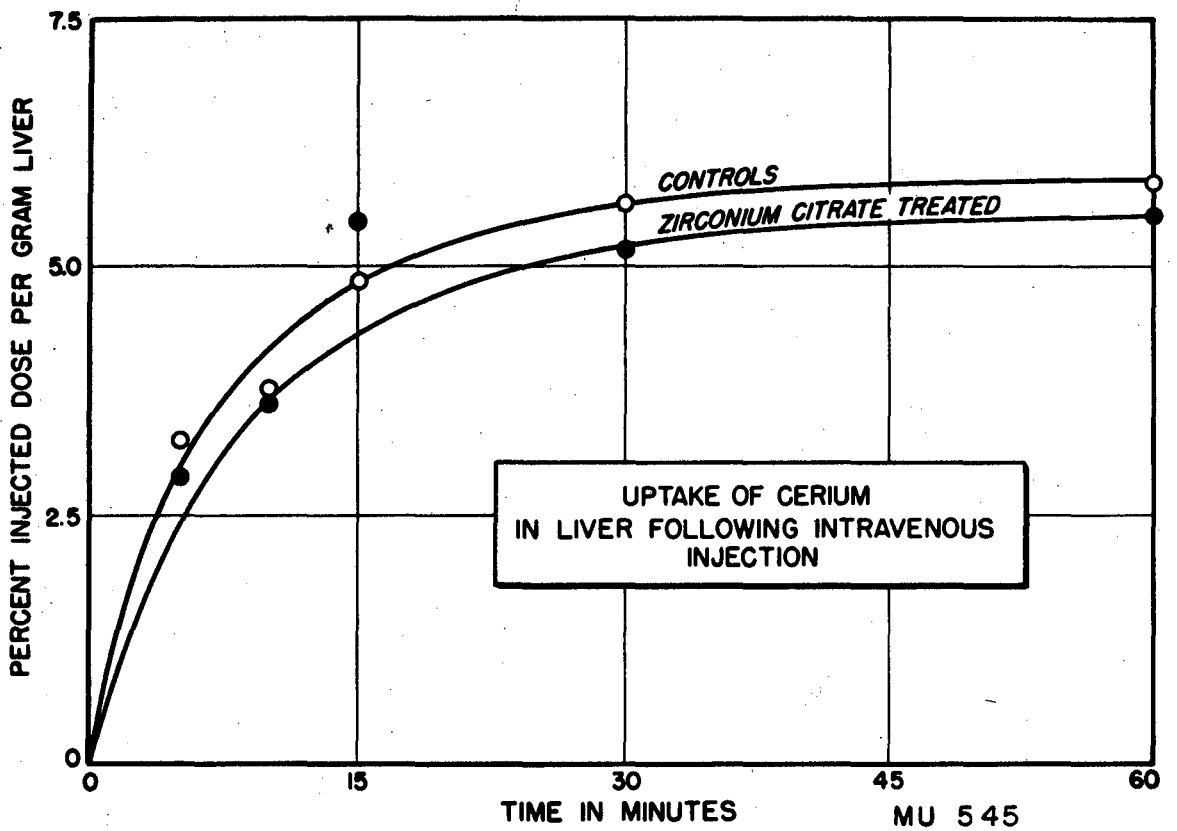
7.5
5.0
2.5
0
PERCENT INJECTED DOSE PER GRAM LIVER
CONTROLS
ZIRCONIUM CITRATE TREATED
UPTAKE OF CERIUM
IN LIVER FOLLOWING INTRAVENOUS
INJECTION
0
15
30
45
60
TIME IN MINUTES
MU 545

Fig. 11

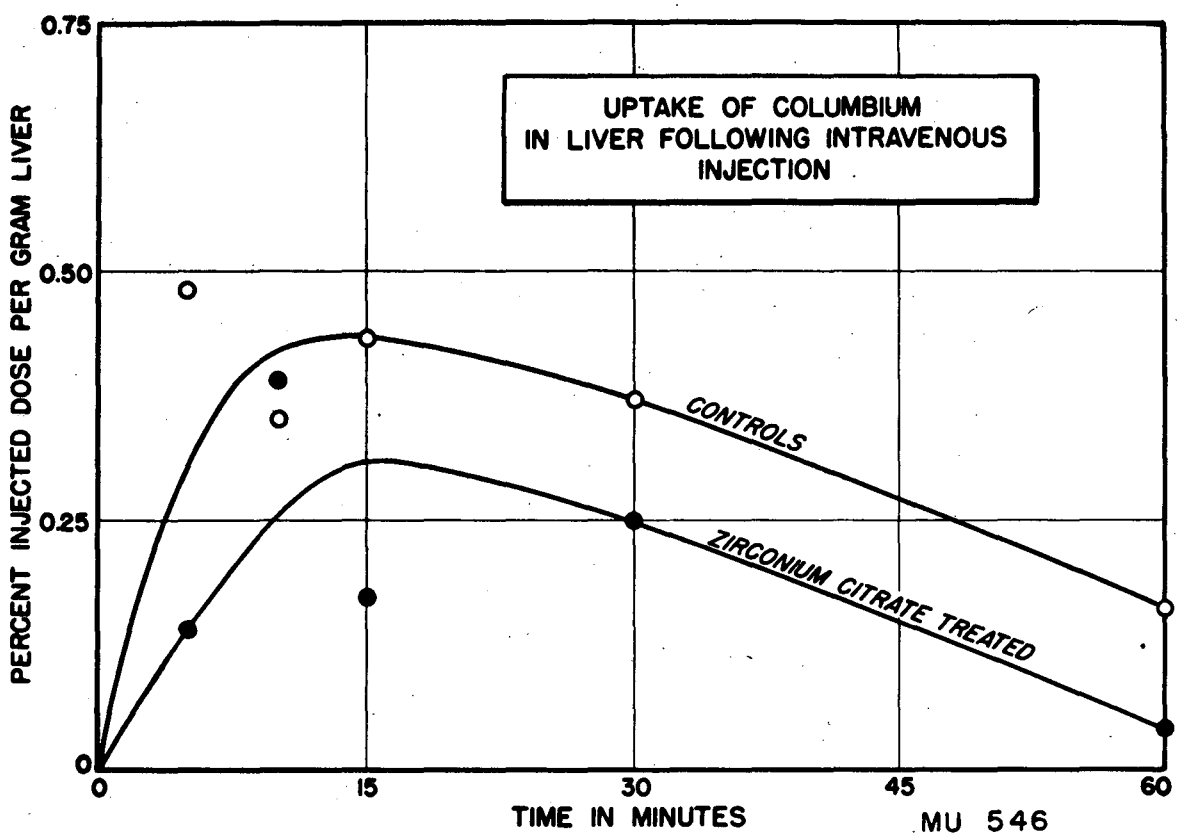
UPTAKE OF COLUMBIUM
IN LIVER FOLLOWING INTRAVENOUS
INJECTION
PERCENT INJECTED DOSE PER GRAM LIVER
0.75
0.50
0.25
0
CONTROLS
ZIRCONIUM CITRATE TREATED
0
15
30
45
60
TIME IN MINUTES
MU 546

Fig. 12

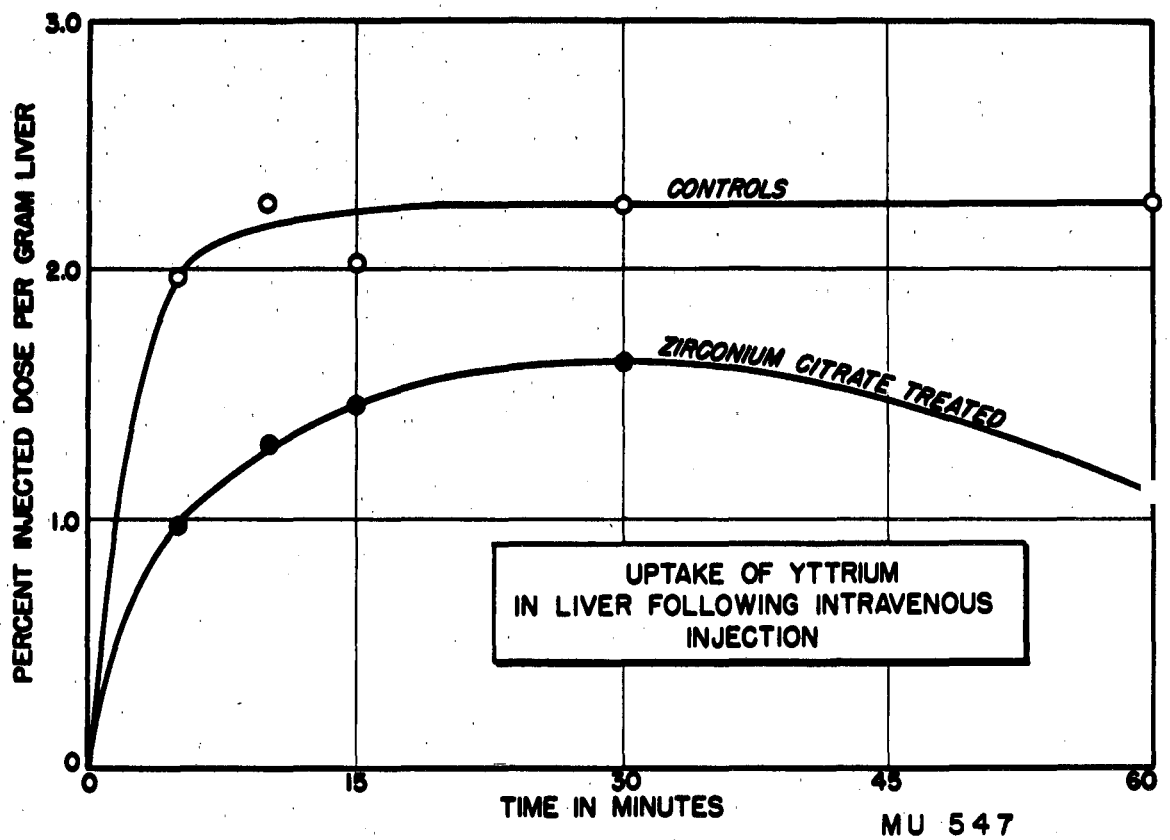
3.0
2.0
1.0
0
PERCENT INJECTED DOSE PER GRAM LIVER
CONTROLS
ZIRCONIUM CITRATE TREATED
UPTAKE OF YTTRIUM
IN LIVER FOLLOWING INTRAVENOUS
INJECTION
0
15
30
45
60
TIME IN MINUTES
MU 547

Fig. 13

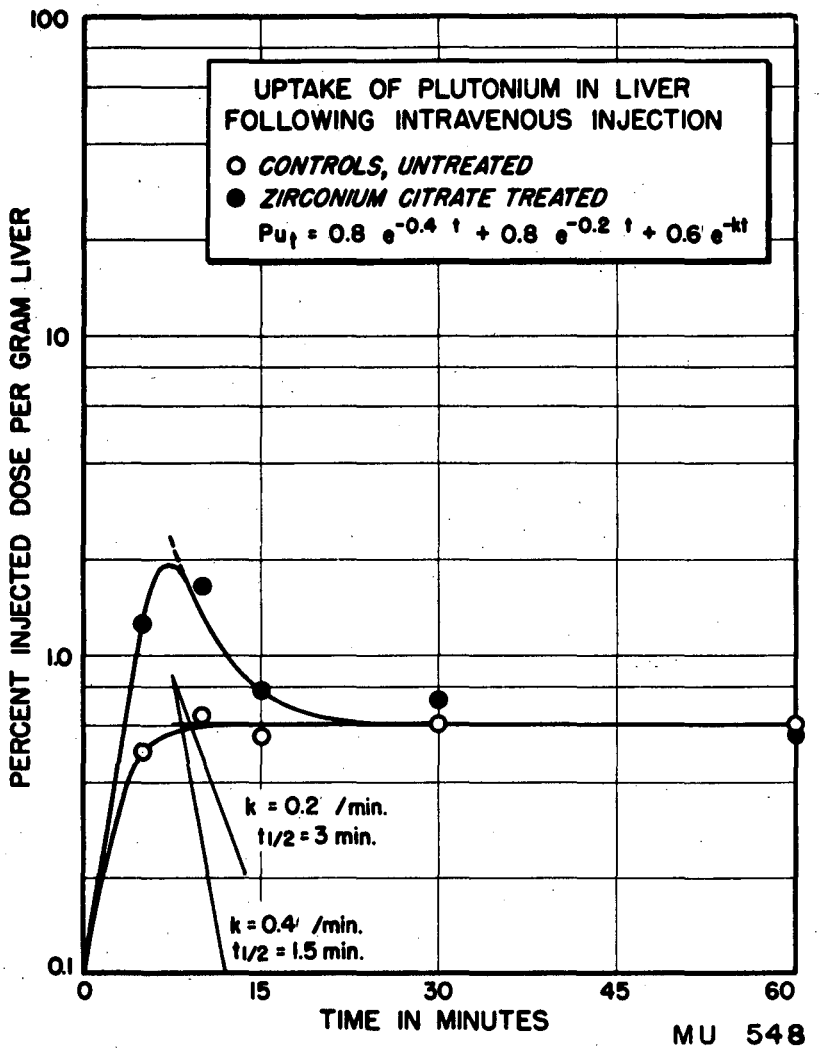
UPTAKE OF PLUTONIUM IN LIVER
FOLLOWING INTRAVENOUS INJECTION
O CONTROLS, UNTREATED
● ZIRCONIUM CITRATE TREATED
$Pu_t = 0.8\ e^{-0.4\ t} + 0.8\ e^{-0.2\ t} + 0.6\ e^{-kt}$
PERCENT INJECTED DOSE PER GRAM LIVER
100
10
1.0
0.1
k = 0.2 /min.
t1/2 = 3 min.
k = 0.4 /min.
t1/2 = 1.5 min.
0
15
30
45
60
TIME IN MINUTES
MU 548

Fig. 14

The Effect of Calcium-Versene Complex on the Excretion of Radio-calcium in the Rat

Versene, the tetrasodium salt of ethylenediamine tetra-acetic acid, is a chelating agent which forms a very tight complex with calcium. It has already been shown to have value for removal of certain radioactive metals from the body. Because of its affinity for calcium and other alkaline earths, it was felt that it might be of value for removal of radio-calcium and radio-strontium.

In the following experiment, the effect of a large dose of a calcium-versene complex on the excretion of Ca^{45} has been studied.

Procedures:

Mature adult rats were used for this experiment. They were injected with approximately .5 microcuries of Ca^{45} in isotonic solution containing 1.5 mg of calcium. The controls received no further treatment. The second group received 100 mg of versene as the disodium calcium versenate complex, by intraperitoneal injection at the same time the Ca^{45} was administered. This solution was twice isotonic strength, but appeared to cause no discomfort to the animals. The third group received the same dose of the versene complex 15 minutes after the injection of Ca^{45}.

There were six rats in each group, and they were placed in individual metabolism cages so that urine and feces could be collected separately. The animals were sacrificed after 48 hours, and urine and femurs were analyzed for Ca^{45}. The results are given in Table I.

The calcium-versene complex used was made up as follows. Ten grams of versenic acid, 3 grams of sodium carbonate and 3 grams of calcium carbonate were dissolved in 100 cc of distilled water. Using methyl red as indicator, the solution was brought to neutral pH by addition of sodium carbonate. The dose used for treatment was 1 cc of this solution, administered by intraperitoneal injection.

Discussion:

Treatment with calcium-versene complex resulted in a very significant increase in the urinary excretion of Ca^{45}, which was most marked (10x) treatment was given at the same time as the radio-calcium, but was considerable (5x) even when the treatment had been delayed 15 minutes. The reduction in the Ca^{45} deposited in the femur was significant, but much less marked. It is probable that the calcium-versene complex acts as "carrier", exchanging with Ca^{45} in the blood and soft tissues, and increasing the excretion in urine. Its effectiveness appears to decrease as the Ca^{45} becomes fixed in bone. This preliminary experiment suggests that prompt treatment with calcium-versene complex may have some value in removing radio-calcium from the body. It is planned to test its effectiveness with radio-strontium.

Conclusions:

1. Calcium-versene complex injected 0 or 15 minutes after administration of Ca^{45}, resulted in a very significant increase in the urinary excretion of radio-calcium.

TABLE I

EFFECT OF CALCIUM-VERSENE COMPLEX ON THE EXCRETION OF RADIO-CALCIUM

	Percent Dose of Ca^{45} ± Std. Error	
	Urine	Femur
Controls (untreated)	3.9 ± 1.0	5.05 ± 0.14
Calcium-versene complex at 0 minutes	34.1 ± 2.7	3.90 ± 0.15
Calcium-versene complex at 15 minutes	16.8 ± 1.9	4.68 ± 0.17

2. This treatment also produced a small reduction in the amount of Ca^{45} in bone.

3. Prompt treatment with calcium-versene complex may have some value for biological decontamination of radio-calcium and radio-strontium.

Radiochemistry

W. M. Garrison

Carrier-Free Be^7 from Lithium. The 52.9-day Be^7, produced by (d,2p) reaction on lithium, was isolated using a procedure based on the observation that Be^7 forms a radio-colloid in dilute alkaline solution. The bombarded lithium metal is dissolved in water to give a solution of lithium hydroxide containing the Be^7 as a radio-colloid which is removed by passing the solution through a sintered glass filter. The adsorbed radio-colloid of Be^7 is removed from the sintered glass filter by washing with dilute hydrochloric acid. Half-life and mass absorption data obtained with Be^7 separated by this method agree with published values.

Carrier-Free $Ta^{176, 177, 178, 182}$ from Hafnium. The long-lived radio-isotopes of tantalum, $Ta^{178,182}$ were prepared by alpha particle bombardment of hafnium according to the reaction Hf(d,αpn)Ta. A carrier-free procedure was developed for isolating the radio-tantalum from the hafnium oxide target material and from the radio-wolfram concurrently produced by (α,xn) reaction. The bombarded HfO_2 is fused with $NaOH-NaNO_3$ and leached with a minimum volume of cold water. The radio-tantalum and radio-wolfram are soluble and are separated from the HfO_2 residue by centrifugation. The supernatant is evaporated with excess concentrated HCl and the precipitated NaCl is centrifuged down. The HCl solution containing the radio-tantalum and radio-wolfram is evaporated to dryness in a platinum dish. HfO_2 hold-back carrier is added and the mixture is re-dissolved in $HF-H_2SO_4$. The HF is removed by evaporating the solution to sulfuric acid fumes and the resultant solution is neutralized with excess NH_4OH and heated after the addition of $(NH_4)_2S$ solution. The carrier-free radio-tantalum is retained on the HfO_2 precipitate which is formed and the radio-wolfram remains in the supernatant solution. The HfO_2 carrier is separated from the carrier-free radio-tantalum by a second $NaOH-NaNO_3$ fusion.

The shorter-lived radioisotopes of tantalum, $Ta^{176,177}$ were prepared by deuteron bombardment of HfO_2 according to the reaction Hf(d,xn)Ta to isolate the carrier-free radio-tantalum, the bombarded HfO_2 is fused with $NaOH-NaNO_3$ and digested with a minimum volume of distilled water. The radio-tantalum is separated from the HfO_2 by centrifugation to give a supernatant solution of $Ta^{176,177}$ free from radioactive contaminants.

Astatine. At^{211} was routinely prepared in millicurie amounts. A more rapid procedure has been developed for the separation of At^{211} from the bombarded bismuth foils. After bombardment, the bismuth section is cut from the aluminum and At^{211} is isolated by heating the bismuth to 425°C in a stream of nitrogen carrier-gas at a pressure of 10^{-2} to 10^{-3} mm. The At^{211} is collected on a cold-finger which is covered with a thin layer of ice. After heating the bismuth for approximately 20 minutes, a solution of At^{211} in a minimum volume of water is obtained simply by removing the cold-finger from the vacuum line and warming to room temperature.

Other Activities. Solutions of Oak Ridge Tb^{160} in millicurie amounts have been prepared for biological studies.

II BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge

Project 48A - I

Metabolism of Carbon^{14} Labeled Glycine

N. I. Berlin, T. Prentice, and J. H. Lawrence

Introduction. The nature of the anemia in chronic leukemia and the polycythemia in polycythemia vera remains unexplained. Studies in this laboratory with radioactive iron indicate that in both leukemia and in polycythemia the rate of production of red blood cells may be considerably altered[1]. However, from these studies no conclusions can be definitely drawn with regard to the life span of the red blood cells, although an estimate of the mean cell life can be made. Glycine has been shown to be a specific precursor for the protoporphyrin of hemoglobin and from the results of the assay of the amount of isotopic nitrogen^{15} in hematin following the ingestion of nitrogen^{15} labeled glycine the life span of the red cell may be measured[2]. The purpose of this study was to measure the life span of the red blood cell in leukemia and polycythemia, with C^{14} labeled glycine, to investigate the excretion of carbon^{14} following the administration of carbon^{14} labeled glycine, and to measure the turnover rate of the plasma proteins.

Methods. Approximately 8 mg of glycine labeled in the alpha position with 100 microcuries of carbon^{14} was injected intravenously into a series of three patients. The patients were placed in an oxygen tent (however, no supplemental oxygen was supplied) and the air was allowed to circulate through the tent and through a soda-lime filter to remove the carbon dioxide. In addition another opening in the tent was used to continually evacuate air from the inside of the tent to the outside of the building. Frequent samples of the expired air were collected by means of an apparatus designed so that the patient could freely breathe in air, with the expired air being delivered quantitatively to a rubber balloon. This expired air in the balloon was then drawn through two columns of sodium hydroxide solution in order to remove the carbon dioxide. The carbon dioxide was then precipitated as barium carbonate. Frequent blood samples were obtained for the purpose of making hemoglobin and protein analyses. The total urine and total feces excreted were collected for a period of fourteen days. All the samples were dried *in vacuo* and converted to carbon dioxide by the method of Van Slyke and Folch[3] and precipitated as barium carbonate. The red blood cell samples were treated in the following manner; the whole blood was centrifuged, supernatant plasma removed and saved, the cells were then washed three times with sterile saline. Following the third washing the cells were laked with a volume of water approximately twice that of the cell volume; after laking was completed 0.5 cc of toluene was added, shaken up vigorously and then allowed to stand overnight. This was then centrifuged, the toluene lipid containing layer floated to the top and by sticking an aspirating needle through this layer a portion of the hemoglobin solution could be removed, and subsequently dried. Analysis of five of these dry samples for iron show that by dry weight this material was approximately 95 percent hemoglobin. The proteins were separated into the globulin and albumin fractions by the method of Majoor[4]. Aliquots of the urine and feces were taken for carbon^{14} measurement.

A few samples were measured in the nucleometer; the remainder having an activity below 10 disintegrations per minute per milligram of barium carbonate were measured in an ionization chamber.

Results. I. Excretion. The pulmonary excretion of carbon^{14} when administered in the manner described may be described in terms of three rate processes, the first with a half-time of approximately two to four hours, the second with a half time of 10-20 hours, and the third with a half time of about 170 hours. The total pulmonary excretion of carbon^{14} in the first patient amounted to 90 percent and in the second patient to 86 percent of the injected dose. Fig. 1 shows the data from Patient 1 with regard to the half times of these three processes, and Fig. 2 shows cumulative excretion of the Patient 1. In Patient 2 the results were entirely similar. Patient 3 has not been followed for a sufficiently long period of time to observe the slowest component. The urine and feces curves for the first patient have not been completed although enough data is available from the urine excretion to indicate that about five percent of the carbon^{14} was excreted by this route. There is not enough data from the feces curves yet to make any statement except that the excretion by this route is small, probably of the order of one percent or less.

II. Plasma Proteins. Figs. 3-6 show the specific activity of carbon^{14} in the plasma globulins and plasma albumins in the first two patients. The procedure for the separation of the protein was slightly different in the second patient as compared to the first and the two results are not exactly comparable for that reason. The separation of the components of these graphs, particularly that of the first patient for globulins and the second patient for both the globulin and albumin into two components merely indicates that the activity present at any one time may be described by an equation containing the time constants obtained from these components. At the present time we are unable to state definitely which of these components represents the rate of synthesis from glycine and which represents the rate of turnover of this protein in the plasma. However, other data from other experiments cited in the literature would indicate that the slower components in these three graphs, that is with the exception of the albumin in the first patient, represent turnover rate and that the rapid components represent the over-all rate of synthesis of these proteins from glycine.

III. Life Span of Red Blood Cell. Because the life span of the red cell is approximately 120 days in the normal, we have been able so far to follow to completion or almost to completion only the first patient. Fig. 7 shows the specific activity of the hemoglobin in this patient. Analysis by a method of Shemin and Rittenberg[2] shows that the life span of the red blood cell in this patient is approximately 90 days. Fig. 8 shows the initial part of the curve for the specific activity of the hemoglobin of the second and third patients.

Discussion. I. Pulmonary excretion. The data on pulmonary excretion indicate that approximately 90 percent of carbon^{14} is excreted by way of the lungs as carbon dioxide, and, furthermore, that the majority of this compound is excreted very rapidly so that at the end of one day approximately 55 percent of the carbon^{14} has been excreted and at the end of two days approximately 65 percent, 80 percent by eight days and the remaining 10 percent being excreted over a slower period of time. At approximately 40 to 50 days following the injection of the carbon^{14} labeled glycine the specific activity of the carbon dioxide in the expired air is

too low to measure on the most sensitive routine instrument for the assay of carbon^{14} i.e., the ionization chamber. This indicates that at that time the amount of carbon^{14} present in actively metabolizing compounds in the body is extremely low. This pattern of excretion as carbon dioxide would indicate that the use of carbon^{14} in this compound is perfectly safe for human experiments.

II. Plasma Proteins. At the present time no conclusions can be drawn regarding the turn over of proteins, although as mentioned above the slower rate constants probably are those associated with the turnover of these compounds in the blood.

III. Life Span of Red Blood Cells. We can draw no conclusions at this time regarding the life span of the red blood cells in leukemia and polycythemia.

Conclusions. I. Carbon^{14} labeled glycine may be safely administered to human patients because of the large and rapid excretion by way of the lungs as carbon dioxide and the smaller excretion by way of the urine and feces and the almost complete accountability in the excreted products for the labeled carbon.

II. The changes in the activity following the single injection of carbon^{14} in the plasma protein is presented.

III. The life span of the red blood cells of the first patient given carbon^{14} labeled glycine was approximately 90 days.

References

1 Huff, Rex; Hennessy, Thomas G.; Austin, Robert E.; Garcia, Joseph G.; Roberts, Bonnie M.; and Lawrence, John H.; J. C. L. - to be published.
2 Shemin, D.; and Rittenberg, D.; J. B. C., 166, 627, 1946.
3 Van Slyke, D. D. and Folch, J.; J. B. C., 136, 509, 1940.
4 Majoor, C. L. H.; J. B. C., 169, 583, 1949.

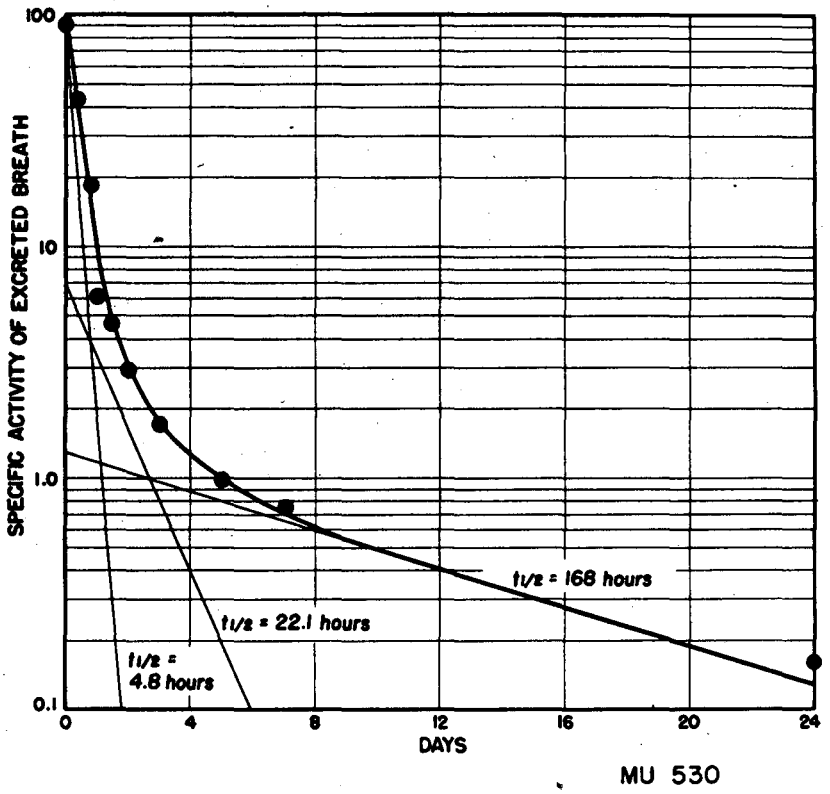
100
10
1.0
0.1
SPECIFIC ACTIVITY OF EXCRETED BREATH
0
4
8
12
16
20
24
DAYS
t1/2 = 168 hours
t1/2 = 22.1 hours
t1/2 = 4.8 hours
MU 530

FIGURE 1

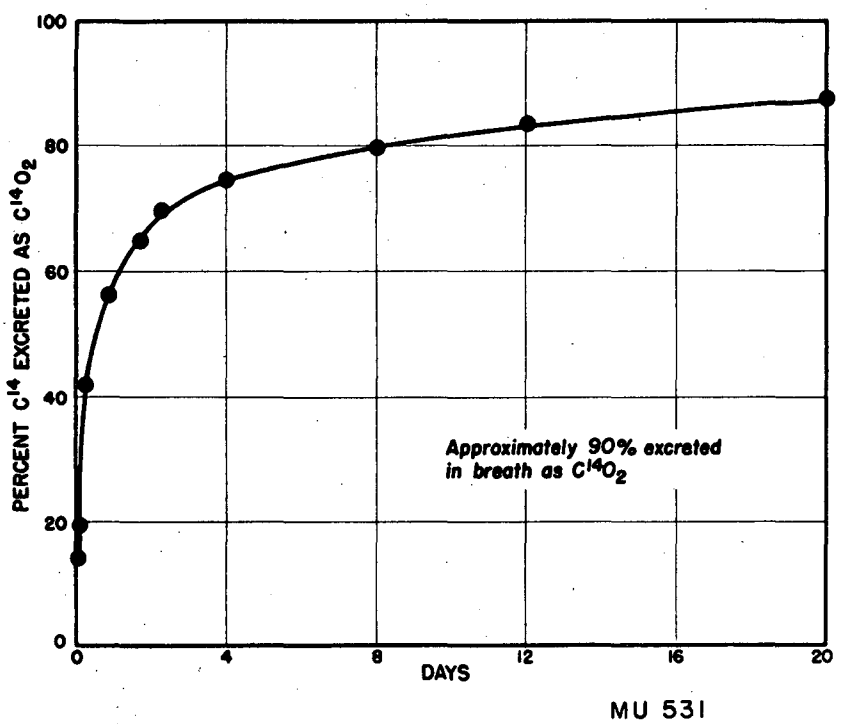
100
80
60
40
20
0
PERCENT C^{14} EXCRETED AS $C^{14}O_2$
0
4
8
12
16
20
DAYS
Approximately 90% excreted in breath as $C^{14}O_2$
MU 531

FIGURE 2

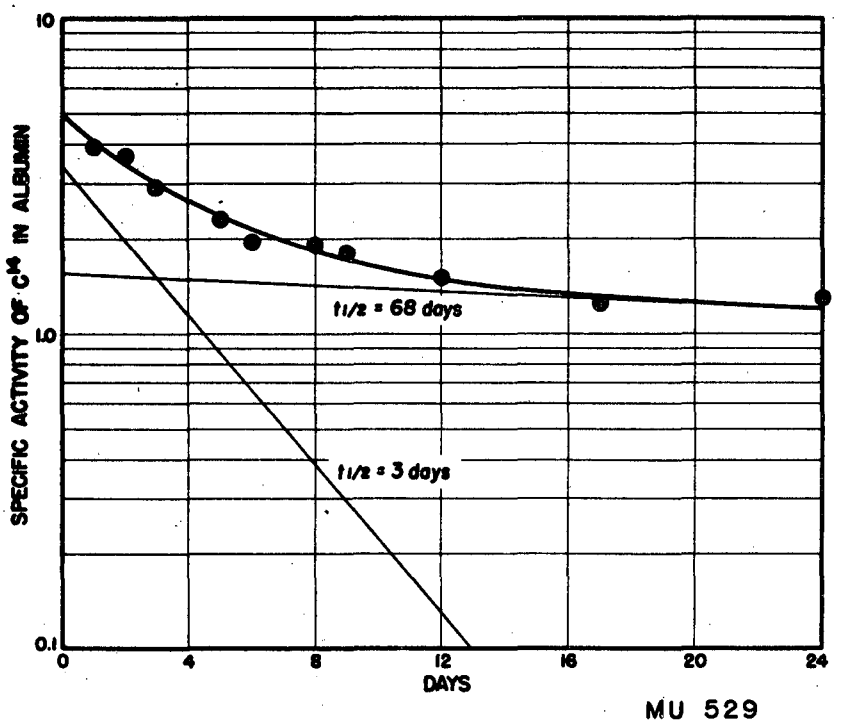
10
1.0
0.1
SPECIFIC ACTIVITY OF C14 IN ALBUMIN
t1/2 = 68 days
t1/2 = 3 days
0
4
8
12
16
20
24
DAYS
MU 529

FIGURE 3

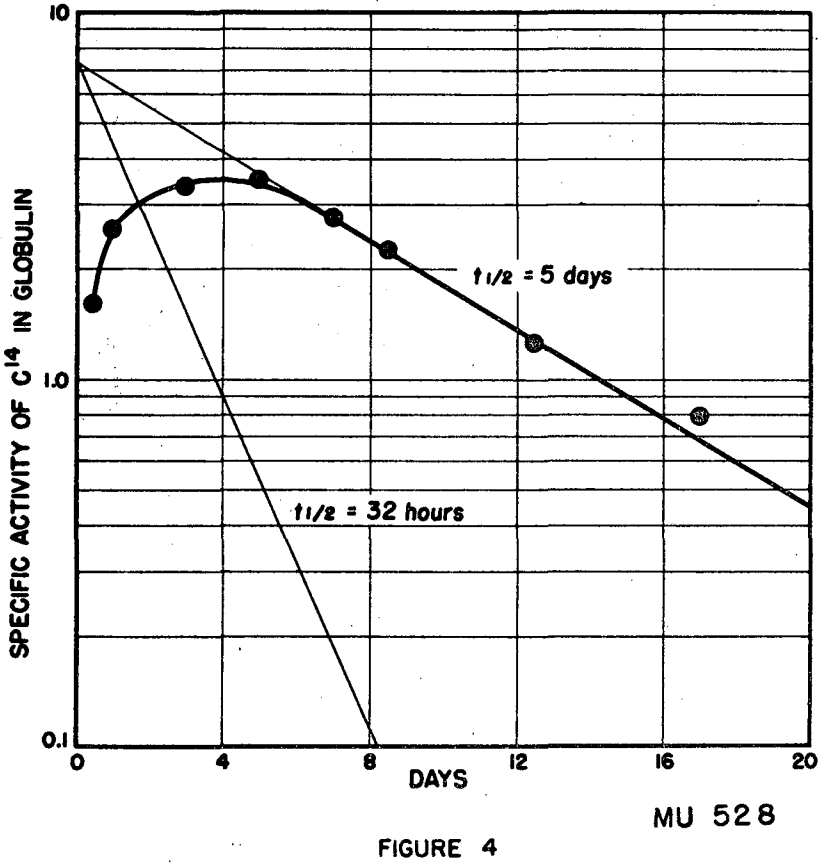
10
1.0
0.1
SPECIFIC ACTIVITY OF C14 IN GLOBULIN
t1/2 = 5 days
t1/2 = 32 hours
0
4
8
12
16
20
DAYS
MU 528

FIGURE 4

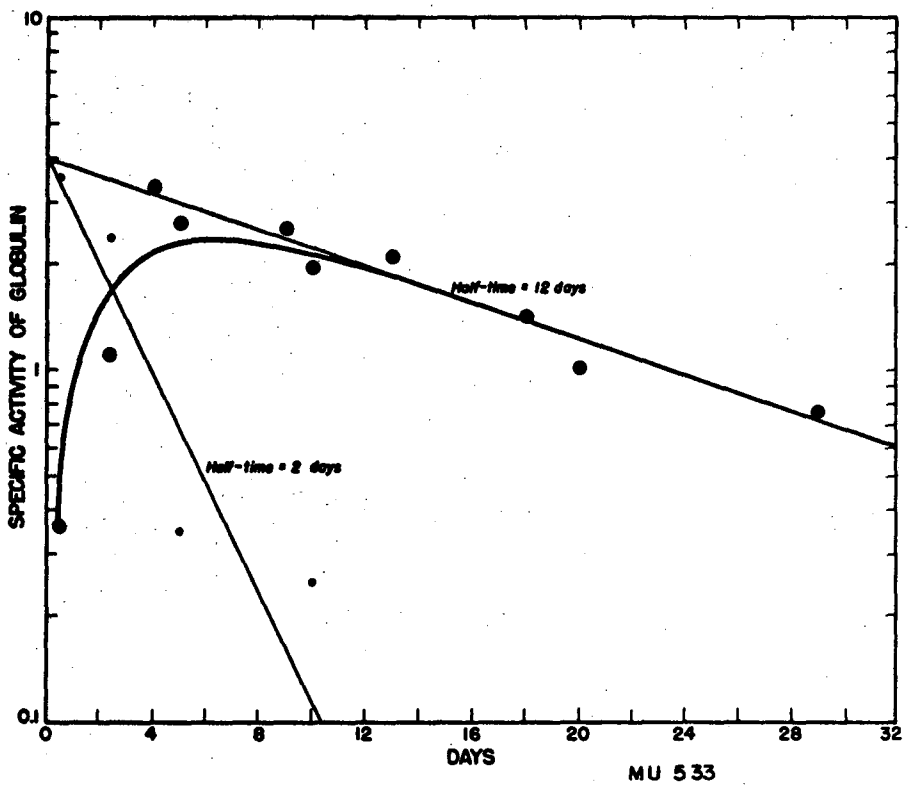
10
1
0.1
SPECIFIC ACTIVITY OF GLOBULIN
Half-time = 12 days
Half-time = 2 days
0
4
8
12
16
20
24
28
32
DAYS
MU 533

FIGURE 5

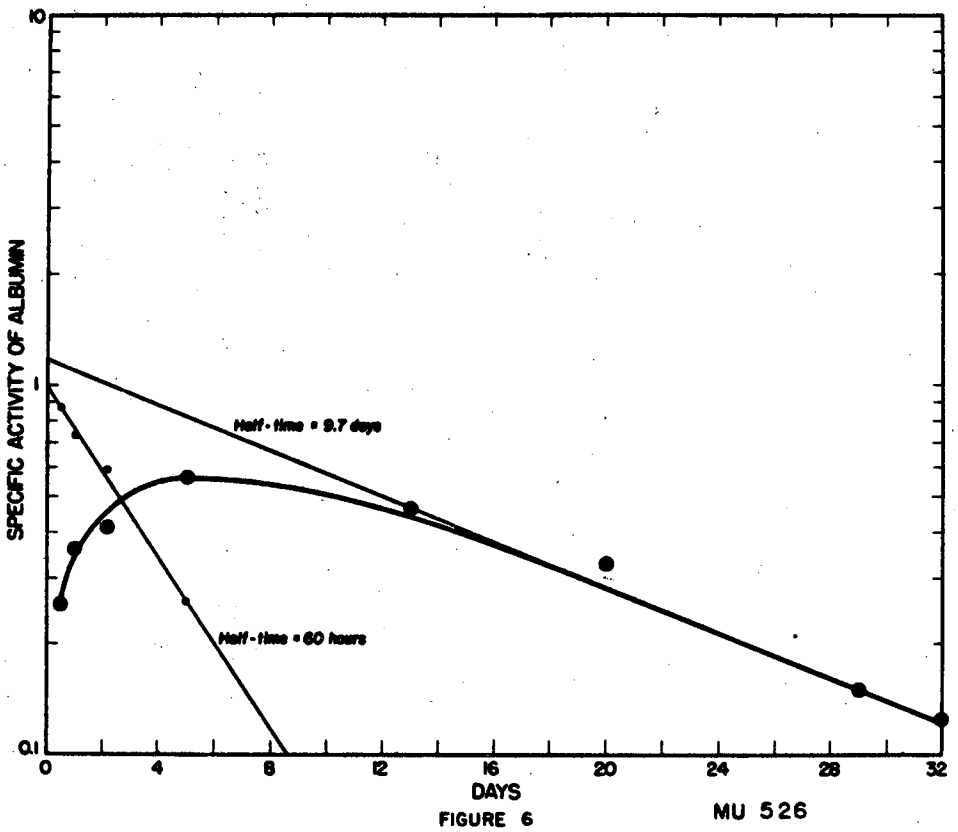
10
1
0.1
SPECIFIC ACTIVITY OF ALBUMIN
Half-time = 9.7 days
Half-time = 60 hours
0
4
8
12
16
20
24
28
32
DAYS
MU 526

FIGURE 6

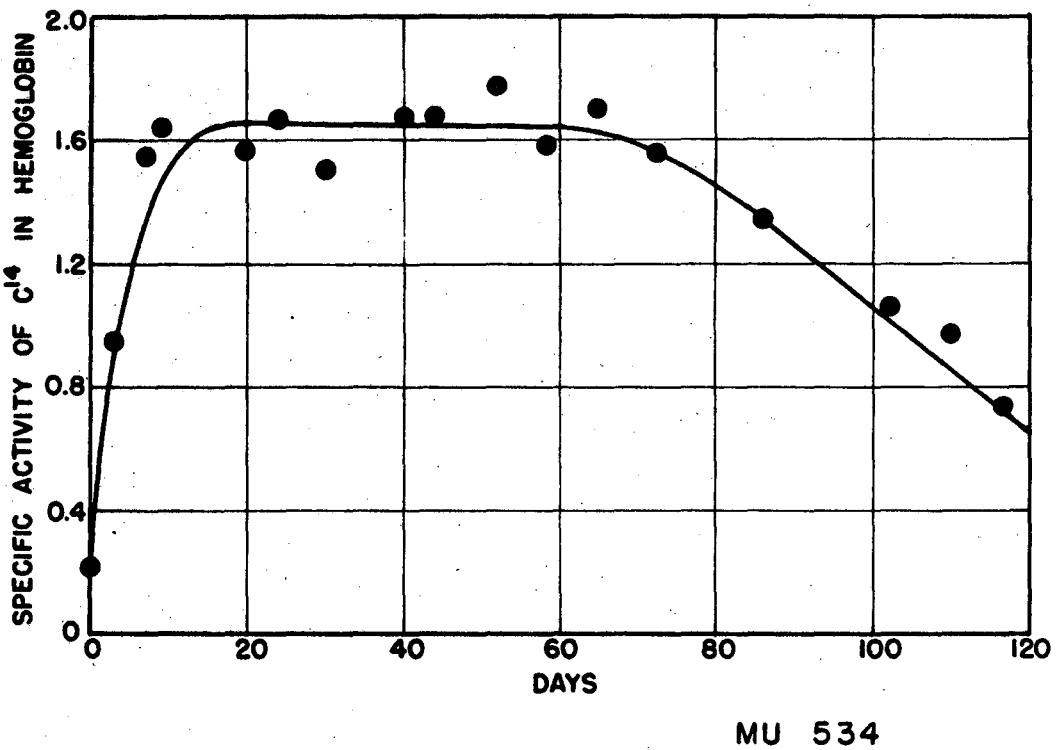
SPECIFIC ACTIVITY OF C14 IN HEMOGLOBIN
2.0
1.6
1.2
0.8
0.4
0
0
20
40
60
80
100
120
DAYS
MU 534

FIG. 7

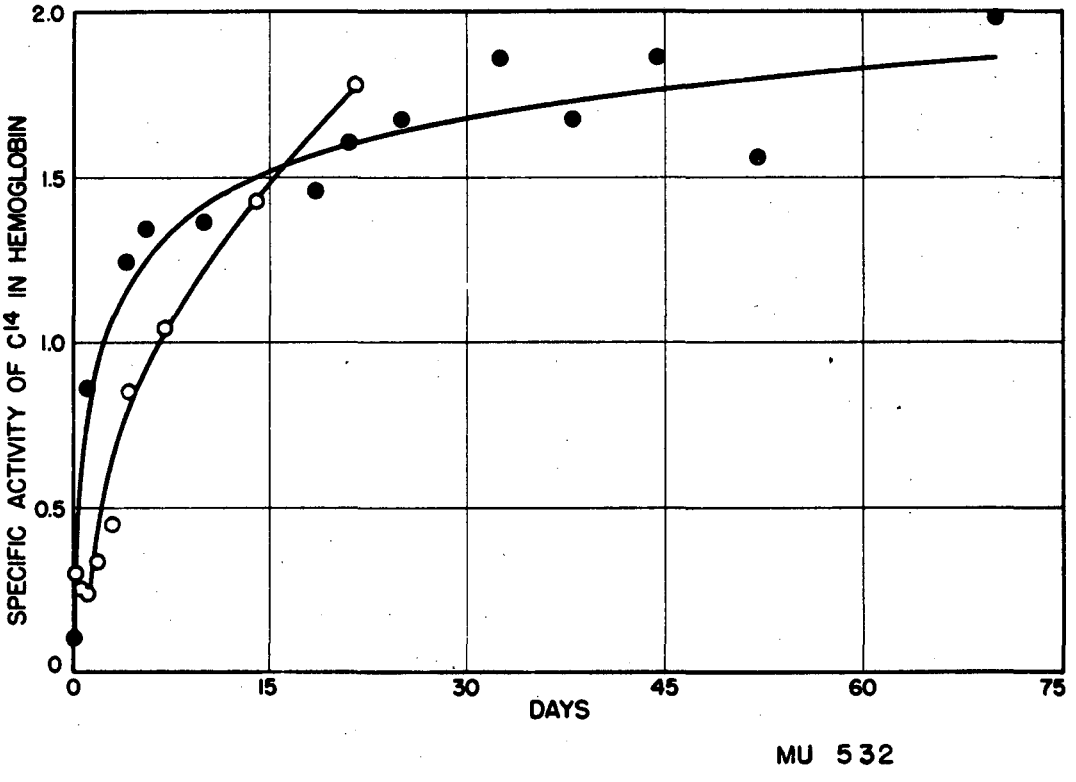
SPECIFIC ACTIVITY OF C14 IN HEMOGLOBIN
2.0
1.5
1.0
0.5
0
0
15
30
45
60
75
DAYS
MU 532

FIGURE 8

The Metabolism of C^{14} Labeled Stilbamidine in Multiple Myeloma

J. C. Weaver, J. C. Reid, B. J. Krueckel and J. H. Lawrence

The studies of Snapper[1] and his colleagues have shown that stilbamidine is effective in alleviating the severe bone pain of multiple myeloma, and that following the administration of this compound for a long period of time granules appear in the myeloma cells which by physical-chemical analyses, principly by means of staining reactions and ultra-violet light absorptions, appear to be stilbamidine-ribose-nucleic acid complex. For that reason a study of the distribution of C^{14} labeled stilbamidine was undertaken in experimental animals and is being reported elsewhere[2]. Following the study in experimental animals, a patient with multiple myeloma was selected for study with C^{14} labeled stilbamidine.

Methods. A patient with multiple myeloma in whom the diagnosis was established by sternal puncture and the presence of multiple lytic lesions in the bone was given intravenously 60 mg of C^{14} labeled stilbamidine. The exhaled breath was collected at frequent intervals up to 17 days by the same method as described in the first part of this progress report on the metabolism of glycine. Frequent blood samples were taken and the urine and stools collected during the lifetime of this patient (3 months). The samples were all dried in vacuo, combusted in a furnace, and the CO_2 collected in sodium hydroxide and precipitated as barium carbonate. The samples were measured with an end window counter, Nucleometer, or ionization chamber, depending upon the activity.

Results. Breath. A minute but measurable amount of C^{14} was found in the breath in only one sample and that at fifteen minutes after administration.

Plasma Levels. The first blood sample was taken 3 minutes after end of administration. Subsequent samples were taken at increasing intervals for 3 months. The first sample showed that approximately 10 percent of the injected activity was still present in the total plasma. Thereafter the plasma concentration rapidly fell. The amount present in the total plasma 24 hours after injection was 0.1 percent of the administered activity. The first plasma sample that did not contain a measurable quantity of C^{14} was 36 days after injection.

Red Cells. The red cell concentration was small and possibly in part represented contamination from the plasma.

Excreta. Urine
1st 24 hours: (2 percent injected dose)
2nd 24 hours: (1 percent injected dose)
3rd 24 hours: (0.7 percent injected dose)

Thereafter the daily excretion of activity was roughly between 0.1 - 0.3 percent of the injected dose. Subsequent samples have not yet been counted.

Feces. Results vary considerably from sample to sample, perhaps due to irregularity of fecal excretion. Several aliquots of each sample are being run in an effort to minimize the error produced by inhomogeneity. Samples are not yet completely analyzed but the present indications are that more activity is excreted in the feces

than by the urine during the first week (approximately 5 percent).

Biopsy Specimens. The following tissues were analyzed at intervals of 2, 10 and 75 days after injection: tumor, bone, muscle, skin and fat. Results:

Date	Tissue	Relative Activity
1/19/50	Tumor	9.8
	Muscle	4.1
1/27/50	Tumor	9.1
	Muscle	1.9
4/6/50	Tumor	1.8
	Muscle	2.0

The other tissues were consistently lower in activity.

Autopsy: (Death occurred three months after injection).

4/14/50. The following results are being verified by the analysis of duplicate samples.

Tissue	% of injected dose
Liver	67.
Kidneys	1.3
Lungs	0.6
Adrenals	0.016

Summary. Although results are not complete, the indications are that over the three month period between injection and autopsy roughly 15 percent of the administered activity was excreted in the urine and possibly between 10-15 percent in the feces.

By far the largest site of localization of activity in this patient occurred in the liver, where almost 70 percent of the activity was still present three months after administration. Other tissues so far tested including tumor contain insignificant concentrations in comparison. This very large liver concentration is in contrast to the findings in mice[2].

During the early period of the experiment the tumor concentrated more activity than other tissues analyzed, but the concentration was not sufficient to suggest that this material could be given in therapeutic doses to this patient.

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[1] Snapper, I. J.A.M.A. 137, 513, 1948.
[2] Reid, J. C. and J. C. Weaver - to be published.

Measurement of Total Body Water by Means of Tritium

N. I. Berlin, W. Siri, T. Prentice, and J. H. Lawrence

Introduction. The measurement of total body water is of great importance in the clinical investigation and management of certain classes of diseases, particularly those associated with congestive heart failure and renal disease. With the determination of total body water, together with blood volume studies and sodium space studies, one can completely quantitate the body fluids. The purpose of this report is to present the data obtained so far in total body water measurements.

Method. The patient is given 1 cc of an isotonic solution of HTO containing approximately 2 mc of tritium. Blood samples are taken at three, six, and twenty-four hours following the administration of the tritium. The tritium was analyzed by the method of Siri[1].

Results. Fig. 1 shows the rate of disappearance of tritium from the plasma of the first three patients and the method of calculation of the total body water. Table I shows the total body water in a small group of selected patients.

Discussion. The data at present do not permit any conclusion to be drawn with regard to disease states, and for the present the principle conclusion to be drawn is that tritium forms the most satisfactory and simple method for the measurement of total body water. These measurements should prove to be of considerable value in understanding the pathological physiology and the treatment of patients who have disturbances in water metabolism.

TABLE I

Subject	Volume in Liters	% Body Weight
A	38.7	53
B	38.9	69
C	43.4	68.7
D	40.3	73.0

[1] William Siri, to be published.

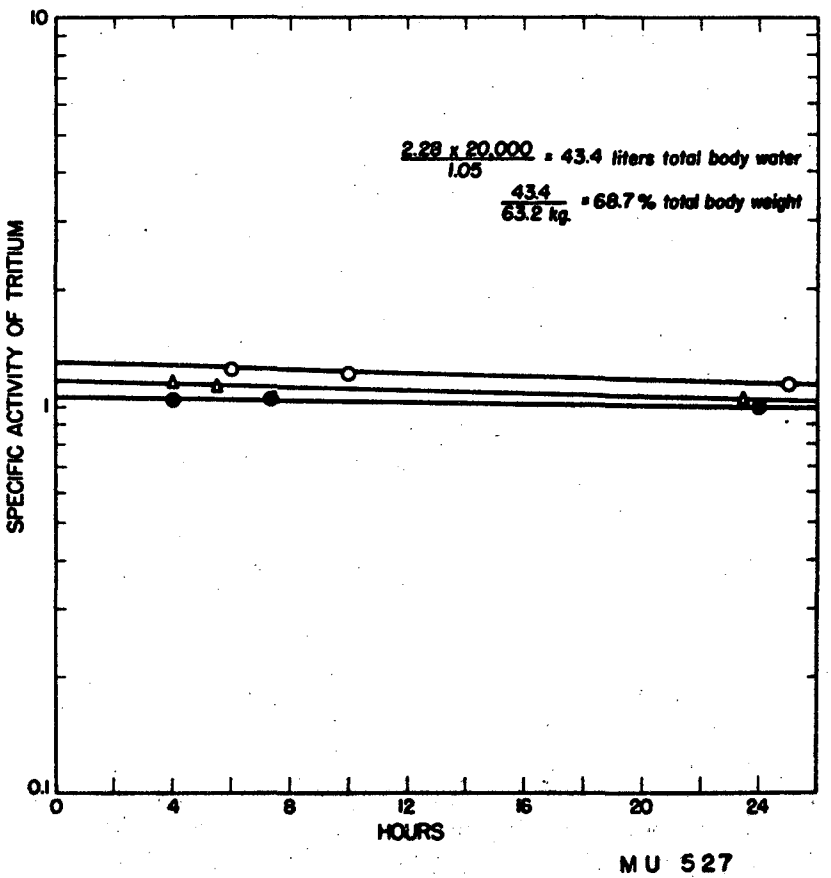
10
1
0.1
SPECIFIC ACTIVITY OF TRITIUM
0
4
8
12
16
20
24
HOURS
2.28 x 20,000 / 1.05 = 43.4 liters total body water
43.4 / 63.2 kg. = 68.7 % total body weight
M U 527

FIGURE 1

III HEALTH CHEMISTRY AND PHYSICS

Health Chemistry

N. B. Garden

Monitoring. In addition to the routine monitoring activities of checking areas for the presence of unconfined activity, furnishing routinely needed supplies, monitoring targets and samples, new processes have been developed which provide further safety features for handling radioactive materials. A setup has been created and employed with excellent success for injecting rats with plutonium, feeding them, capturing all excreta, sacrificing them, ashing and performing desired chemistry all within a Berkeley Box. A system has been set up whereby radioactive samples are loaded and transferred to the beta spectrometer, also in enclosed areas at all times. In similar fashion, a procedure has been designed and successfully put into practice whereby curium and other high alpha activity specimens for x-ray analysis are loaded on the camera stage within a Berkeley Box, transported to the x-ray laboratory, mounted into the camera again within a box. During the last step the whole system is connected to an exhausted vessel for the purpose of capturing the activity, should the curium-containing sample rupture. A special filter was created for placement between the pump and the exhausted vessel while evacuation was being maintained. The vacuum-operated carrier system originally designed to carry special foil-and powder-loaded targets to be bombarded to study short-lived isotopes, has been adapted to handle essentially most of the regular targets off the cyclotron. A room, used extensively during the war and the last five years for processing large quantities of alpha-emitting materials, has been readied for conversion to a regular clean laboratory. A completely automatic process for the liquid-liquid phase extraction of cobalt has been set up and used with success. A system has been invoked whereby coordination between chemists and guards with respect to apparatus and equipment left running during the night is achieved.

Transportation, Decontamination, Disposal and Storage. In addition to the routine transportation of radioactive materials, targets, shipments in and out of the project, waste disposal and storage of materials, the decontamination chamber in the new annex has been put into use. This plywood chamber is considered a working model. High level decontamination will be done in it for about a year during which time any difficulties presented by its design will be worked out. Following this the permanent metal chamber will be constructed. The main high-level activity objects which are being decontaminated are gloved boxes and their contents. The chamber, with its glove-port-studded sides and mechanized dolly, has proved to be a very successful attack on the decontamination problem. After only a few weeks use, it appears that the basic idea is sound and only minor changes will be made in the permanent model.

Research and Development. Three bombardments from Hanford were received during this period, the equipment for processing of which was put in working order by this group, entailing all the gloved- or lead-box fittings requisite to the flow sheet for each sample. This group has also been working with the dissolver-solution processing group whose equipment includes a pilot plant and six gloved box installations. The largest portion of time has been spent in preparing for a bombardment from the Chalk River reactor, to arrive in July.

Health Physics

B. J. Moyer

Neutron Fields in the 184-inch Area. Study of the fast neutron fields around the 184-in. cyclotron has been continued. With a high-energy, high-intensity proton beam in the reversed direction it had been found that a region on the north side within 10 ft. of the shielding and about 60° wide had from 10 to 20 times the tolerance energy flux density of 86 Mev per cm^2 per second. This was determined on several different days under slightly different conditions. Moreover a shop within Building 6 on the mezzanine received considerably above tolerances fluxes also. It was decided to try to reduce the intensity of neutrons by putting a lead wall 4 ft high by 2 ft wide by 2 ft thick in the north end of the cyclotron vacuum tank. Under the best conditions of normal operation this lead shield reduced the intensity to about one-third of previous high values, around the walls, while also spreading out the cone of highest intensity another 30°.

It was noticed during a recent survey that one region near the north door at normal beam levels and very close to the concrete shielding door, but ordinarily inaccessible, was at a level of 70 times tolerance, indicating weakness in the concrete shielding. Since some concrete blocks will soon be available it will be possible to cut down this level considerably. A recent survey with 5 ft. of additional shielding consisting of a block 5 ft. thick of concrete at 10 ft. from the permanent shielding showed that going only 2° of arc into the shadow of this block from the region directly outside the north door steps reduced the intensity from 16 times tolerance to twice tolerance.

With these 5 ft. thick by 13 ft. high blocks projecting five feet above the cyclotrons median plane the intensity in the mezzanine shop was from 1-1/2 to 2 times tolerance in the block's shadow.

It has been found that the area survey meter in the region studied showed intensities closely correlated with the neutron intensities, and may therefore be used roughly as a neutron monitor for this region.

Development of High Energy Neutron Counter with Increased Efficiency. The requirements of surveying the neutron field outside the shielding of the 184-in. cyclotron have led to the development of a bismuth fission ionization chamber counter with efficiency increased at least ten fold over those formerly employed in high energy neutron research.

For this purpose a multiple plate chamber, employing ten grams of bismuth, deposited by chemical processes in the form of bismuth oxide in a layer possessing about 1.5 milligrams per square centimeter of bismuth, has been constructed. After some routine difficulties in holding the necessary voltage, leading finally to the use of teflon insulation, the chamber has demonstrated satisfactory voltage and bias plateaus. Its counting rate outside the shielding is in a range which gives sufficient statistical accuracy for survey work. As elsewhere reported the neutron energy threshold for the fission of bismuth is about 50 Mev and the increase in fission cross section with neutron energy has been roughly determined in connection with other experimental work. Consequently, approximate estimates of the actual flux of neutrons over 50 Mev in energy can be made.

Statistical Summary of Monitoring Program. Survey Instruments Maintained:

1. B-Y Ionization Chambers	28
2. Victoreen 263 Meters	19
3. I.D.L. Portable Survey Meters	18
4. Cutie Pies	2
5. Recording Y-intensity Meters	11
6. Victoreen Proteximeters	3
7. Fast Neutron Proportional Counters	5
8. Slow Neutron Proportional Counters	5
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	1625
2. Total man days coverage with pocket chambers	1503
3. Total man days coverage with pocket dosimeters	3311
4. Total man days coverage with pocket chambers (SN)	3068

Cases of weekly exposure above .3r:

Weekly film exposure above	184" Area	60" Area	Linear Accelerator	Synchrotron	Chemistry	Total
.3r	8	15	37	0	13	73
.5r	2	3	4	0	5	14
1.0r	0	1	0	0	1	2
1.5r	0	1	0	0	0	1
5.0r	0	1	0	0	0	* 1

*This exposure was received during an experiment on the 60-in cyclotron. The experiment necessitated the removal of several targets immediately after bombardment.

The experimenter failed to notify the Health Chemistry or Health Physics groups that this experiment was to be performed. The responsible people at the 60-in. cyclotron also failed to notify either Health group.

The experimenter took no special precaution to protect himself from being overexposed.

It has been estimated that the total dose received was not in excess of 10r. This person is being studied by the medical group. At this time his blood picture has presented no abnormalities.

LMB/7-26-50
Information Division