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I THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

J. G. Hamilton

Project 48 A-I

Radioautographic Studies

Berniece Jue and C. W. Asling

The radioautographs in the series of studies on the uptake of various elements by skeletal tissues of the rat at the costochondral junction have just been completed. The series now includes localization 1 and 24 hours after injection of strontium, calcium, element 61, americium and plutonium. Noteworthy differences exist, particularly with respect to deposition of the tracer elements in the calcified cartilage region. Calcium and strontium were similar in their localization throughout this region. Element 61 and americium showed surface localization only. The uptake of plutonium in this calcified cartilage was so slight as to necessitate unusually long exposures to the film in order to obtain any evidence of its presence. Counterstains of the sections are being prepared to facilitate the exact localization of the various elements in the bony, cartilaginous, and ancillary tissues of this site, and a full description and photographic presentation will be included in the next report.

Astatine (At^{211}). Berniece Jue, C. W. Asling, Patricia Wallace, and K. G. Scott. A study on the effectiveness of radioactive At^{211} in the destruction of thyroid tissue is being conducted using dose levels ranging from 1.2 microcuries to 157 microcuries with post injection intervals of 2 and 41 days. Complete autopsies will be made on five groups of rats. Routine histological work will be done on the skin, lachrymal gland, salivary gland, thyroid, trachea, muscle, gonads, cervical lymph node, adrenals, kidney, spleen, pancreas, intestine, stomach, liver, bone marrow, lungs, brain, pituitary, thymus, and heart. The findings will be compared with those after injection of radioactive I^{131}. (See Table I) Red cell counts, white cell counts, and differential white cell counts were taken before injection as controls and at various intervals until autopsy of the animals or until the animals showed sufficient recovery (to 75 percent of normal count).

Changes in the blood picture due to radiation have been well characterized and were used here as a criterion of the extent of radiation damage and the general physical condition of the animals. The major effect is a destruction of the circulating lymphocytes which is noticeable in the decrease in the white cell count and the apparent increase in the percentage of polymorphonuclear leukocytes in the differential count.

The animals used for this study were both males and females of a Curtis-Dunning strain. In a series of blood counts on 24 normal animals the following

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TABLE I

HISTOLOGICAL STUDIES IN PROGRESS OF At^{211} ON THE RAT

No. of Rats	Dosage	Days Interval	Organs to be Studied
1	121 μc	3	Parotid, thyroid area of trachea, stomach, small intestine, large intestine, caecum.
3	1.2 μc	41	Thyroid and trachea
3	6 μc	41	Thyroid and trachea
3	30 μc	41	Complete autopsy
1	82 μc	2	Complete autopsy
2	41.5 μc	41	Complete autopsy
1	157 μc	3	Complete autopsy
1	157 μc	41	Complete autopsy
3	78.5 μc	41	Complete autopsy

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values were established for the blood constituents; red blood cells averaged 7,500,000 per cubic millimeter with a range of from 6,000,000 to 8,500,000, white blood cells average 13,000 per cublic millimeter with a range of from 8,850 to 17,800. In the differential counts 100 cells were counted on slides stained with Wright's stain and the following values were obtained; lymphocytes (these figures combine both adult forms and late juvenile forms) 74 percent with a range of from 64 percent to 85 percent, polymorphonuclear leukocytes (neutrophils) 20 percent with a range of from 11 percent to 30 percent, monocytes averaged 2 percent, eosinophilic leukocytes 4 percent, no basophilic leukocytes were seen.

At the lowest level of At^{211} in which blood counts were taken, dosage used (41 μc) the white count began to fall at 48 hours to about 60 percent of normal and recovery was complete at 13 days. The red cell count remained normal throughout the 13 day period, and the differential counts also remained within normal limits.

At the next dosage level of 78 μc the white count fell to nearly 25 percent of normal in 20 hours and remained at this low level for 8 days with a moderate amount of recovery to the extent of 60 percent of normal at 10 days. Within the ranges given above for the differential counts an almost complete reversal of the percentages of lymphocytes and neutrophilic leukocytes was seen which lasted for 48 hours at which time recovery started and the picture was completely normal at 10 days. The red count remained normal.

At higher dosage levels the effect is essentially the same as for the 78 μc group except that it is slightly more marked. The white count is further depressed to 23 percent of normal and returns to 50 percent at 10 days, although the differential count returns to normal limits in 8 days. Thus with higher dosage level damage is more extensive and recovery is slower. It is too early to tell how completely these animals at higher dosage levels will recover. Data for the above cited dosages are given in Table II.

No notable change was seen in the red cell picture. Such a change may appear later in the higher dose levels.

Even at the highest dosage level only an initially slight loss in weight was noted, and this may be attributed to the animal's loss of appetite following the severe trauma of an intravenous injection.

Grossly we can say that except for the initial blood changes following injection the animals at the dosage levels here used were still in good health. They were alert, showed no dehydration, and seemed to be eating normally.

An investigation is being conducted to show the effects of high dosage levels of the rare earth elements on the gastrointestinal tract, following stomach tube administration of 500-1000 microcuries of Ho^{166}, Yb^{175}, and Lu^{177}. The animals were sacrificed at 8 days following injections, and sections of the stomach, small and large intestine and caecum were taken for routine histological work. These sections will be studied to determine any possible tissue damage.

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TABLE II

BLOOD STUDIES IN PROGRESS OF At^{211} ON THE RAT

Dosage	No. Animals	Av.Wt.	Interval	Count Interval	$RBCx10^6$	WBC	Differential Lymphocytes	White Count Neutrophils
41.5 µc	2	190 gm	40 days	control	8.06	10,000	74	20
				46 hrs	7.54	7,490	64	29
				6 days	7.95	5,800	72	25
				13 days	8.51	10,850	66	29
78 µc	3	212 gm	30 days	control	7.12	16,700	67	26
				20 hrs	8.61	4,400	43	57
				44 hrs	7.88	4,350	44	54
				6.7 days	8.22	7,660	81	17
				10 days	9.32	9,900	70	30
83 µc	1	201 gm	2 days	control	7.34	12,900	76	16
				21.5 hrs	6.63	6,850	37	56
				26 hrs	6.42	8,120	46	53
				46 hrs	7.42	5,600	19	76
157 µc	2	230 gm	*	control	8.80	14,200	77	22
				17 hrs	8.18	5,800	25	74
				44 hrs	7.87	4,150	17	82
				3 days	7.53	3,050	49	49
				6.7 days	7.72	8,060	79	20
				10 days	7.97	7,700	71	27

*One animal autopsied at 3 days.

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Tracer Studies * The Metabolism of the Fission Products

Kenneth G. Scott, Josephine Crowley, Harry Forman

Holmium. The metabolism of microgram quantities of holmium, tagged with Ho^{166}, has been studied in rats following parenteral and oral administration. In addition to this, distribution of holmium complexed with citrate was compared to the uncomplexed element. The fate of 50 micrograms of Ho following intramuscular injection is summarized in Table I. Studies were made at 1 and 4 days after administration with both the citrate complexed and the uncomplexed material. Complexing with citrate increased the absorption from the injection site 95 percent, and 95 percent of the material administered in the uncomplexed state remained at the injection site 1 and 4 days after its administration. For similar time periods for the citrate complex, 36.4 and 34 percent remained at the injection site. The deposition of the uncomplexed Ho following its absorption is typical of that of the lanthanide rare earths. Large amounts of the material were accumulated by the liver 1 day after administration and it is presumed that the high activity noted in the large intestine is indicative of liver excretion into the gastrointestinal tract. There were measurable amounts of Ho in the other soft tissues of the body. The skeleton accumulated the greatest amount of the holmium retained by the animal, being in excess of 30 percent of the absorbed dose. The material was excreted in the urine and feces. Complexing of holmium with citrate reduced the accumulation in the liver to some extent with a large increase of the percent of the dose deposited in the skeleton. These latter values were in excess of 50 percent, 1 and 4 days after intramuscular administration. In addition to this, appreciable amounts were found in the kidney which were between 10 and 20 times greater than the similar studies with the uncomplexed holmium.

Similar studies were conducted with holmium, using Ho^{166} as a tracer following intravenous administration. The results of these studied are summarized in Table II. Twenty-one micrograms of Ho were administered with and without the citrate complex. In all of these studies, the major organ of deposition was liver and skeleton. The complexed Ho when administered intravenously, somewhat facilitates both fecal and urinary excretion. This excretion, however, stems from the deposition which originally occurred in the soft tissues of the body rather than from the skeleton since high skeletal deposition of Ho complexed with citrate occurred in the 4 day intravenous studies and is somewhat comparable with the 4 day intramuscular studies.

The fate of Ho and Ho complexed with citrate following oral administration has been studied in rats as shown in Table III. The animals were sacrificed 4 days after stomach intubation. Less than .01 percent of the material administered was found in any of the tissues assayed. This value represents the limit of the accuracy of the method rather than a true index of the Ho absorbed from the intestinal tract. The activity in the urine presumably resulted from contamination by the feces rather than renal excretion.

Ytterbium. The metabolism of ytterbium, by using tracer quantities of Yb^{175} has been studied in rats. The fate of 33 micrograms of Yb with and without citrate, following intramuscular injection is presented in Table IV. As with holmium,

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TABLE I

DISTRIBUTION OF HOLMIUM IN THE RAT AT 1 AND 4 DAYS FOLLOWING INTRAMUSCULAR INJECTION WITH AND WITHOUT CITRATE COMPLEXING AGENT. VALUES EXPRESSED AS PERCENT OF ABSORBED DOSE CORRECTED TO 100 PERCENT RECOVERY. Ho^{166} USED AS TRACER

	1 day after		4 days after		1 day after		4 days after	
mg. citrate	--		--		2.4		2.4	
µg. holmium	50		50		50		50	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.28	.28	.31	.31	.19	.32	.09	.15
Lungs	.28	.20	.31	.31	.44	.25	.18	.13
Spleen	.28	.28	.31	.31	.30	.53	.26	.37
Blood	.28	.03	.47	.03	.19	.02	.04	.004
Liver	22.9	3.97	15.9	1.56	17.8	2.98	6.21	.88
Kidney	.85	.57	1.87	.93	8.81	6.78	9.24	5.90
Adrenals	.28	-	.31	-	.04	-		
Thyroid	.28	-	.31	-	.02	-		
Lymph Gl.	-	.85	-	.62	-	.59		
Pancreas	.28	.28	.31	.31	.04	.02	.07	.06
Fat	-	.28	-	.31	-	.08	-	.02
Stomach	.28	.25	.31	.06	.65	.40	.22	.11
Sm. Int.	1.98	.25	.62	.06	.95	.17	.53	.07
Lg. Int.	15.6	1.98	.93	.09	1.29	.27	.57	.07
Skeleton	36.8	1.98	34.2	1.87	51.3	2.75	55.5	3.29
Muscle	1.98	.03	4.04	.04	4.84	.06	5.23	.07
Skin	1.13	.06	1.87	.06	3.34	.19	2.53	.13
Eyes	.28	.57			.02	.04		
Pituitary	.28	-	.31	-	.02	-		
Gonads	.28	.28	.31	.31	.02	.09	.02	.04
Urine	11.0	-	12.1	-	7.05	-	15.1	-
Feces	6.80	-	27.1	-	2.72	-	4.24	-
Brain	<.28	<.28	<.31	<.31	.04	.02	.07	.06
Unabsorbed from left leg	95.2		95.0		36.4		34.0	

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TABLE II

DISTRIBUTION OF HOLMIUM IN THE RAT AT 1 and 4 DAYS FOLLOWING INTRAVENOUS INJECTION WITH AND WITHOUT CITRATE COMPLEXING AGENT. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE CORRECTED TO 100% RECOVERY. Ho^{166} USED AS TRACER.

	1 day after		4 days after		1 day after		4 days after	
mg. citrate	--		--		2.4		2.4	
µg. holmium	21		21		21		21	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.08	.09	.05	.05	.19	.21	.15	.16
Lungs	.27	.14	.34	.17	.24	.11	.26	.17
Spleen	1.10	1.47	1.80	1.28	.85	.93	.58	.72
Blood	.97	.07	.14	.01	1.44	.11	.15	.01
Liver	58.2	7.44	52.9	4.87	43.2	5.88	18.7	2.28
Kidney	2.67	1.35	2.72	1.29	4.35	2.22	2.43	1.16
Adrenals	.06	-	.08	-	.06	-	.09	-
Thyroid	.02	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.55	-	.19	-	.51	-	.54
Pancreas	.10	.05	.05	.11	.10	.14	.12	.10
Brain	.02	.01	<.01	<.01	<.01	<.01	.01	.01
Fat	-	.02	-	.01			-	.01
Stomach	.27	.16	.20	.04	.41	.23	.35	.21
Sm. Int.	1.97	.30	1.53	.17	1.94	.26	1.27	.16
Lg. Int.	2.68	.69	1.34	.15	3.44	.62	1.81	.27
Skeleton	16.5	.93	21.1	1.12	17.0	.96	34.5	2.09
Muscle	1.18	.01	1.85	.02	2.09	.02	1.75	.02
Balance	4.70	-	1.64	-	2.46	-	5.74	-
Skin	3.46	.09	2.77	.10	4.50	.13	3.48	.12
Eyes	.01	.08			<.01	.03	<.01	.03
Pituitary	.01	-	<.01	-	.01	-	<.01	-
Gonads	.10	.04	.08	.03	.15	.07	.12	.05
Urine	3.06	-	2.37	-	11.1	-	10.6	-
Feces	2.51	-	9.02	-	6.52	-	17.9	-

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TABLE III

DISTRIBUTION OF HOLMIUM IN THE RAT AT FOUR DAYS FOLLOWING STOMACH TUBE ADMINISTRATION WITH AND WITHOUT 4.8 MILLIGRAMS CITRATE. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE, CORRECTED TO 100% RECOVERY. Ho^{166} USED AS A TRACER.

	no added citrate 21 micrograms holmium		4.8 milligrams citrate 100 micrograms holmium	
Tissues	% per organ	% per gram	% per organ	% per gram
Heart	<.01	<.01	<.01	<.01
Lungs	<.01	<.01	<.01	<.01
Spleen	<.01	<.01	<.01	<.01
Blood	.01	.0008	<.01	<.01
Liver	<.01	<.01	.05	.005
Kidney	<.01	<.01	<.01	<.01
Adrenals	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-
Lymph Gl.	-	<.01	-	.19
Pancreas	<.01	<.01	<.01	<.01
Brain	<.01	<.01	<.01	<.01
Fat	-	<.01		
Stomach	<.01	<.01	.01	.004
Sm. Int.	<.01	<.01	.01	.001
Lg. Int.	<.01	<.01	.04	.005
Skeleton	<.01	<.01	.14	.008
Muscle	.03	.0003	<.01	<.01
Balance	.07	-	.31	-
Skin	<.01	.0004	.07	.002
Eyes	<.01	<.01	<.01	<.01
Pituitary	<.01	-	<.01	-
Gonads	.01	.005	<.01	<.01
Urine	2.49	-	9.88	-
Feces	97.4	-	89.5	-

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TABLE IV

DISTRIBUTION OF YTTERBIUM IN THE RAT AT 1 and 4 DAYS FOLLOWING INTRAMUSCULAR INJECTION WITH AND WITHOUT CITRATE COMPLEXING AGENT. VALUES EXPRESSED AS PERCENT OF ABSORBED DOSE CORRECTED TO 100% RECOVERY. Yb^{175} USED AS A TRACER

	1 day after		4 days after		1 day after		4 days after	
mg. citrate	--		--		4.8		4.8	
μg. ytterbium	33		33		33		33	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	<.23	<.23	<.30	<.30	.32	.35	.26	.28
Lungs	<.23	<.23	<.30	<.30	1.73	.77	.67	.42
Spleen	.23	.46	.59	.59	4.79	5.70	2.61	3.37
Blood	.46	.05	.30	.03	6.10	.45	.11	.01
Liver	13.4	1.85	11.2	.89	42.3	5.52	22.8	2.56
Kidney	.23	.12	.30	.18	7.51	3.52	5.15	2.31
Adrenals	<.23	-	<.30	-	.05	-	.08	-
Thyroid	<.23	-	<.30	-	<.02	-	<.02	-
Lymph Gl.	-	<.23	-	<.30	-	.27	-	.34
Pancreas	<.23	<.23	<.30	<.30	.06	.13	.03	.08
Brain	<.23	<.23	<.30	<.30	<.02	<.02	<.02	<.02
Fat	-	<.23	-	<.30	-	.03	-	<.02
Stomach	<.23	<.23	<.30	<.30	.94	.59	.84	.57
Sm. Int.	2.08	.23	.30	.03	3.92	.48	2.54	.23
Lg. Int.	8.33	2.78	.30	.03	2.62	.56	1.33	.14
Skeleton	3.94	.21	13.0	.89	16.8	.90	19.4	1.07
Muscle	1.39	.02	1.78	.02	3.54	.03	3.90	.04
Skin	2.78	.09	1.48	.06	4.03	.13	2.76	.08
Pituitary	<.23	-	<.30	-	<.02	-	<.02	-
Gonads	<.23	<.23	<.30	<.30	.10	.03	.06	.03
Urine	12.0	-	36.1	-	3.12	-	7.81	-
Feces	55.1	-	34.6	-	2.11	-	29.6	-
Unabsorbed from left leg.	95.0		96.0		34.7		34.4	

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citrate complexing facilitates the absorption from the injection site, the values being 34.7 and 34.4 percent respectively at 1 and 4 days after intramuscular injection. Similar values for the uncomplexed material were 95 and 96 percent respectively after intramuscular injection. Yb is apparently excreted in much larger quantities when uncomplexed than when it is complexed. It must be pointed out, however, that because of the low absorption from the injection site, the animal handles much more of the complexed material if the micrograms excreted are compared. As with other lanthanide rare earths, the major organs of deposition were liver and skeleton. Complexing with citrate increases the skeletal deposition at 1 and 4 days after intramuscular administration and in the case of Yb increased the liver deposition as well. This latter effect appears to be a matter of a reduction in the ability of the liver to excrete the material deposited. Ninety-two micrograms of uncomplexed Yb and Yb complexed with citrate was administered to rats intravenously. The deposition in the rat obtained from these studies is summarized in Table V. The uncomplexed material is deposited in the liver to a greater extent than when complexed with citrate whereas citrate complexing increases the deposition in the kidney. This agrees with the data obtained upon holmium. In addition, citrate complexing increases the deposition in the musculature of the rat from a factor of 5 to 10 at 1 and 4 days after administration.

Studies following the oral administration of ytterbium in doses of 500 and 50 microcuries are summarized in Table VI. Less than .01 percent of the material administered could be isolated from any of the tissues studied. The radiation received by the intestinal tract by the 500 microcurie dose did not alter the absorption in the body.

Lutecium. The metabolism of microgram quantities of lutecium following intramuscular administration and with or without citrate complexing, is summarized in Table VII. Citrate complexing facilitated absorption from the injection site, there remaining only 10.6 and 8.4 percent at 1 and 4 days after administration. The major organ of deposition was the skeleton. Citrate complexing increased the skeletal deposition by a factor of two. However, it must be remembered that approximately 10 times more lutecium was present in the tissues with the complexed material because of the greater absorption from the injection site. Excretion of lutecium occurs in both urine and feces, being much greater in the feces 4 days after administration of the uncomplexed material. The reverse is true of the complexed lutecium, the excretion being almost equal from urine and feces 4 days after administration.

The deposition of 6 to 15 micrograms of lutecium with and without citrate complex following intravenous administration is summarized in Table VIII. Complexing of the material reduced the deposition in the liver by a factor of 3 to 5, 1 and 4 days after administration. However, as with the intramuscular studies, the main organ of deposition was the skeleton. Complexing of lutecium with citrate increased the skeletal deposition and is comparable to holmium and ytterbium. Consequently, less lutecium was excreted 4 days after administration when complexed than when not complexed.

Lanthanum. The effect of various complexing agents upon carrier-free La^{140} is summarized in Table IX. Ascorbic acid, nicotinic acid, picolinic acid, isothiopropionic acid, and carboxylethyl sulfide were used as complexing agents and compared

TABLE V

DISTRIBUTION OF YTTERBIUM IN THE RAT AT 1 AND 4 DAYS FOLLOWING INTRAVENOUS INJECTION WITH AND WITHOUT 4.8 MG. CITRATE COMPLEXING AGENT. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE CORRECTED TO 100% RECOVERY. Yb^{175} USED AS A TRACER

	1 day after		4 days after		1 day after		4 days after	
mg. citrate	--		--		4.8		4.8	
µg. ytterbium	92		92		92		92	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.07	.09	.03	.05	.33	.47	.16	.22
Lungs	.36	.17	.24	.11	.56	.40	.35	.23
Spleen	2.29	2.10	.89	.79	.73	1.22	.40	.68
Blood	2.63	.20	.22	.02	.40	.04	.05	.004
Liver	58.4	5.67	26.9	2.49	21.4	2.84	13.7	1.68
Kidney	2.41	1.19	.85	.43	6.94	4.39	4.88	2.25
Adrenals	.06	-	.07	-	.05	-	.10	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.43	-	.20	-	.28	-	.23
Pancreas	.18	.13	.03	.08	.47	.46	.28	.26
Brain	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Fat	-	.03	-	<.01	-	.07	-	.06
Stomach	.25	.04	.39	.09	1.42	.74	.95	.61
Sm. Int.	2.31	.25	1.09	.09	3.12	.47	2.76	.34
Lg. Int.	5.08	.66	.93	.10	5.10	.70	2.15	.30
Skeleton	15.9	.91	31.5	1.76	34.9	1.95	34.5	1.81
Muscle	1.95	.02	1.16	.01	13.4	.17	11.3	.14
Balance	2.31	-	2.22	-	2.54	-	1.86	-
Skin	3.77	.12	2.85	.08	3.30	.14	3.38	.13
Eyes	<.01	.01	<.01	.01	.01	.03	<.01	.03
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.20	.08	.17	.06	.05	.15	.03	.15
Urine	.85	-	5.89	-	3.41	-	6.69	-
Feces	.97	-	24.6	-	1.83	-	16.4	-

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TABLE VI

DISTRIBUTION OF YTTERBIUM IN THE RAT AT EIGHT DAYS FOLLOWING STOMACH TUBE ADMINISTRATION OF TWO LEVELS OF Yb: 500 AND 50 MICROCURIES. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE, CORRECTED TO 100% RECOVERY. Yb^{175} USED AS A TRACER.

	500 microcuries Yb^{175} 1 milligram ytterbium		50 microcuries Yb^{175} 0.1 milligram ytterbium	
Tissues	% per organ	% per gram	% per organ	% per gram
Heart	<.01	<.01	<.01	<.01
Lungs	<.01	<.01	<.01	<.01
Spleen	<.01	<.01	<.01	<.01
Blood	<.01	<.01	<.01	<.01
Liver	<.01	<.01	<.01	<.01
Kidney	<.01	<.01	<.01	<.01
Adrenals	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-
Lymph Gl.	-	<.01	-	<.01
Pancreas	<.01	<.01	<.01	<.01
Brain	<.01	<.01	<.01	<.01
Fat	-	<.01	-	<.01
Stomach	<.01	<.01	<.01	<.01
Sm. Int.	<.01	<.01	<.01	<.01
Lg. Int.	<.01	<.01	<.01	<.01
Skeleton	<.01	<.01	<.01	<.01
Muscle	<.01	<.01	<.01	<.01
Balance	<.01	-	<.07	-
Skin	<.01	<.01	<.01	<.01
Eyes	<.01	<.01	<.01	<.01
Pituitary	<.01	-	<.01	-
Gonads	<.01	<.01	<.01	<.01
Urine	.19	-	1.46	-
Feces	99.8	-	98.5	-

1174697

TABLE VII

DISTRIBUTION OF LUTECIUM IN THE RAT AT ONE AND FOUR DAYS FOLLOWING INTRAMUSCULAR INJECTION WITH AND WITHOUT CITRATE COMPLEXING AGENT. VALUES EXPRESSED AS PERCENT OF ABSORBED DOSE CORRECTED TO 100% RECOVERY. Lu^{177} USED AS A TRACER.

	1 day after		4 days after		1 day after		4 days after	
mg. citrate	--		--		2.4		2.4	
µg. lutecium	6		15		6		15	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.10	.10	<.11	<.11	.29	.32	.08	.10
Lungs	1.13	.62	.33	.11	.26	.19	.22	.23
Spleen	.82	.82	.65	.54	.25	.41	.53	.37
Blood	2.77	.26	.98	.08	.30	.03	.21	.02
Liver	20.7	2.57	11.5	.98	7.10	1.13	4.29	.50
Kidney	2.16	1.34	1.52	.87	3.51	2.29	1.13	.58
Adrenals	<.10	-	<.11	-	<.01	-	<.01	-
Thyroid	<.10	-	<.11	-	<.01	-	.01	-
Lymph Gl.	-	<.10	-	<.11	-	.17	-	.16
Pancreas	.10	.10	<.11	<.11	.06	.08	.07	.05
Brain	<.10	<.10	<.11	<.11	.03	.01	.02	.01
Fat	-	<.10			-	.10	-	.02
Stomach	.62	.41	.54	.10	.99	.46	.57	.22
Sm. Int.	3.29	.51	.87	.08	2.47	.36	.73	.09
Lg. Int.	9.04	1.95	.98	.10	2.40	.44	.49	.07
Skeleton	35.3	2.26	27.7	1.63	62.3	3.89	51.6	2.57
Muscle	5.76	.07	2.29	.02	3.41	.05	5.94	.07
Skin	3.39	.21	1.85	.07	2.06	.12	4.23	.16
Eyes	<.10	<.10	<.11	<.11	<.01	.03	<.01	.02
Pituitary	<.10	-	<.11	-	<.01	-	<.01	-
Gonads	.31	.10	.11	.05	.03	.08	.13	.05
Urine	9.87	-	12.8	-	11.9	-	16.9	-
Feces	4.73	-	37.8	-	2.65	-	12.9	-
Left Leg	89.4		89.3		10.6		8.4	

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TABLE VIII

DISTRIBUTION OF LUTECIUM IN THE RAT AT ONE AND FOUR DAYS FOLLOWING INTRAVENOUS INJECTION WITH AND WITHOUT CITRATE COMPLEXING AGENT. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE CORRECTED TO 100% RECOVERY. Lu^{177} USED AS A TRACER.

	1 day after		4 days after		1 day after		4 days after	
mg. citrate	--		--		2.4		2.4	
µg. lutecium	6		15		6		15	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	<.01	<.01	.04	.04	.11	.11	.04	.07
Lungs	.32	.15	.23	.13	.53	.28	.16	.13
Spleen	.77	.77	.54	.61	.93	.74	.47	.38
Blood	.59	.05	.19	.01	.79	.06	.13	.01
Liver	19.3	2.18	17.6	1.82	7.21	.86	4.26	.46
Kidney	1.21	.74	.49	.26	1.69	.92	.88	.55
Adrenals	.03	-	.08	-	.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	
Lymph Gl.	-	.20	-	.23	-	.20	-	.12
Pancreas	.07	.12	.09	.06	.07	.16	.07	.08
Brain	.02	.01	.01	.01	.02	.02	.03	.02
Fat	-	.02	-	.01	-	.02	-	<.01
Stomach	.50	.29	.35	.12	.90	.43	.41	.17
Sm. Int.	2.73	.41	.68	.08	3.71	.58	.58	.06
Lg. Int.	3.84	.80	.61	.07	4.74	.86	.28	.05
Skeleton	44.4	2.82	31.1	1.91	44.0	2.70	50.8	3.91
Muscle	3.43	.04	2.56	.03	4.54	.05	3.87	.05
Balance	4.45	-	4.63	-	7.14	-	5.34	-
Skin	4.88	.15	2.99	.08	7.04	.20	4.18	.14
Eyes	<.01	.01	<.01	.02	.01	.03	<.01	.01
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.10	.04	.12	.05	.30	.11	.12	.05
Urine	6.52	-	11.3	-	12.7	-	16.8	-
Feces	6.89	-	26.4	-	3.54	-	11.6	-

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TABLE IX

DISTRIBUTION OF CARRIER-FREE La^{140} IN THE RAT AT ONE DAY FOLLOWING INTRAVENOUS INJECTION OF La^{140} WITH AND WITHOUT COMPLEXING AGENTS. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE, CORRECTED TO 100% RECOVERY.

	+25 mg. Ascorbic Acid		+25 mg. Nicotinic Acid		+15 mg. Picolinic Acid		+15 mg. Isothiopropionic Acid		+15 mg. Carboxylethl Sulfide		No Complexing Agent	
Tissues	% 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	.08	.10	.08	.10	.10	.10	.12	.12	.07	.08	.19	.15
Lungs	.27	.14	.64	.34	.25	.13	7.47	3.86	.41	.23	3.97	1.40
Spleen	.12	.12	.29	.40	.11	.12	6.81	10.6	.79	1.04	.91	.96
Blood	.03	.003	.11	.007	.08	.005	.52	.03	.19	.01	2.76	.19
Liver	58.3	7.31	58.1	5.81	64.9	5.87	58.0	5.16	82.8	7.79	56.6	6.78
Kidney	2.01	1.12	2.80	1.25	3.27	1.75	1.96	.77	1.81	.80	2.29	1.04
Pancreas	.02	.04	.06	.06	.03	.07	.05	.06	.01	.02	.14	.07
Brain	<.01	<.01	<.01	<.01	.02	.01	.02	.008	<.01	<.01	<.01	<.01
Fat	-	<.01	-	<.01	-	.02	-	.06	-	<.01	-	-
Stomach	.37	.22	.61	.29	.35	.21	.17	.09	.15	.08	.29	.13
Sm. Int.	.52	.08	.53	.07	.53	.06	.37	.05	.24	.03	1.36	.16
Lg. Int.	1.21	.19	1.24	.17	1.23	.16	.51	.06	.29	.05	2.37	.31
Skeleton	26.3	1.43	20.9	.91	21.5	.74	20.0	.84	8.65	.34	14.7	.76
Muscle	2.83	.032	1.30	.011	1.95	.015	1.80	.014	1.29	.011	2.20	.02
Balance	4.54	-	7.37	-	2.92	-	0	-	1.46	-	5.27	-
Skin	2.06	.06	2.41	.05	1.83	.04	1.70	.04	1.08	.02	3.15	.09
Gonads	.03	.01	.07	.02	.06	.01	.04	.01	.05	.02	.16	.07
Urine	1.06	-	2.88	-	.70	-	.45	-	.20	-	3.52	-
Feces	.18	-	.57	-	.25	-	.06	-	.57	-	.05	-

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to the data obtained when no complexing agent was used. These materials were administered simultaneously with the La^{140} by intravenous injection. The rats were killed at 1 day following injection. With the exception of carboxylethyl sulfide, the net result of the other complexing agents appears to have been the same namely, retention in the liver as was observed with the uncomplexed lanthanum with a slightly increased skeletal deposition. In the case of carboxylethyl sulfide, the retention by the liver of the La complex was greater with a parallel retention of the deposition in the skeleton. These studies are being continued.

Yttrium 91. Y^{91} has been administered to rats intravenously complexed with glutathione, cholic acid, picolinic acid and dithiocarbanyl, also versene, versene and BAL, creatine, and creatine and BAL. The animals were sacrificed 1 day following administration. The data is summarized in Table X and Table XI. The distribution of Y^{91} so complexed is not essentially different from carrier-free uncomplexed yttrium. It was found primarily in the liver and skeleton. Of the complexing agents mentioned, versene was capable of greatly increasing the urinary excretion of Y^{91} with the subsequent retention of liver deposition but not skeletal deposition. These studies are being continued.

Cerium. Carrier-free Ce^{144} has been administered to the rat as a trimethylamine tricarboxylic acid complex. This was given both intramuscularly and intravenously, the animals being sacrificed at 1 and 4 days after administration. With respect to the intramuscular studies, absorption was greatly facilitated from the injection site. Following absorption, the primary organ of deposition was liver with appricable amounts found in spleen, kidney, and skeleton. When administered intravenously, 20 percent of the dose was found in the musculature 4 days after administration, this value being 7 times higher than that observed following intramuscular administration. This complexing agent reduces the depostion of cerium in the skeleton and increases the deposition in the liver. However, very little of the material is excreted, being less than 10 percent, 4 days after intramuscular or intravenous administration. This data is summarized in Table XII.

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TABLE X

DISTRIBUTION OF CARRIER-FREE Y^{91} IN THE RAT AT ONE DAY FOLLOWING INTRAVENOUS INJECTION OF Y^{91} WITH COMPLEXING AGENTS. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE CORRECTED TO 100% RECOVERY.

	25 mg. Glutathione		12.5 mg. Cholic acid		15 mg. Picolinic acid		15 mg. Dithiocarbamyl	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.07	.07	.11	.14	.07	.12	.16	.17
Lungs	.69	.38	6.59	2.92	.20	.12	.83	.41
Spleen	2.52	2.20	2.05	1.92	.07	.12	1.25	1.50
Blood	.21	.01	.36	.03	.04	.004	.35	.03
Liver	53.4	6.52	55.7	6.88	61.0	8.95	64.5	8.78
Kidney	4.91	2.51	2.23	1.34	1.04	.69	2.23	1.34
Adrenals	<.01	-	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.06	-	.12	-	.11	-	.24
Pancreas	.04	.05	.10	.07	.06	.06	.15	.18
Brain	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Fat	-	.01	-	<.01	-	.01	-	.02
Stomach	.27	.18	.24	.14	.25	.13	.33	.20
Sm. Int.	.50	.07	.39	.07	.40	.06	.36	.06
Lg. Int.	.57	.14	.94	.17	.96	.12	.64	.19
Skeleton	20.9	1.01	18.3	1.31	21.5	1.24	17.8	1.01
Muscle	1.74	.02	1.49	.02	.90	.01	1.87	.02
Balance	5.23	-	4.42	-	3.90	-	4.21	-
Skin	3.16	.07	2.34	.07	1.52	.07	1.61	.06
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.06	.02	.05	.02	.04	.17	.04	.02
Urine	5.41	-	4.39	-	6.76	-	3.34	-
Feces	.30	-	.26	-	1.29	-	.37	-

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TABLE XI

DISTRIBUTION OF CARRIER-FREE Y^{91} IN THE RAT AT ONE DAY FOLLOWING INTRAVENOUS INJECTION OF Y^{91} WITH COMPLEXING AGENTS. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE, CORRECTED TO 100% RECOVERY.

	15 mg. Versene		15 mg. Versene and BAL		25 mg. Creatine		25 mg. Creatine and BAL	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.01	.01	.03	.02	.11	.13	.14	.14
Lungs	.05	.02	.04	.01	.31	.16	.33	.17
Spleen	.02	.02	.02	.02	.23	.29	.19	.27
Blood	.01	.001	.01	.001	.15	.01	.23	.01
Liver	3.92	.45	3.58	.35	48.4	5.69	30.8	3.34
Kidney	.73	.38	.76	.30	4.23	2.33	3.58	1.63
Adrenals	<.01	-	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-	<.01	-
Lymph Gl.	-	.02	-	.02	-	.13	-	.20
Pancreas	<.01	<.01	<.01	<.01	.03	.04	.08	.08
Brain	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Fat			-	<.01	-	.01	-	.04
Stomach	.05	.03	.05	.02	.44	.20	.33	.18
Sm. Int.	.12	.02	.21	.03	.67	.09	.69	.10
Lg. Int.	1.45	.26	.62	.16	.79	.17	1.48	.29
Skeleton	19.0	.67	19.8	.57	25.0	1.51	25.8	1.09
Muscle	.71	.007	.38	.003	2.04	.02	2.42	.02
Balance	1.18	-	2.53	-	7.64	-	22.3	-
Skin	.66	.02	.50	.02	2.75	.08	5.72	.13
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.01	.003	.03	.01	.08	.03	.08	.04
Urine	68.7	-	69.9	-	6.74	-	5.51	-
Feces	3.41	-	1.55	-	.36	-	.33	-

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TABLE XII

DISTRIBUTION OF Ce^{144} IN THE RAT AT ONE AND FOUR DAYS FOLLOWING INTRAMUSCULAR AND INTRAVENOUS INJECTION OF Ce^{144} AND 0.2 mg. CERIUM CARRIER WITH 2 mg. NITRILOTRIACETIC ACID (TRIMETHYLAMINE TRICARBOXYLIC ACID). VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE, CORRECTED TO 100% RECOVERY.

	INTRAMUSCULAR STUDIES				INTRAVENOUS STUDIES			
	1 Day		4 Days		1 Day		4 Days	
Tissues	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.29	.48	.25	.34	.35	.33	.19	.24
Lungs	2.91	1.74	2.31	1.67	.70	.39	.67	.39
Spleen	3.02	4.38	2.97	3.83	1.81	1.81	1.12	1.47
Blood	.22	.02	.05	.005	.60	.04	.04	.003
Liver	74.0	12.6	68.4	10.5	59.3	7.06	40.8	4.84
Kidney	3.17	2.38	2.24	1.59	2.39	1.35	3.39	2.41
Adrenals	<.01	-	.10	-	.06	-	.03	-
Thyroid	<.01	-	<.01	-	.01	-	.02	-
Lymph Gl.	-	.22	-	1.17	-	.50	-	.70
Pancreas	.18	.26	.17	.28	.56	.66	.50	.56
Brain	.04	.03	<.01	<.01	<.01	<.01	<.01	<.01
Fat	-	.10	-	<.01	-	.04	-	.02
Stomach	.79	.45	.52	.22	1.21	.86	.84	.56
Sm. Int.	2.33	.35	1.39	.16	2.44	.37	2.61	.22
Lg. Int.	2.19	.34	.70	.10	2.43	.42	1.42	.18
Skeleton	6.90	.42	8.48	.63	7.72	.47	12.5	.72
Muscle	1.70	.02	1.84	.03	5.02	.05	20.0	.23
Balance					8.37	-	2.66	-
Skin	.83	.05	1.33	.05	4.28	.13	5.32	.19
Eyes	<.01	.04	<.01	.03	.01	.04	.03	.13
Pituitary	<.01	-	<.01	-	<.01	-	<.01	-
Gonads	.03	.11	.04	.04	.09	.03	.02	.20
Urine	1.39	-	2.28	-	1.59	-	2.68	-
Feces	.03	-	6.97	-	1.07	-	5.13	-
Unabsorbed in left leg	21.5		21.3					

1174704

Decontamination and Bone Metabolism Studies

D. Harold Copp and Ruth Lerner.

Effect of Immediate Treatment with Sodium Citrate and Zirconium Citrate on Decontamination of Radio-Niobium and Plutonium. B. Kawin. It has been shown previously[1] that about 10 percent of the niobium (Cb) absorbed from the site of intramuscular injection is excreted in the urine. Somewhat less than 10 percent of injected plutonium is normally excreted in the urine. The major unexcreted proportion of both of these elements is deposited in the skeleton. The retention of these radioelements may constitute a major radiation hazard. It has been shown[2] that the excretion of both yttrium and plutonium may be increased by the use of massive doses of injected zirconium citrate. Previous studies made in this laboratory have shown that prompt treatment of experimental animals with massive doses of sodium and zirconium citrate increased the urinary excretion of radio-yttrium and radio-cerium. The deposition of these elements in the skeleton and other tissues was correspondingly decreased.

In this study the effects of sodium citrate and zirconium citrate upon the deposition and excretion of simultaneously administered Cb^{95} and Pu^{239} have been studied.

Methods. Fourteen young female rats, ranging in weight from 150 to 175 grams, were injected by way of the great saphenous vein with a mixture of 5 μc Cb^{95} and 8 μg of Pu^{239}(VI), contained in 1/4 ml of a 0.01 percent sodium citrate solution. The Cb^{95} was carrier free. The pH of the solution was about 6.0.

Five of these rats received an intraperitoneal injection of 40 mg of zirconium (1.6 ml as the citrate) pH 6.0, at the time of the administration of the radioisotopes.

Four of the animals received an intraperitoneal injection of 1.6 ml of 10 percent sodium citrate at the time of the administration of the radioisotopes.

The remaining 5 animals were not treated, and served as controls.

The animals were placed in metabolism cages and fed a standard stock diet for three days. At the end of this time they were sacrificed and tissues and excreta were assayed for Cb^{95} and Pu^{239}.

Results. The results of the experiment are shown in Tables I (Cb^{95}) and II (Pu^{239}).

Table I shows that neither zirconium citrate nor sodium citrate had any appreciable effect upon the distribution of the niobium in the skeleton, soft tissues, or excreta. However, treatment with zirconium citrate appeared to increase the amount of niobium deposited in the teeth.

Table II indicates that zirconium citrate treatment has a distinct effect in reducing the amount of plutonium in the skeleton and increasing the urinary

TABLE I

EFFECT OF SODIUM AND ZIRCONIUM CITRATE UPON THE DEPOSITION AND EXCRETION OF Cb^{95}. VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE OF Cb^{95}.*

	Controls	Zirconium Citrate Treated	Sodium Citrate Treated
Femur	1.4 ± 0.2	1.8 ± 0.4	2.2 ± 0.3
Carcass	42.6 ± 4.6	29.4 ± 3.8	36.1 ± 0.8
Liver	9.1 ± 0.9	12.4 ± 2.4	6.8 ± 3.0
Kidneys	2.6 ± 0.7	2.0 ± 0.7	3.4 ± 0.9
Molars	0.3 ± 0.02	1.8 ± 0.4	0.14 ± 0.09
Incisors	0.24 ± 0.09	0.7 ± 0.1	0.19 ± 0.09
Urine	36.5 ± 4.9	43.7 ± 6.4	41.8 ± 3.9
Feces	7.2 ± 1.4	8.2 ± 2.7	9.4 ± 3.0
Total Excretion	43.7 ± 3.6	51.9 ± 7.3	51.2 ± 5.8

* Values given are averages ± standard error.

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TABLE II

EFFECT OF ZIRCONIUM CITRATE AND SODIUM CITRATE UPON THE DEPOSITION AND EXCRETION OF Pu(VI). VALUES EXPRESSED AS PERCENT OF ADMINISTERED DOSE OF PLUTONIUM*.

	Controls	Zirconium Citrate Treated	Sodium Citrate Treated
Femur	5.7 ± 0.8	1.6 ± 0.2	4.9 ± 0.7
Carcass	70.8 ± 3.0	32.9 ± 2.3	56.4 ± 13.0
Liver	12.0 ± 1.4	12.1 ± 2.0	24.8 ± 4.2
Kidneys	0.9 ± 0.1	0.6 ± 0.1	1.0 ± 0.1
Molars	0.11 ± 0.03	0.08 ± 0.01	0.09 ± 0.01
Incisors	0.2 ± 0.04	0.1 ± 0.03	0.21 ± 0.04
Urine	4.7 ± 1.3	48.4 ± 6.5	7.2 ± 1.7
Feces	5.6 ± 0.4	4.2 ± 0.8	5.4 ± 0.5
Total Excretion	10.3 ± 1.4	52.6 ± 5.9	12.6 ± 1.6

*Values given are averages ± standard error.

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excretion of plutonium. The skeletal deposition was decreased from 70.8 percent in the controls to 32.9 percent for the zirconium-treated animals. In addition, there was a corresponding reduction of the femur deposition from 5.7 to 1.6 percent.

Treatment with sodium citrate did not bring about this marked reduction in the skeletal deposition. However, the use of this treatment appeared to double the amount of plutonium in the liver, bringing about a rise from the control value of 12.0 to 24.8 percent. Treatment with zirconium citrate had no effect upon the liver as compared to the controls.

The zirconium citrate treated animals excreted 48.4 as compared to 4.7 percent of the injected plutonium, while no effect was apparent in the sodium citrate treated group. The fecal excretion was essentially unaffected by all treatments. The enhanced urinary excretion of the zirconium treated animals is directly reflected in their total excretion of 52.6 as compared to the 10.3 percent total excretion of the controls.

Summary. 1. Prompt treatment with zirconium citrate or sodium citrate appears not to have any significant effect upon the distribution and excretion of intravenously-injected Cb^{95}.

2. Zirconium citrate markedly decreased the skeletal deposition, and increased the urinary excretion of plutonium. Sodium citrate increases the liver plutonium, but had no significant effect on either the skeletal deposition or urinary excretion.

3. Prompt treatment with zirconium citrate appears to have definite value for the decontamination of internally administered plutonium, but appears to have no effect on Cb^{95}.

Study of Rickets and Rachitogenic Diets. D. Thomson. Various modifications of the rachitogenic diet were tested in an effort to produce a more consistent experimental rickets in which bone mineralization would be inhibited, but body growth and health would be improved. Growth is important for the production of the rachitic cartilage and osteoid which is characteristic of clinical rickets. Such a preparation is of value in studying rickets, calcification and the deposition of fission products in bone.

In this laboratory, rickets has been produced by rearing rats on a synthetic diet very low in phosphorus. The composition of this diet has been given in earlier reports. The following modifications of this basic diet were studied with a view to improving the condition of the animals and the severity of the rickets.

1. Use of unwashed powdered beef blood fibrin as protein source in place of the water washed fibrin. This appeared to produce just as satisfactory results, and saved the time and expense involved in washing the fibrin.

2. Increase of the protein content of the diet from 20 percent to 25 percent fibrin. This change appeared to be benificial.

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3. Increase in the amounts of water soluble vitamins added, to double the recommended level. This supplement is particularly important in the case of the deficient animals which consume less than half the normal amount of diet.

4. Pulverization of the sugar in the diet and all other components. This gives a diet of much better consistency, and ensures complete mixing of all ingredients.

5. Use of Elvehjem's salt mixture #4.

6. Addition of 1 percent aluminum acetate to the diet in one series, to increase the severity of the phosphorus deficiency by combining with phosphate in the intestinal tract.

7. Weaning the rats at 21 days, and feeding them a complete diet for 4 days before transferring them to the deficient diet was found to prevent the initial weight loss after weaning. The improved growth even on the deficient diet appeared to give healthier animals and more severe rickets.

8. The deficient animals were kept in individual cages, ensuring even food consumption and preventing canniballism. The condition of the animals was also much better than when several animals were kept in the same cage.

The composition of the modified diet is given in Table III.

The development of rickets in these animals was studied by the following criteria:

1. Growth curves.

2. X-ray of knee region to demonstrate width of the uncalcified epiphyseal plate.

3. Silver line test (von Kossa) of upper end of tibia.

4. Ratio of ash weight/dry weight for femur.

5. Level of calcium and phosphorus in the serum.

6. Level of alkaline phosphatase in serum and bone.

7. Distribution and excretion of injected radio-strontium, radio-calcium and radio-barium.

8. Radioautographs of femur and tibia from animals injected with radioisotopes.

9. Histology of bones and teeth.

Although the evaluation of these studies is far from complete, preliminary data indicate that the greatest severity of rickets is obtained from 60-70 days

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TABLE III

RACHITOGENIC DIET CF 25-1

Item	Percent	Component
1.	25	Crude powdered beef blood fibrin.
2.	10	Hydrogenated vegetable oil.
3.	1	Sardilene, fish oil; 20 mg. Vit. E per gram, added 3000 units Vit. A per gram 400 units Vit. D per gram.
4.	4	*Salt mixture, modified Elvehjem #4.
5.	-	**B-Vitamins and Vit. K.
6.	60	Ground granulated sucrose.

**Included in weight of sucrose. See below.

*Salt mixture, modified Elvehjem #4.

1.	.67	Sodium Chloride
2.	1.29	Potassium Chloride
(3.)	(1.29	Potassium phosphate dibasic for normal controls)
(4.)	(.30	Calcium phosphate dibasic for normal controls)
5.	.30	Calcium carbonate as substitute for weight of above 4.
6.	1.20	Calcium carbonate
7.	.40	Magnesium Sulfate, anhydrous
8.	.11	Feric Citrate
9.	.0032	Manganese Sulfate
10.	.0012	Copper Sulfate
11.	.0010	Zinc Sulfate
12.	.0010	Cobalt Acetate
13.	.0008	Potassium Iodide

B-VITAMINS AND VITAMIN K

1.	.001	Thiamine HCl
2.	.001	Riboflavin (Add last)
3.	.005	Niacin
4.	.001	Para Amino-Benzoic Acid
5.	.00055	Felic Acid
6.	.0005	Pyridoxine
7.	.005	D-Calcium Pantothenate
8.	.100	Choline (Add when mixing diet itself)
9.	.00003	Biotin, crystalline
10.	.020	Inositol
11.	.001	Vitamin K

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of age in the rat, and hence this appears to be the best period for conducting studies of the uptake of radioactive metals by bone osteoid.

The Effect of Plutonium on Alkaline Phosphatase of Bone and Serum. S. Cohn and Frank Ulrich. One of the important biological effects of radiation is the cessation of bone growth. Elucidation of this mechanism will, it is hoped, result in a better understanding of the physiological mechanism of the process of calcification, which is not as yet clearly understood.

As an approach to the general problem of the effect of radiation on bone, a study is being made of the effect of radiation on alkaline phosphatase, which most investigators agree plays an important role in the process of calcification, although the complete explanation of this role has not yet been achieved.

In a previous series of experiments, the influence of radium as an internal alpha-emitter was shown by S. Cohn[3]. Radium was chosen for the experiment because it is one of the group of alkaline earths which are known to deposit almost exclusively in bone, and more particularly, in the region of active calcification, thus providing an intense concentration of ionization in this region. It has been demonstrated that alkaline phosphatase is also present in its largest quantities in the site of active calcification, and thus the radium is deposited in the very region where it can exercise a maximum effect on the alkaline phosphatase.

It was found in this previous series of experiments that the deposition of radium in bone resulted in a marked depression of alkaline phosphatase activity of bone and serum, but did not affect the alkaline phosphatase activity of the soft tissues.

A second series of experiments has been proposed in which Pu^{239} was chosen as the internal alpha-emitter. Pu was chosen because: 1. like radium, it is a "bone seeker"; 2. it is an alpha-emitter, a highly localized ionization; 3. its pattern of deposition in bone has been shown to differ from radium, and therefore its effects as compared with those of radium may elucidate some localized bone processes, particularly with regard to alkaline phosphatase.

It is proposed to run a series of experiments to study the effect of Pu^{239} on alkaline phosphatase as a function of dose and of time in order to determine the optimum values of these two variables for maximum effect on alkaline phosphatase. The first of these experiments is reported below. As a starting point a dose of .05 μc/gm was chosen, because this dose of radium or plutonium is known to produce histological damage. A time of 48 hours between injection and sacrifice was chosen for this initial experiment.

Experimental. 1. Determinations were made of the phosphatase activity in 4 young rats injected with approximately 0.05 μc/gm Pu IV, and in 4 similar uninjected controls.

2. The animals were sacrificed 48 hours after injection, after a blood sample was first obtained by heart puncture.

3. Both femurs and tibiae-fibulae were carefully dissected and weighed. They were then ground with water in a steel homogenizer until a fine suspension of the bone in water was obtained.

4. Aliquots of this homogenate were analyzed for phosphatase along with aliquots of serum, by the method of King and Armstrong. Values obtained are given in Tabel IV. These figures represent mgms phenol liberated in 30 min. from a substrate of disodium phenyl phosphate by the enzyme at 37.5°. The buffer for serum determination was di-ethyl barbiturate, which enabled the reaction to be carried out at a pH = 9.3. The bone phosphatase was determined in a buffer of sodium carbonate-bicarbonate at a pH of 10.1. These are the optimal pH values for serum and bone.

5. Sections of the control and the injected bones are being prepared for histological examination by Gomori staining for alkaline phosphatase, and for radioautographs to show the site of deposited plutonium.

Discussion. The irradiation of bones of rats by injection of Pu (IV) in the dose administered (0.05 μc/gm) caused a slight lowering of the alkaline phosphatase activities of the bones investigated, and a more marked depression of serum alkaline phosphatase.

The lowering of alkaline phosphatase in bones was considerably less than that noted with rats when radium was used as the internal alpha-emitter at corresponding dose levels.

This can probably be attributed to the following:

1. The average amount of Pu(IV) which was found by radioactive assay to have deposited in the bone was 0.4 percent of the injected dose, or roughly 0.032 μc. It may be that this amount of Pu is insufficient to affect seriously the alkaline phosphatase, although an equivalent amount of radium has a marked effect.

2. There is a possibility that 48 hours is not a sufficiently long time for the plutonium radiations to affect the bone cells. Radium is known to cause more rapid and striking histological changes in the early intervals[4] than does plutonium. Histological sections (not yet completed) which were prepared on control animals and animals given the same dose as those above, should indicate the extent of the histological damage to bone and this can be compared with the chemical findings. Since radiation effects are cumulative, greater changes may be expected after longer intervals.

3. Radium is known to be deposited in the bone in the region of active calcification; that is, at sites of greatest physiological activity. Pu on the other hand has been shown, in the early intervals after injection, to be deposited largely on the endosteal surface of the shaft. Staining of sections by the Gomori method along with radioautographs of the same sections should show the relationship between the site of Pu deposition in bone and the alkaline phosphatase concentration.

Summary. Pu(IV) as an internal alpha emitter (0.05 μc/gm) when intravenously injected into a number of young rats, produced only slight reduction in the alkaline phosphatase of bone, and a more marked reduction in alkaline phosphatase of serum after a period of 48 hours.

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TABLE IV

SUMMARY OF DATA ON EFFECTS OF PLUTONIUM ON ALKALINE PHOSPHATASE

	Femur		Std. Dev.	Tibia-Fibula		Std. Dev.	Serum/100 ml
	30.25		0.78	34.9		2.02	45.0
	35.00		1.26	39.9		1.80	
	26.70		1.10	29.8		1.10	45.0
	30.90		1.50	26.0		2.05	
Mean Value	30.7	±	1.16	35.1	±	1.74	45.0
	27.5		0.45	31.4		1.30	25.5
	26.7		0.25	33.7		1.70	
	26.0		0.05	27.6		1.03	25.5
	26.2		1.02	30.3		1.30	27.0
Mean Value	26.6	±	0.44	30.5	±	1.33	26.0

Indicated in the above table are the average alkaline phosphatase values of young rats (55 days) after I.V. injection of Pu(IV) at a dose of 0.05 μc/gm.

These values are compared with the average values of four control rats.

Each value represents the mean value of two bones, with duplicate determinations of each of the two.

The units of alkaline phosphatase activity are expressed in King-Armstrong units per gm of bone (wet weight), at a pH of 10.1, and in the case of serum in units/100 ml at a pH of 9.3.

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As compared with previous experiments in which radium was used as the internal alpha-emitter in comparable doses, the Pu exhibits a much smaller effect which may be attributed to (1) insufficient amount deposited in bone; (2) different regions of deposition; (3) insufficient time of irradiation. In the next experiment of this series therefore both the variables, time and dose, will be increased. It may also be desirable to use Pu(VI), which is deposited in large amounts in bone, especially in the early intervals after injection.

References

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Radiochemistry

Warren Garrison, H. R. Haymond, and Jeanne Gile

One millicurie of Na^{22} was isolated from a magnesium target. The target was dissolved in dilute HNO_3 and Mg was precipitated with NH_4OH. Na^{22} was quantitatively retained in the supernatant. To remove traces of Mg, the supernatant was adjusted to pH 7 and passed through a column of Dowex 50. Na^{22} was eluted with NH_4NO_3 at pH 5

Millicurie amounts of Lu^{177}, Y^{175}, and Ho^{166} were prepared for injection in isotonic saline and isotonic citrate solutions. Carrier-free Cb^{95} was separated from Cb^{95} - Zr^{95} mixture using a previously reported procedure. Carrier-free La^{140} was separated from Ba^{140} using a ferric hydroxide scavenger with Ba hold-back at pH 8.

Work continued on the development of production, isolation, and analytical procedures for At^{211}. Millicurie quantities of At^{211} were prepared for injection using procedures previously reported. Approximately 200 microcuries of At^{211}/μ a hr. is obtained with present target designs, using 40 Mev alpha particles degraded through 68 mg of aluminum. The yield of At^{210}/At^{211} at full energy was found to be approximately 4. At^{210} will be produced for radioautographic studies.

The extraction of carrier-free elemental I^{131} into benzene, carbon tetrachloride and carbon bisulfide has been studied. I^{131} was extracted into the organic phase from 6N HNO_3, washed with water, and reextracted with 0.1N $NaHSO_3$. Approximately 50 percent of the carrier-free I^{131}, independent of the solvent, is retained in the organic phase. Carrier amounts of iodine are completely removed under these conditions. Factors influencing the retention of carrier-free I^{131} in organic solvents are being studied.

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II BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge
Project 48A-1

Plasma and Red Cell Iron Turnover Studies in Normal Subjects and in Patients having Various Hematopoietic Disorders.

R.L. Huff, T.G. Hennessey, R.E. Austin, J.F. Garcia, B.M. Roberts, J.H. Lawrence

Iron tagged with iron 59 was injected intravenously into normal human subjects and patients having the following disorders: polycythemia vera, secondary polycythemia, lymphatic leukemia, myelogenous leukemia, pernicious animia, hemolytic anemia, and refractory anemia. The concentration of the iron 59 in the plasma and the red cells was determined as a function of time. One or more total plasma iron analyses were made on each subject. Circulating red cell mass and plasma volumes were determined on each subject. In addition, clinical and laboratory studies were carried out.

The purpose of the studies was to determine the rates of turnover of plasma iron and red cell iron in order that comparisons might be made of the values in diseased subjects with those of normal subjects. This report concerns the comparison of the plasma iron and red cell iron turnover constants with the clinical diagnosis.

Methods. The radio iron was prepared from a deuteron bombarded cobalt target in the cyclotron or was obtained from the AEC. The latter was prepared by neutron bombardment of enriched iron 58. The cobalt targets were dissolved in hydrochloric acid and extracted with isopropl ether. The stock preparation was ferric chloride in dilute hydrochloric acid solution. The final preparation for injection was made up on the day of the study in the following manner: an appropriate aliquot of the stock solution was buffered to a pH of approximately 6 with sodium citrate, and this was autoclaved. The 10-30 ml of the subjects plasma was added and the specimen allowed to stand at room temperature for at least 10 minutes before intravenous injection. The amount of radioactivity injected was approximately 10^6 counts/min. (4 microcuries).

The iron injected varied from 4 to 80 micrograms. All blood samples were drawn in heparinized syringes and transferred to 15 ml graduated centrifuge cones. At least five blood samples were taken during the first five hours after injection. The intervals differed in the various subjects. For example, if a fast plasma turnover were expected, most of the first day samples would be taken in the first hour; however, if the turnover were expected to be slow, sampling might be spread over an eight hour period. After the first day, nearly daily samples were taken for a period of two weeks in some cases. In other instances only one or two samples were taken at the end of two weeks. The packed cell volume was recorded from the graduated centrifuge cone after spinning for one-half hour at 3000 rpm in an International centrifuge, size 2. Plasma aliquots were pipetted from all samples on the first day, and in some cases throughout the study, on which total iron and radio iron determinations were made. The remaining parts of the sample, containing all the red cells and an aliquot of plasma, were analyzed for

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radio iron. If the corresponding plasma sample contained a significant amount of radioactivity the values for the cell samples were corrected. The amounts of iron per packed volume of red cells were taken as 1 mg/ml unless the cells were particularly abnormal with respect to volume, shape, or hemoglobin content. In the latter case, the total iron value was calculated from a colorimetric hemoglobin determination.

Total plasma iron determinations were by the method of Kietzes[1] et al. If radio iron analyses were to be carried out on samples which had to be run for total plasma iron, carrier iron was added to the final colorimetric solution, then this was subjected to the usual procedure for radio analysis, a modification of the method described by Peacock[2] and is as follows:

To each sample, in an Erlenmeyer flask, sufficient carrier iron was added in the form of ferric chloride to assure the presence of 10 mg Fe. After the samples had been dried at 70 degrees C., 3-10 ml of concentrated nitric acid were added to each and this allowed to evaporate at a temperature of 90° - 100°C. Then 1-3 ml of concentrated sulfuric acid was added and the mixture brought to fuming. If any blackening occurred the mixture was cooled and 30 percent hydrogen peroxide or perchloric acid (3-10 gtts.) were added and the mixture again heated. The ashed samples were transferred to 100 ml centrifuge cones by repeated washing with .1 N hydrochloric acid. The iron was precipitated with concentrated sodium hydroxide. Phenol red was used to indicate that a sufficient amount of hydroxide had been added. After 15 hours the samples were centrifuged, the supernatant decanted, and the precipitate dissolved in 1 ml of concentrated hydrochloric acid. The precipitation and centrifugation were repeated and the ferric hydroxide was then dissolved in .1 ml concentrated hydrochloric acid. The ferric chloride solution was transferred to electrodeposition cells with 35 ml of plating solution (one part saturated solution of oxalic acid and five parts of saturated solution of ammonium oxalate). Electrodeposition was carried out at .8 amperes on 2.7 cm copper planchets. After 20 min. 3 ml of saturated oxalic acid solution were added and the electrodeposition continued for 40 to 60 min. more, at which time the samples were spot tested with ammonium polysulfide. Usually the spot tests were negative at this time; if they were not, plating was continued.

Red cell mass and plasma volume were determined by one or more of three methods. In a few subjects, iron tagged cells were used according to methods previously described by both Hahn[3] and Gibson[4]. Red cell mass was measured in most subjects with P^{32} tagged cells[5]. In most instances, the concentration of radio iron found by extrapolating the curve of plasma clearance of the injected radio iron to zero time, when used to calculate a plasma volume gave a value which agreed well with the plasma volume calculated from the P^{32} red cell mass determination. In the event the values were different, the latter was used in the turnover computations.

<u>Analysis of Data.</u> Radio iron plasma concentration was plotted on semi-logarithmic paper as a function of time (Fig. 1). In general this plot was a straight line. It was expected that the concentration of radioactivity, a, would eventually reach some constant value, ka_c, where the value of k would be determined by the ratio of iron in plasma Fe_p to the amount of iron in the body, Fe_t. Usually no such horizontal component was observed. The ratio, Fe_p/Fe_t, is known to be of the order of 10^{-3} and the value, a_o, (radioactivity/ml of plasma) was approximately 10^3;

thus it is obvious that it would be impossible to detect this component by sampling a few milliliters of plasma. Symbolically the concentration of tracer as a function of time might be given as:

$$a_t = a_o e^{-Kt} + a_o k$$

More precisely it might be expected that the function would be more complicated than above since there is no assurance that the feed-back from other systems could be considered as a single entity. Actually, as mentioned above, the value of $a_o k$ was so small as to be neglected in the analysis. Likewise there was no evidence of any significant feedback. Thus the equation becomes:

$$a_t = a_o e^{-Kt}$$

The solution for K, the quantity of biological interest is as follows:

$$K = \frac{-\ln (a_t/a_o)}{t}$$

This constant represents the fraction of iron in plasma, Fe_p, turned over per unit time. Thus K was considered as r/Fe_p, where r is given in milligrams/day. The K values for the various subjects are column 5, Table I. The values for r for the various subjects constitute column 1, Table I; while column 2, Table I is milligrams/day/kg body weight. The evaluation of r is made as follows:

$$r = \frac{-\ln (a_t/a_o)}{t} Fe_p$$

Experimentally Fe_p is determined by the product of V_p, plasma volume and Fe_{cp}, the concentration of iron in plasma. The value for plasma iron concentration in some subjects was determined each time a plasma sample was analyzed for radioactivity; however, it became apparent that this was unnecessary since the value was nearly constant for the period of study. Thus in most instances only one plasma iron determination was made. The methods for determining plasma volume have been discussed.

The third column of Table I contains the values, $r(A_t/A_o)$, where A_o is the total amount of radioactivity injected and A_t is the amount of radioactivity in the circulating red cell mass when equilibrium of the radio iron in the red cells had been reached. This equilibrium state appears in many cases but not all. In the latter instance, the highest concentration achieved was the one used. The value, A_t, is the product of the circulating red cell mass and the radioactivity per unit of red cell mass. It is not thought that the value, $r(A_t/A_o)$, is a precise measure of red cell iron turnover, but rather it is a good approximation. A discussion of its reliability and validity as an indicator of red cell iron turnover involves tracer theory that is beyond the scope of this paper. The fourth column in Table I is the same value per kg of body weight.

The sixth column of Table I is:

$$\frac{r(A_t/A_o)}{\text{Fe cells}}$$

where, r, is in mg/day and, Fe cells, is the amount of iron in the circulating red cell mass.

Summary of Symbols:

A_o	quantity of radioactivity injected.
A_t	quantity of radioactivity present at any time t after injection.
a_o	concentration radioactivity/ml plasma (extrapolated value to t=0).
a_t	concentration of radioactivity/ml plasma at any time t after injection.
Fe_{po}	plasma iron concentration (micrograms/ml).
Fe_p	circulating plasma iron.
Fe_{cells}	circulating red cell iron.
r	turnover rate of plasma iron (in Table I, mg/day).
V_p	plasma volume.
Fe_t	total iron in the body.

Results and Discussion. Cases 1-5 normal male subjects:

All normal subjects were males over the age of 40 except for one who was 32. This age group was chosen because it most nearly matched the average age of the patients. The average plasma iron turnover in the five subjects was .35 mg/kg body weight/day, with a range of .31-.39 or 27 mg/day, range 21-37. The average values for the red cell iron turnover was .26 mg/kg body weight/day or 20 mg/day with ranges of 15-31 and .22-.28 respectively. The K values ranged from .37-.48 with an average of .41 (hours^{-1}). See Table I and Fig. 1a. The average value for the fraction of red cell iron renewed/day was .0085. There is little experimental data or discussion indicating what might be expected insofar as the quantity of iron entering and leaving the plasma per unit time might be. As pointed out by Hahn no adequate studies of the true distribution of iron in the human body have been made[6]. Estimates of 60-75 percent of the body iron being present in red cells are probably not greatly in error, and erythrocyte longevity studies indicate that .85 percent of the red cells are removed from the circulation per day[7]. Other studies have shown that the iron in red cells does not exchange exclusive of cell destruction[8] except in the case of reticulocytes[9]. Values for circulating red cell mass determined by cell isotope dilution techniques[1] in normal human males are approximately 30 ml/kg body weight[4, 10, 11]. There is about 1 mg of iron per ml of packed red cells. It might be expected then that .26 mg/kg body weight/day would enter and leave the plasma for the destruction and preparation of red cells. It would appear that, at least in normal subjects, the method used here in estimating the red cell iron turnover is valid. (Table I, column 6 and 4, normal subjects). This is about 75 percent of the total plasma iron turnover of .35 mg/kg body weight/day and indicates that the total remaining iron in the body has almost the same turnover rate as the red cells, although it does not preclude the possibility that some particular chemical entity containing a small amount of iron may turn over with an altogether different rate. Iron turnover in the cytochromes has been shown to occur but the rate was not determined[12]. So far as is known there is no data on the rate of liver iron turnover in human subjects. If its rate is proportional to the fraction of the total body iron present there, then it might be expected to be one tenth of the total plasma turnover or about 2.7 mg/day. Feeding experiments in this laboratory with normal foodstuffs labeled with radio iron and fed to normal subjects indicate that probably less than 1 percent of the total plasma iron turnover is concerned with absorption. These results are, in general, in agreement with the hypothesized system of iron metabolism of Moore, Doan, and Arrowsmith[13], except it would seem that Fe should be returning from cytochrome to the plasma.

Since their description, more has been learned about the mechanism of carriage of iron in the plasma. Vannotti has demonstrated by various chemical methods the presence of what he believes are at least four types of iron circulating in the plasma[14]. By his method of determination the total plasma iron is from 2-3 times the amount gotten by methods like that of Kietzes et al[1]. It is suggested by Vannotti that the "biologically active" plasma iron is the part corresponding to the fractions which he has called A and B. The method for plasma iron used in these experiments includes only the iron fractions referred to as A and B by Vannotti. In some of the cases here reported, recovery experiments for tracer in samples which had been subjected to the usual analysis for plasma iron were carried out. In such an instance the colorimetric solution as finally developed and read, and the precipitated residue were analyzed separately for radioactivity. No significant amount of radio iron was ever found in the residue. This indicates that the turnover of the tracer, as manifest in these experiments, is the same as the iron in the plasma classed by Vannotti as A and B. With the isolation of the plasma globulin which carries iron[15], following the work of Schade[16,17] and Laurell and Holmberg[18,19], additional correlative work was carried out by Rath and Finch[20], and Cartwright and Wintrobe[21] who confirmed the fact that clinically this protein was normally only about one-third saturated with iron. The method for plasma iron used by these investigators corresponds to the one used in these experiments. It is apparent that this protein iron complex furnishes the iron which corresponds to the Vannotti parts A and B of the plasma iron.

It appears that at least the iron from such a protein iron compound is susceptible to removal by the bone marrow without further reaction, since the time concentration relationship of the radio iron in the marrow when compared to the plasma is for all practical purposes inversely identical. Fig. 2 demonstrates an in vivo study of a polycythemic patient, No. 12. This subject was given enough radio iron so that an external counter placed over the proximal end of the femur and pointed toward the distal end gave the simple growth curve of Fig. 2. Simultaneously the plasma concentration of radioactivity was determined and is also plotted on the graph. If there were an interposed metabolic reaction which required any time, it would be expected that the rise in concentration in the marrow would be influenced so that it would not be a simple growth curve ($f(t) = 1-e^{-Kt}$). This same phenomenon has been observed in serial studies on the concentration of radioactivity in the bone marrow of animals following a single intravenous injection of iron 59. In the case of the animals, the marrow was actually removed. Fig. 3 shows the time concentration relationship of radio iron in the plasma and bone marrow of rabbits killed serially following single intravenous injections of radio iron.

Polycythemia Vera (non-treated or treated with radio isotopes and having an unsatisfactory remission): Studies 6-24:

Subjects having an asterisk before the name in Table I were not treated prior to the experiment. Those having no asterisk in this group are cases which were treated at some time prior to the experiment. Such subjects were in clinical relapse at the time of the study. Cases 23 and 24 are excluded from the group average because their plasma iron level was so low that turnover rates are limited by circulatory rates to the various removing tissues and are not purely a function of the maximum removal rate of the areas utilizing iron.

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The average value of plasma iron turnover in 17 studies on 13 cases was 1.81 mg/kg body weight/day. This is approximately 5 times the normal value of .35. Fig. 1b illustrates the concentration of radio iron in plasma of polycythemic subjects as a function of time after intravenous injection. Comparison with Fig. 1a shows the rapidity of iron turnover in the plasma of polycythemic subjects. Some of the K values were extremely high, for example, Study 15. This subject had extraordinary splenomegaly, so much so, that she felt it necessary to wear a maternity garment to appear presentable After the first three determinations of plasma iron turnover it was thought possible that the subjects marrow was not responsible for the very rapid rate but that spleen might be playing a significant role in iron removal. The in vivo study presented in Fig. 2 is from this patient. Although this evidence of the accumulation of tracer iron in marrow is not quantitative, the fact that the usual amount of tracer appeared in the red cells in the subsequent days is highly indicative of an extremely avid utilization of iron by the marrow for red cells. A counter which was placed over the spleen during the study showed no accumulation of radioactivity.

Nearly all the high values for plasma iron turnover were associated with values for red cell iron turnover which were high. This was to be expected since the subjects have a greater than normal red cell mass; however, the red cell iron turnover values were often inordinately high. That is, if the longevity of red cells were normal, the values for red cell iron turnover would be expected to be in accordance with the red cell mass providing the patients red cell mass were in a steady state. The usual increase in the cell mass in these subjects is by a factor of 1.5 - 3.0 of normal yet some of them showed red cell iron turnover values as great as 10 times normal. This may indicate that the longevity of red cells in polycythemia vera is significantly shortened, - perhaps by virtue of malformation or simply by increase in the number of collisions. Since the latter increases as the square of the concentration it could play a significant role. On the other hand, no analyses were done to show that the iron in the cells was present in the form of hemoglobin, thus it is possible that this rapid turnover rate does not involve cell longevity but only the cellular function of hemoglobin synthesis or a peculiar exchange reaction. Other investigators have studied stool urobilinogen excretion in polycythemia vera subjects and found the value lower; however, as was pointed out, the low excretion can be explained without the implication of decreased cell destruction[22].

Several cases of polycythemia vera have been referred to this clinic, having a serious complaint of generalized pruritus. These subjects often have a history of treatment by venesection. Their red cells are hypochromic, the plasma iron is very low, and the K values for the radio iron turnover are extremely high. Study 24 was a case of this type. The pruritus may disappear with only the institution of radio isotope therapy; but if the iron deficiency remains too great, iron may need be administered. These findings raise the question of whether it is not possible for the hematopoietic system to rob other systems of iron which may be necessary for important metabolic processes. This topic has already been discussed by Darby[23] and by Vannotti[14] in relation to iron deficiency in anemia.

Polycythemia Vera (Treated with radio isotopes and having a satisfactory remission at the time of study) Studies 25-30:

The range of plasma iron turnover in these subjects is some greater than the normals, 14-41 mg/day. Likewise the red cell iron turnover shows a more marked

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variation than the normal. The important point is the absence of any high turnover values in the group, either of plasma or cells. It is to be noted that in Studies 28 and 29 (Table I, column 6) the fraction of the red cell iron which is being renewed per day is quite low and indicates that if this condition continues to prevail, the red cell mass will gradually diminish. Two of the subjects studied before treatment were repeated after treatment when the patients were in remission, 23 and 24 and 25 and 28 respectively. Fig. 1c demonstrates the change in K values for these patients following treatment.

It is believed that this sort of determination is of value in the control of such patients because of the great changes which can occur in red cell production before there is clinical or routine laboratory evidence of an increase in red cell mass. Moreover there is a tendency because of the slow effect of radiophosphorus to over treat. If therapy appears to be unsatisfactory but it is thought that further effects may be seen later, then a radio iron study of this type can be extraordinarily helpful. In Study 29 precisely this question arose. The usual clinical and laboratory data were not decisive. Reference to Table I shows that radiophosphorus therapy at this time would have been inadvisable. Further observation of this patient over several months sustained this contention; for there was no increase in red cell mass, - rather, a slight decrease.

Patients referred with presumptive diagnosis of polycythemia vera. Studies 31-33:

Routinely polycythemia vera is suspected when there is a high hematocrit, hemoglobin, or red cell count. In most clinics, the diagnosis is considered made if in addition to this finding a red cell mass determination gives a value in excess of normal, and all evidence of secondary polycythemia has been ruled out. In this laboratory this situation has been observed on occasion, when the plasma iron turnover and red cell iron turnover values have been normal. It is believed that transitory rises in red cell mass may occur "normally". This might occur because a production rate of 10 percent above normal had prevailed for a year or so for some unknown reason and then had become normal. A hypothetical situation might be as follows: a patient may have been having chronic hemorrhage - enough to cause a higher production of red cells, then the hemorrhage stops with a consequent transient rise in red cell mass. Succinctly, it is thought that the name polycythemia vera is a descriptive term and not a disease. The symptom should not be given as a diagnosis nor should it be used as an excuse for treatment with radio isotopes. The underlying abnormality of this disease is unknown but we believe that the most nearly immediate manifestation of its presence is given by abnormal ion turnover data as described above. Isotope therapy should be directed at excessive production rate and not excessive red cell mass. The latter is easily removed by venesection.

Cases 31-33 were referred with a presumptive diagnosis of polycythemia vera; yet the iron turnover data indicated no excessive utilization of iron (Table I).

Secondary Polycythemia
Studies 34-39.

As in the studies of polycythemia vera, the plasma iron turnover and the red cell turnover are above normal. In these cases, however, the mean value of the plasma iron turnover .68 mg/kg body weight/day is only approximately twice normal

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and the variation of the individual values are not markedly great, in contrast to the cases of polycythemia vera where there may be a quite marked difference. The red cell iron turnover values are also less variable than in the polycythemia vera subjects and are certainly not as high. It appears that in such a subject the turnover of iron is regulated so that it quite closely approximates a nearly normal turnover rate for circulating red cell mass. Note column 6, Table I, where the mean value of fraction of red cell iron renewed per day for the five studies was .0111. It is hoped that studies of this nature may be used diagnostically in the separation of secondary polycythemia and polycythemia vera where the differential diagnosis might be difficult.

The data on polycythemia brings in contrast the apparent complete lack of control of regulation of iron turnover and possibly cell production in polycythemia vera and emphasizes the similarity of the disease to neoplastic disorders. It also is an argument against the type of pathogenesis for polycythemia vera suggested by Reznikoff[24] of bone marrow anoxia subsequent to arteriosclerosis.

Myelogenous Leukemia, Studies 40-46

These subjects were studied without selection for any particular reason except the clinical diagnosis of leukemia. They were in varying states of remission and relapse, although all of them were ambulatory. It should be noted that only one of the group has a normal plasma iron turnover value (Study 44) and that the group average, .84 mg/kg body wt/day is higher than even the secondary polycythemias. Some of the cases, for example, Study 40, had an almost normal uptake of radio iron in red cells so that the value for his red cell iron turnover was particularly high. In spite of this the patient was slightly anemic, had been so for several months before, and is now - one year later, developing a more severe anemia. The tendency here for iron turnover to be accelerated is apparent and although it is not as excessive as in polycythemia vera, the similarity is striking. Again it is not certain that the excessive rate indicates that cell destruction is going on at a greater than normal pace or that a peculiar cellular iron exchange is occurring. In addition, there is the possibility that abnormal white cell production in such subjects is concerned per se with excessive iron turnover. No cell separations were made, thus it is possible that radio iron was associated with white cells. Urobilinogen excretion studies were not carried out simultaneously. Nevertheless, these data suggest the possibility that in leukemia, red cell production may be adequate but abnormal.

Lymphatic Leukemia, Studies 47-65

These cases were also unselected and are similar to the myelogenous leukemia subjects insofar as iron turnover is concerned. In general the acceleration of iron turnover is not as great as in the latter. Study 56 and 57, at two different times on the same subject, is of interest from the standpoint of prognosis. The first study showed a quite high turnover value in plasma and a significant cell utilization so that the fraction of red cell iron renewed per day was high, .0220. The study was repeated several months later and the plasma iron turnover remained practically the same; however, the amount of tracer appearing in red cells was low. Shortly after the last test was performed, the patient became severely anemic and died. Although corroborative studies for cell longevity are not available, it appears that in both polycythemia vera and the leukemias, the red cells have a

lack of staying power and that as the clinical condition becomes worse, the ability of the red cells to sustain themselves becomes negligible. One of the polycythemia cases falls into this category, Study 9. This subject was studied at an earlier time, the data for which does not appear in the table; but at that time he had an excessive turnover and a rather high red cell mass. Two years elapsed and the test was repeated, and at this time the patient was slightly anemia, with turnover data which continues to be high. It is rather certain that the anemia did not appear in relation to isotope therapy; for bleeding had constituted the major form of therapy. The rate of venesection had not been increased.

Pernicious Anemia (without therapy), Studies 66-67.
Pernicious Anemia (with therapy), Study 68.

The plasma iron turnover values in the two untreated cases were as great as some of the most severe polycythemics, 1.89 and 2.70 mg/kg body wt/day. The red cell uptake of radio iron was low; but the red cell iron turnover was excessively high in relation to the circulating red cell mass, the fraction of red cell iron renewed per day being .0340 and .0650. In pernicious anemia the corroborative evidence for erythropoietic hyperplasia, the formation of abnormal erythrocytes, lack of staying power of the red cells[25], and excessive urobilinogen excretion is good[22].

The treated pernicious anemia patient showed a definite tendency to return to normal, however, there remains a tendency for accelerated iron turnover. The subject was studied about three months after the institution of therapy. Morphologic cellular studies and other clinical studies showed him to be in a satisfactory remission.

Refractory Anemia, Studies 69-74.

These cases fall into two categories so far as plasma iron turnover is concerned. Cases 69, 72 and 74 show excessively high values which correspond to polycythemia vera; whereas Cases 70, 71, and 73 are nearly normal or below normal. (Table I, column 2). Of the first group, the last two had outright indications of excessive cell destruction such as reticulocytosis, splenomegaly and hyperplastic marrow; but the first showed no reticulocytes and a marrow which avoided classification in the usual sense. The characteristic finding of the marrow was numerous young cells which appeared to be of the red cell series. Both marrow aspiration and biopsy were unsuccessful in Case 70. The marrow of Case 71 was described as hypoplastic while that of Case 73 was similar to that of 69. The red cell iron turnover differed markedly among the members of the group also. Note Case 74, 1.51 mg/kg body wt/day, and compare to Cases 69 and 70, which are .05 and .13 mg/kg/body wt/day. In cases where extremely rapid destruction of marrow cellular output occurs the method of computation of red cell iron turnover previously described breaks down and a more complicated analysis must be used. Some of these cases, for example 69, where the marrow was questionably hypoplastic and at the same time presented a great plasma iron turnover, probably fall into this class. The accuracy of the computation of red cell iron turnover in Case 73 is questionable because there appeared to be no smooth function of accumulation of plasma iron in the circulating red cells; instead the function was very irregular and compared to those cases of hemolytic anemia studied by Moore[26]. Calculations of the fraction of red cell iron turnover in these cases are also not valid when it is impossible to determine

the amount of circulating red cells which have been transfused.

In some of the refractory anemia cases the loss of radio iron from the plasma was not a simple exponential but was complicated by a rapid early loss which accounted for approximately 60 percent of the tracer. The K value of the rapid component was about 4 hours^{-1} while the slow component (on which the calculations were made when such a situation arose) was from .1-.2 - hours^{-1}. It was thought that since these patients had high plasma iron values, there might be insufficient protein for binding or that the protein was abnormal, and the fast component merely represented diffusion into the extracellular fluid. Case 71 was repeated incubating the radio iron, not with the subject's plasma, but with a normal individual's plasma; however, the result was the same. Simultaneous in vivo marrow studies would be very helpful in such cases.

Blood Donor, Case 75.

The data on this subject was included because it is felt that it demonstrates the sensitivity of the method. He was chosen originally as a normal subject; later it was learned that he sold a pint of blood almost regularly every two months. Both his plasma iron turnover and red cell iron accumulation are above normal. The latter more than the former. The test was performed about one week after the last venesection.

Summary. The plasma iron turnover rate has been determined and red cell iron turnover rate approximated in seventy-five subjects. Five of the subjects were normal males in which the average turnover rate of plasma iron and red cell iron were respectively .35/mg/kg body wt/day and .26 mg/kg body wt/day. These values are discussed in terms of what might be expected from known rates of red cell destruction from and quantities of iron in the body and in cells. The data indicate that if iron from all systems when turned over enters the plasma at one time or another that the rate constant of iron other than that in red cells is approximately equal to that of the red cells. This does not preclude the possibility that small quantities of iron in some system may have rate constants which are altogether different.

Nineteen of the subjects studied were polycythemia vera subjects which had either not been treated or had been treated and were in relapse. The turnover rate for these patients was invariably high and the average value, 1.81 mg/kg body wt/day was approximately five times the normal value. The red cell iron turnover value was also high. It appeared that the rate of renewal of red cell iron was out of proportion to the amount of circulating red cell mass and that either a faster rate of destruction of red cells or a peculiar exchange of iron occurred.

Six studies were made on secondary polycythemia subjects. Again the plasma and red cell iron turnover values were above normal but in this instance the red cell iron turnover approached very closely the expected value for the increased red cell mass.

The effect of radio isotope therapy on iron turnover in polycythmia vera subjects is demonstrated in two cases which were studied before and after therapy. The iron turnover data are presented in six cases of polycythemia vera which are in satisfactory clinical remission following therapy. There is a marked difference in plasma iron turnover values following therapy. They may be restored to normal

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or may be even below normal. The red cell iron turnover values may also become lower than normal following therapy.

The use of iron turnover data in the management and diagnosis of polycythemia vera is discussed.

Plasma iron turnover was found to be consistently high in seven cases of myelogenous leukemia but not as great as in polycythemia vera. Likewise the red cell iron turnover was increased in some instances indicating again the possibility of rapid cell destruction.

In nineteen cases of lymphatic leukemia the plasma iron turnover was often above normal. In general this increase was mild when compared to the cases of polycythemia vera.

In two cases of pernicious anemia in relapse values for plasma iron turnover were as high as some of the most severe polycythemics. Likewise the red cell iron turnover was far above the amount needed to replace the iron in the circulating red cell mass at a rate corresponding to a cell life of 125 days.

The sensitivity of the method is demonstrated in a blood donor who shows a slightly increased turnover rate of plasma and red cell iron.

Conclusions. 1. Plasma iron turnover in normal men is approximately one and one-half times the amount required for the renewal of red cell iron at a rate of .85 percent per day.

2. Plasma iron turnover is increased in the polycythemias, in the leukemias, in pernicious anemia, and in hemolytic anemia.

3. Radio isotope therapy reduces the excessive plasma iron turnover rates in polycythemia vera.

4. In some cases of refractory anemia the plasma iron turnover rate is reduced.

5. Iron turnover data are useful in the management and diagnosis of polycythemia vera.

6. The excessive plasma iron turnover rate of a pernicious anemia patient in relapse returns to near normal with therapy.

7. The turnover rate of plasma iron is a much more sensitive indicator of abnormalities of iron metabolism than a plasma iron determination alone.

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TABLE I

Fe TURNOVER DATA

PRIVACY ACT MATERIAL REMOVED

SUBJECT	Plasma Iron Turnover		Red Cell Iron Turnover		Fraction of Plasma Iron Removed/Hour	Fraction of Red Cell Iron Renewed/Day
	Mg/Day	Mg/Kg/Day	Mg/Day	Mg/Kg/Day		
Column	1.	2.	3.	4.	5.	6.
NORMAL SUBJECTS						
1.	30	.40	20	.26	.39	.0072
2.	28	.39	20	.28	.48	.0074
3.	20	.31	14	.22	.42	.0076
4.	37	.32	31	.26	.38	.0101
5.	21	.31	15	.22	.37	.0103
avg.	27	.35	20	.26	.41	.0085
POLYCYTHEMIA VERA Non treated cases* or treated cases with unsatisfactory remission						
6.*	41	.82	26	.50	.85	.0070
7.*	245	3.70	165	2.40	3.10	.0370
8.*	65	.83	57	.72	.84	.0170
9.	111	1.40	74	.93	1.09	.0427
10.*	85	1.46	77	1.34	1.87	.0279
11.	246	4.19	209	3.58	2.97	.0695
12.*	104	1.62	-	-	3.15	-
13.	175	2.71	-	-	2.30	-
14.	148	2.28	70	1.79	3.15	.0202
15.	182	2.88	113	2.71	4.15	.0352
16.*	61	1.19	45	.87	1.65	.0213
17.*	67	.72	57	.58	.93	.0118
18.*	88	1.24	47	.63	1.21	.0142
19.*	107	1.55	-	-	2.77	-
20.*	68	.93	61	.84	1.04	.0350
21.*	44	.61	41	.57	1.26	.0120
22.	62	.84	-	-	1.73	-
	112	1.81	80	1.34	2.00	.0239
23.*	33	.51	21	.33	1.71	.0100
24.*	19	.36	15	.30	3.64	.0097

PRIVACY ACT MATERIAL REMOVED

PRIVACY ACT MATERIAL REMOVED

TABLE I
(Continued)

SUBJECT	Plasma Iron Turnover		Red Cell Iron Turnover		Fraction of Plasma Iron Removed/Hour	Fraction of Red Cell Iron Renewed/Day
	Mg/Day	Mg/Kg/Day	Mg/Day	Mg/Kg/Day		
Column	1.	2.	3.	4.	5.	6.
POLYCYTHEMIA VERA Treated: and having satisfactory remission						
25.	28	.41	-	-	.36	-
26.	41	.55	25	.30	.74	.0115
27.	29	.39	22	.27	.69	.0104
28.	16	.30	11	.20	.20	.0031
29.	14	.16	11	.12	.14	.0030
30.	30	.44	25	.39	.69	.0130
avg.	26	.38	19	.26	.47	.0082
PATIENTS REFERRED WITH PRESUMPTIVE DIAGNOSIS OF POLYCYTHEMIA VERA						
31.	29	.33	25	.28	.73	.0084
32.	22	.28	20	.26	.70	.0073
33.	15	.15	9	.10	.38	.0034
avg.	22	.28	18	.21	.60	.0064
POLYCYTHEMIA SECONDARY						
34.	27	.82	19	.56	.59	.0074
35.	26	.36	18	.25	1.31	.0086
36.	60	.82	42	.57	1.98	.0159
37.	59	.88	46	.70	.35	.0101
38.	38	.70	26	.48	.57	.0140
39.	35	.50	24	.33	.56	.0107
avg.	41	.68	29	.48	.89	.0111
LEUKEMIA MYELOGENOUS						
40.	94	1.46	63	.98	.73	.0342
41.	75	1.13	27	.40	.87	.0120
42.	29	.40	15	.25	.35	.0128
43.	53	.94	22	.39	.54	.0150
44.	21	.35	54	.10	.40	.0033
45.	49	.95	17	.33	.36	.0089
46.	36	.62	30	.49	.38	.0180
avg.	51	.84	33	.42	.62	.0149

PRIVACY ACT MATERIAL REMOVED

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PRIVACY ACT MATERIAL REMOVED

TABLE I
(Continued)

SUBJECT	Plasma Iron Turnover		Red Cell Iron Turnover		Fraction of Plasma Iron Removed/Hour	Fraction of Red Cell Iron Renewed/Day
	Mg/Day	Mg/Kg/Day	Mg/Day	Mg/Kg/Day		
Column	1.	2.	3.	4.	5.	6.
			LEUKEMIA LYMPHATIC			
47.	36	.52	34	.49	.41	.0150
48.	37	.42	31	.35	.54	.0134
49.	50	.80	40	.64	.53	.0304
50.	13	.17	11	.15	.27	.0101
51.	30	.39	26	.33	.40	.0119
52.	39	.66	33	.68	.45	.0190
53.	39	.44	37	.43	.32	.0171
54.	19	.30	19	.30	.30	.0098
55.	35	.49	31	.44	.53	.0220
56.	46	.49	28	.30	.44	.0182
57.	44	.47	12	.13	.20	.0087
58.	31	.40	12	.16	.24	.0094
59.	26	.33	8	.02	.26	.0013
60.	27	.38	23	.26	.39	.0113
61.	73	.76	73	.74	.61	.0270
62.	59	.85	43	.63	.69	.0300
63.	30	.53	27	.44	.44	.0226
64.	45	.64	-	-	.44	-
65.	32	.43	27	.36	.56	.0150
avg.	37	.50	30	.38	.42	.0162
			PERNICIOUS ANEMIA			
66. Brt	78	1.89	11	.26	.94	.0340
67. Hrs_1	137	2.70	27	.50	1.65	.0650
			PERNICIOUS ANEMIA * TREATED		PRIVACY ACT MATERIAL REMOVED	
68. Hrs_2	50	.84	35	.60	.74	.0138
			REFRACTORY ANEMIA			
69.	127	1.74	4	.05	.63	.0040
70.	35	.42	11	.13	.22	.0132
71.	13	.26	1	.01	.10	.0001
72.	220	3.89	17	.22	.73	.0110
73.	43	.52	36	.34	.20	.0340
74.	158	2.14	112	1.51	1.66	.1270
			Blood Donor			
75. Avy	30	.42	25	.36	.60	.0126

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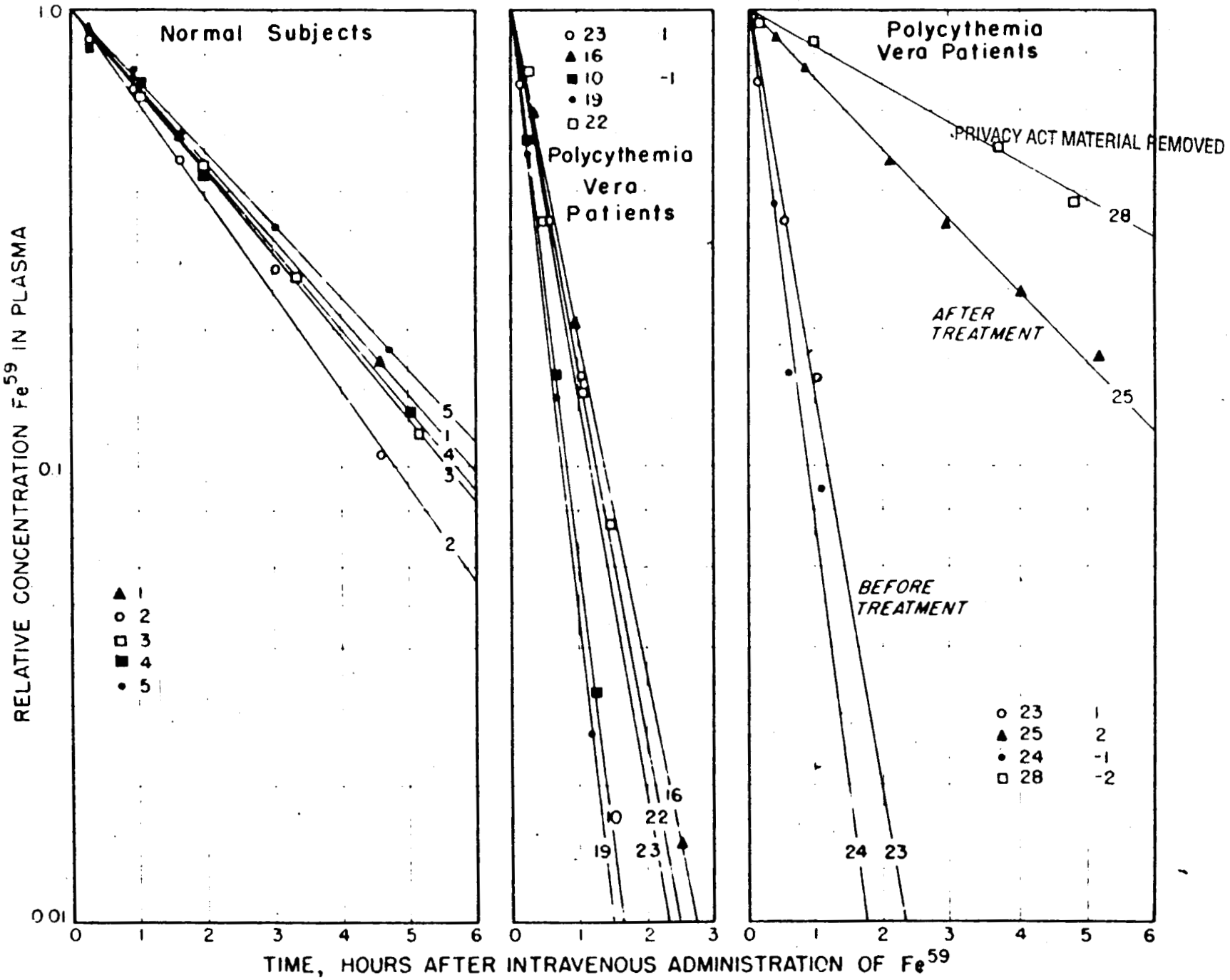
FIG. 1a FIG. 1b FIG. 1c.



$$\text{Relative Concentration} = \frac{\text{Concentration at any } t}{\text{Concentration at } t = 0}$$

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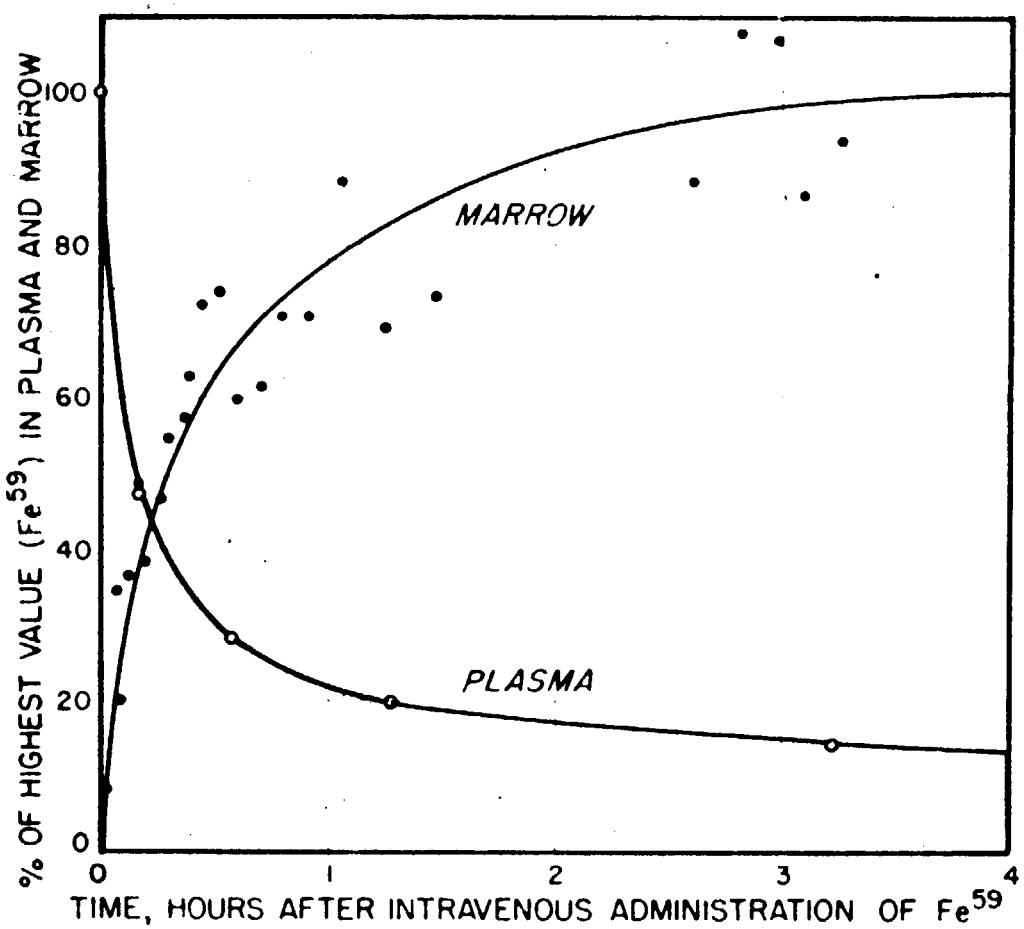
FIG. 2



The accumulation of radio iron (detected by external counter) in the bone marrow of a patient with polycythemia vera; and the loss of radio iron from plasma (in vitro analysis).

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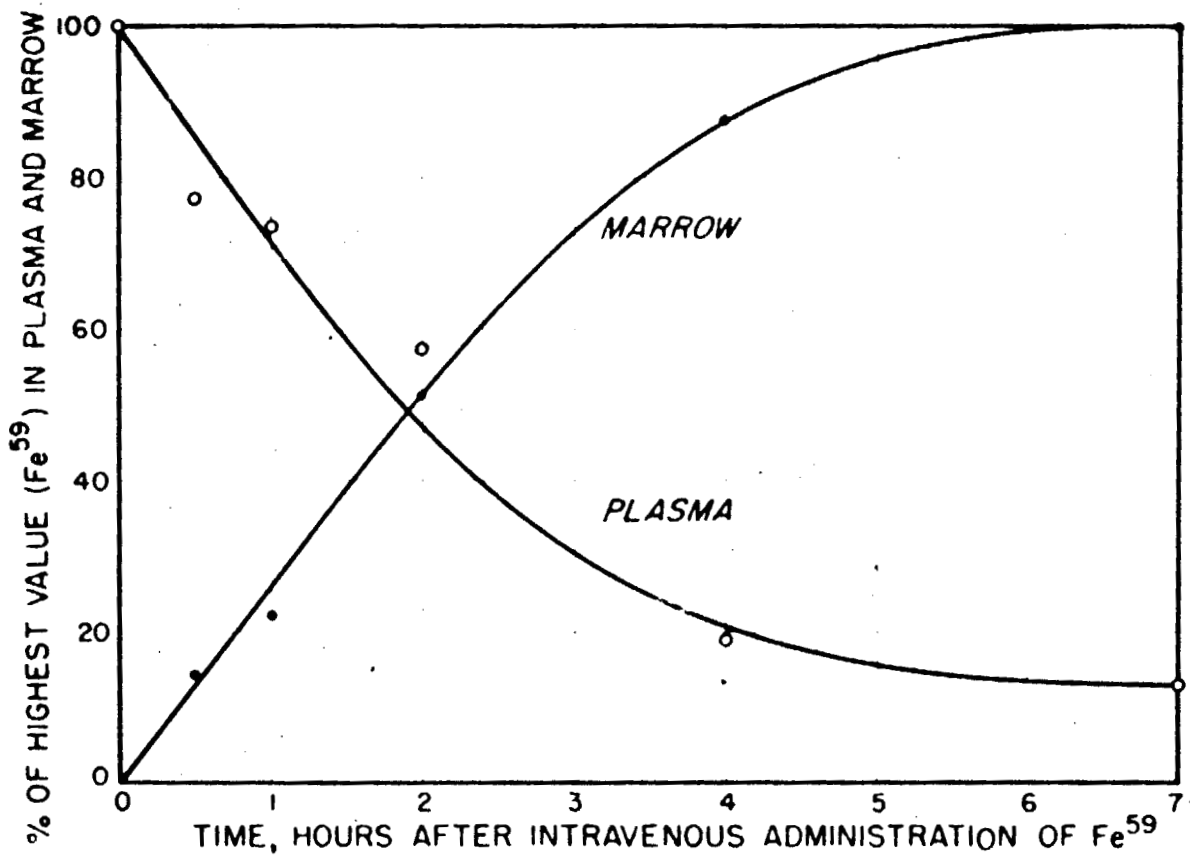
FIG. 3



The accumlation of radio iron in the bone marrow of rabbits and the loss of the radio iron from plasma ; the animals were killed serially and the analysis performed in vitro.

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III HEALTH CHEMISTRY AND PHYSICS

Health Chemistry

N. B. Garden

Monitoring. Chemists using radioactive materials have moved into the new Central Research Laboratories. Monitoring facilities have been set up and survey meters, tongs, manipulators, pipettes, and other instruments have been stocked. A laboratory has been established in Room 106, ORL, for the analysis by members of the Health Chemistry Group of contaminated objects such as filters and pipes found in the course of monitoring. This will assist in pinning down the sources of contamination. The analytical equipment will include a counter for plated disk analysis. Development work is being done on improved scrubbing of active corrosive fumes present in the chemists' hoods.

Transportation, Decontamination, Disposal and Storage. The operation of the pneumatic system which will bring targets from the 184-inch cyclotron to a laboratory in Building 5 in a matter of seconds has been delayed because of faulty specifications by the manufacturer for the compressor motor. The completion and subsequent use of this system should take place in the very near future. During this quarter the target holders used by the chemists have been standardized. Holders have been created for foil, powder and miscellaneous types of targets. Equipment for disassembling targets has been built to improve speed and safety of target handling. A drive has been made during this period to encourage the storage of radioactive materials not being used eventually in Health Chemistry's Central Research Facilities in Building 5 rather than in individual lead caves and boxes in each laboratory. This program will lead to more space in the laboratories and less activity background. The movement of chemists to the new Central Research Laboratories has necessitated those transport of quantities of radioactive materials, gloved boxes and other equipment to the new site. The handling of isotope shipments from Oak Ridge and other installations and the quantity of radioactive waste dumped at sea has increased to a new peak during this period.

Research and Development. Improvements in the equipment used for remote control handling of radioactive materials in both the straight-type cave and the 2-in. lead-shielded manipulator box has been completed and will be used in connection with special slugs and bombardments. A modified glove port for use on Berkeley Boxes, modified for accomplishment of more safe and efficient change of gloves, has been used successfully. Standard Berkeley Boxes have been produced as usual. Modified examples have been produced for special purposes, such as a box with a 10-step extraction unit and a box with a special top for four extraction columns.

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Health Physics

B. J. Moyer

Cyclotron Radiation Field. The installation of a new beam deflecting system in the 184-inch cyclotron has produced an increased intensity in high-energy neutrons projected in the general direction of the control room. Measurements indicated up to 300 Mev/cm^{2}sec, in the form of fast neutrons between 0.5 and 15 Mev, outside the shielding on the west side near the south-west corner; and in the control room the corresponding figure was as high as 100.

As a temporary measure, a wall of concrete ballast blocks, 3 feet in thickness, has been erected to augment the shielding on this side. According to measurements of penetration of 270 Mev neutrons in concrete, this increment should reduce the intensity by about a factor of four. A very brief test has been possible since the installation of the blocks, and the results appear to be about as predicted.

As a permanent protection from this neutron field a 5 foot layer of concrete shielding blocks will be installed in this region, bringing the total thickness here to 15 feet.

The decision has also been made to construct a permanent deflected beam cave with a roof, for work with the external proton beam.

Neutron field of the Linear Accelerator. The recent modifications of the drift tubes in the linear accelerator providing graphite at the points where the protons might impinge, and the realignment of the system has lowered the fast neutron output by a factor of 4.

At present in the upstairs office, the energy flux carried by fast neutrons, per 10^{-8} amps of proton beam at the target, is from 40-50 Mev/cm^{2}sec. The proton beam has attained a maximum of as much as 5×10^{-8} amps in steady operation over limited periods. Consequently, there is still need of either further shielding or of moving the office area if there is possibility of operating the machine for extended periods at this level. One or the other of these measures will be accomplished.

Study of High Energy Neutron Fields by Films. Heretofore information concerning the flux density of high energy neutrons outside the shielding of the 184-inch cyclotron has been obtained by use of a bismuth fission counter which is sensitive to neutrons over 50 Mev and whose fission cross section for the high energy neutrons from the cyclotron is approximately known. As an alternative method, a program has been started to estimate the intensity of these neutrons by counting the stars they produce in Ilford C-2 plates exposed on the outside surface of the cyclotron shielding. Thus far enough information has been acquired to indicate that in a cyclotron operating time of 75 hours, for which only 40 hours employed 350 Mev protons, the number of stars produced by fast neutrons per cubic millimeter of emulsion ranged from 1 to 13 depending upon position.

Further Developments in the Survey of Fast Neutron Fields. Calculations and designs are in process toward the end of making more accurate the estimation of the energy flux delivered by fast neutrons as measured by the proton recoil method. The points

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of improvement concern dealing more accurately with the problem of the minimum pulse size detected, and with the problem of obliquity of path in the hydrogenous material which is of necessity curved into the contour of the counter wall.

Statistical Summary of Monitoring Program. Survey instruments maintained:

B-V Ionization Chambers	28
Victoreen 263 Portable Survey Meters	19
I.D.L. Portable Survey Meters	18
Cutie Pies	2
Recording Area Survey meters	11
Victoreen Proteximeters	3
Fast neutron proportional counters	5
Slow neutron proportional counters	5
Balanced chamber (slow neutron survey instrument)	2
Special tissue wall survey instrument	1

Personnel meters in use:

Number of people wearing film badges	1,360
Total man days coverage with pocket chambers	2,250
Total man days coverage with pocket dosimeters	4,164
Total man days coverage with pocket chambers, (S.N.)	3,076

Cases of weekly exposure above 0.3 r :

Weekly Film Exposures Above	184" Area	60" Area	Linear Accelerator	Synchrotron	Chemistry	Total
0.3 r	9	10	11	0	8	38
0.5 r	2	2	4	0	0	8
1.0 r	2	2	1	0	0	5
1.5 r	1	1	0	0	0	2
2.0 r	1*	0	0	0	0	1

*This exposure was received while undergoing a dental x-ray examination that was in no way connected with the project.