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April, May & June 1948

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I THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

J. G. Hamilton

Project 48A-I

Radioautographic Studies

Radioautographic studies using yttrium, curium, strontium, and protoactinium were undertaken. The results with yttrium indicate that at 16 days after administration, deposition occurs on the periosteal and endosteal surfaces of the shaft, on the endosteal surface of trabecular bone, and there is some yttrium scattered throughout the cortical bone. This latter occurred to a much lesser extent than was found with element 61, curium, americium, or cerium.

Curium deposition after a period of 64 days, was found to be practically identical to that found at 8 days.

Protoactinium studies are underway, but have not been completed.

Radiostrontium was injected into two groups of rats in order to study the strontium uptake at various time intervals after administration. One group was phosphorus deficient and the other was a control group. Animals were sacrificed at 0.5, 1, 4, 12, 24, and 48 hours. The results are as yet incomplete.

A great deal of difficulty has been encountered with the microtome knife sharpener which has resulted in a considerable loss of time.

Tracer Studies

Actinium. Studies have been completed with actinium 227 thirty-two and sixty-four days after intramuscular administration and sixteen days after administration of the actinium orally. Less than 0.3% of the actinium administered orally was found to have been absorbed from the digestive tract. Thirty-two and sixty-four days after intramuscular administration 31% and 18% respectively remained at the injection sits. The actinium that was absorbed was primarily excreted via the intestinal tract or deposited in the liver and skeleton. Other organs in which appreciable concentration occurred were skin, kidney, and lymph nodes. Although measurable amounts of actinium are found in the other tissues of the body, their concentrations are comparatively low. As is typical of the actinide series of elements, bone storage and retention of this element is extensive. The corrected data of the thirty-two and sixty-four day intramuscular studies are presented in Table I.

Beryllium. As reported in the last quarterly report, intramuscular studies with carrier-free beryllium were started. These studies have been completed. Data not previously reported include studies made upon the distribution of Be^7 in rats 16 and 64 days after intramuscular injection. At these time periods, 42 and 20 percent of the Be^7 administered remained at the injection site. After absorption of the beryllium the major organ of deposition was the skeleton. This structure received 28.8% and 26.9% of the absorbed dose at 16 and 64 days after injection.

TABLE I

DISTRIBUTION OF ACTINIUM AS PERCENT OF DOSE IN THE RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR UNABSORBED PORTION IN LEFT LEG AND RECOVERY

	16 days		64 days	
	% per organ	% per gram	% per organ	% per gram
Heart	.03	.04	.02	.03
Lungs	.21	.12	.12	.07
Spleen	.16	.25	.14	.20
Blood	.44	.04	.01	.01
Liver	16.6	2.19	6.67	.92
Kidney	.27	.19	.33	.19
Adrenals	.01	--	.01	.10
Thyroid	0	--	0	0
Lymph Gland	.01	--	.01	.17
Pancreas	.03	.04	.02	.03
Brain	.01	.01	.01	.01
Fat	.04	.04	.01	.01
Stomach	.15	.03	.12	.08
Sm Int	.40	.04	.18	.05
Lg Int	.39	.03	.37	.05
Bone	29.2	1.32	20.8	.99
Muscle	2.47	.03	4.08	.05
Skin	.66	.03	.38	.02
Gonads			.01	.05
Urine	.39	--	.79	--
Feces	48.5		66.0	
	100.0		100.0	

Beryllium is primarily excreted via the urine although fecal excretion takes place to a lesser extent. Beryllium is not deposited in the soft tissues of the rat to any great degree with the exception of liver, kidney, spleen, and blood at the 16 day period. The results obtained upon these and other tissues are summarized in Table II. Although a considerable fraction of the Be^7 was absorbed from the injection site between the 16 and 64 day time intervals, it is apparent that the retention of beryllium in the bone is high under the conditions of these experiments.

Lanthanum. Comparative studies in the rat of carrier versus carrier-free lanthanum, as well as the effect of a complexing agent upon this member of the lanthanide series of rare earths, have been completed. Four groups of three animals in each group were injected intramuscularly and sacrificed two days later. They were given the following: Group 1 - carrier-free La^{140}, Group 2 - La^{140} + 1 mg $La(NO_3)_3$ per rat, Group 3 - Carrier-free La^{140} + 4.5 mg sodium citrate per rat, Group 4 - La^{140} + 1 mg $La(NO_3)_3$ + 4.5 mg Na citrate per rat. The absorption from the injection site was respectively 32, 2, 85, and 11 percent of the injected La^{140} as described above. These data show that carrier-free La^{140} is fairly well absorbed from the injection site, and that this is reduced to a very low value when carrier is added. Complexing the lanthanum greatly enhances the absorption in the carrier-free state and the absorption is increased when citrate is added to lanthanum which contains carrier.

After absorption, the four groups of animals handled lanthanum somewhat differently when administered as described above. For example, carrier-free lanthanum was deposited in the skeleton to the extent of 13% of the absorbed dose. With carrier added, this was found to be 24%. The addition of citrate to the carrier-free lanthanum gave a skeletal deposition of 16%; this was increased to 30% with the addition of carrier plus citrate. Similarly 80% of the absorbed dose was found in the liver with carrier-free La^{140}, 20% with carrier, 74% with citrate but without carrier, and 44% with carrier and citrate. It can be seen that the addition of carrier to La^{140} decreases the percent of total lanthanum present in the liver. The addition of carrier lanthanum increases the fecal excretion of La^{140}. This is not appreciably influenced by citrate. The addition of La carrier increases the La concentration in the blood about 25 times when no citrate was added. The data for the other tissues are presented in Table III.

Praseodynium. The distribution of Pr^{143} in rats after intramuscular administration has been completed for 1, 4, and 16 days after the administration of this member of the lanthanide series. This element is handled by the body in a manner which is similar to the other rare earths as well as actinium, americium, and curium. At 1, 4, and 16 days, 74%, 61%, and 41% of the Pr^{143} administered remained at the injection site.

Of the Pr^{143} absorbed, at 1 day after administration, a major portion is deposited in the skeletal system and in the liver. Four and sixteen days after administration, similar skeletal deposition was shown with a gradual reduction of the Pr^{143} in the liver, this being primarily eliminated via the feces. The data for the other tissues are included in Table IV.

Uranium^{230}. Studies of the metabolism of U^{230} at 1, 4, 16, and 32 days after intramuscular administration have been completed. These agree with the results obtained upon U^{233} with the exception of lower skeletal uptakes. This may indicate that the skeletal retention is in part influenced by the total number of atoms given as would be the case when U^{230}, which has a half-life of 30 days, is compared to U^{233}, which has a half-life of about 150,000 years. The data are summarized in Table V.

TABLE II

DISTRIBUTION OF CARRIER-FREE Be^7 IN RAT AS PERCENT OF DOSE FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR UNABSORBED PORTION IN LEFT LEG AND RECOVERY

	16 days		64 days	
	% per organ	% per gram	% per organ	% per gram
Heart	.07	.09	.01	.01
Lungs	.43	.14	.12	.04
Spleen	.20	.28	.19	.22
Blood	1.44	.11	.23	.01
Liver	5.25	.48	.48	.05
Kidney	.84	.45	.15	.06
Adrenals	.02		.01	.14
Thyroid	.02		.01	
Lymph Glands	.02		.01	
Pancreas	.09	.07	.01	.01
Brain	.02	.01	.02	.01
Fat	.02	.05	.02	.02
Stomach	.12	.04	.06	.01
Sm Intestine	.27	.04	.11	.01
Lg Intestine	.34	.02	.07	.01
Bone	28.8	1.55	26.9	1.43
Muscle	1.60	.01	1.97	.01
Skin	.41	.01	.21	.01
Eyes	.01	.02	.01	.04
Pituitary	--	--	.01	
Gonads	.09	.04	.05	.01
Urine	43.4	--	54.4	--
Feces	16.5	--	15.0	--
	100.0		100.0	

TABLE III

COMPARISON OF DEPOSITION OF RADIO-LANTHANUM AS CARRIER-FREE La^{140}, CARRIER La (1 mg $(Na_3)_3$, COMPLEXED CARRIER FREE AND CARRIER La + CITRATE COMPLEX. VALUES EXPRESSED AS PERCENT OF ABSORBED DOSE

	Carrier-free		1 mg Carrier		C.F. 4.5 mg NaCit		Carrier + Citrate	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	0	0	1.44	1.44	.12	.18	.03	.04
Lungs	.10	.07	1.44	.72	.18	.11	1.16	.58
Spleen	.13	.13	1.44	2.16	.13	.16	1.75	2.33
Blood	.23	.02	5.04	.72	1.02	.08	.19	.02
Liver	80.2	10.9	20.1	3.60	73.9	10.8	44.6	6.69
Kidney	1.17	.60	2.88	1.44	.82	.50	.48	.29
Stomach	.18	.07	--	--	.27	.12	.58	.19
Sm Int	.63	.07	--	--	.47	.15	.39	.05
Lg Int	.50	.07	2.16	.72	.83	.12	.58	.08
Bone	13.1	.57	24.0	.72	16.6	.76	31.1	1.55
Muscle	.80	.01	15.8	.04	2.15	.02	1.94	.02
Skin	.37	.01	4.32	.01	1.12	.03	.68	.03
Pituitary	0	--	1.44	--	.08		.01	--
Urine	.37	--	0	--	.50	--	6.20	--
Feces	2.24	--	13.7	--	1.44	--	10.2	--

TABLE IV

DISTRIBUTION OF Pr^{143} IN RAT AFTER INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR ABSORPTION AND RECOVERY, GIVEN AS PERCENT OF DOSE

	1 day		4 days		16 days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.18	.23	.05	.11	.05	.07
Lungs	.36	.18	.27	.14	.19	.07
Spleen	.27	.41	.21	.27	.19	.19
Blood	.54	.05	.11	.01	.02	.01
Liver	50.4	10.5	51.3	6.61	33.3	4.15
Kidney	3.09	2.13	.84	.41	1.11	.58
Adrenals	.03		.02	1.04	.02	
Thyroid	.04		.01		.01	
Lymph Gland	.03	.36		.30		.09
Pancreas	.14	.18	.05	.09	.03	
Brain	.01	.01	.01	.01	.01	.01
Fat		.04		.03		.02
Stomach	.54	.32	.49	.19	.24	.09
Sm Int	2.86	.41	.81	.09	.53	.05
Lg Int	2.72	.50	1.59	.21	.81	.10
Bone	26.0	1.91	27.5	1.78	29.5	1.97
Muscle	3.04	.04	2.38	.03	1.53	.02
Skin	2.45	.09	1.31	.05	.82	.03
Pituitary			.01	--	.01	--
Gonads	.02	.23	.02	.11	.01	.05
Eyes	.02	.05	.01	.03	.01	.01
Urine	3.54	--	7.07	--	7.32	--
Feces	3.67	--	5.98	--	24.4	--

TABLE V

DEPOSITION OF U^{230} IN THE RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR RECOVERY AND ABSORPTION FROM INJECTION SITE GIVEN AS PERCENT OF DOSE

	1 day		4 days I		4 days II		16 days		32 days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	0	0	0	0	.02 *	.01 *	.01	.01		
Lungs	.03	.02	.01	.01			.02	.02		
Spleen	.02	.03	.01	.01	.04	.04	.01	.02		
Blood	.05	.01	.01	.01			.01	.01		
Liver	.15	.02	.21	.02	.45	.04	.09	.02	.19	.01
Kidney	11.7	7.18	11.8	7.50	13.0	7.30	1.48	.90	.42	.19
Adrenals	.01		.01				.01			
Thyroid	0	0	.01				.01			
Lymph Gl		.09		.01				.01		
Pancreas	0	0	.01	.01			.02	.03		
Brain	0	0	.01	.01			.01	.01		
Fat		.01		.01				.01		
Stomach	.18	.10	.01	.01	.09	.02	.03	.02	.02	.01
Small Int	.53	.08	.07	.01	.15	.01	.03	.01	.13	.01
Large Int	4.94	.57	.23	.04	.22	.03	.10	.02	0	0
Bone	9.46	.60	10.9	.68			3.66	.21	11.4	.46
Muscle	6.15	.07	.57	.01	.16	.01	.37	.01	.97	.01
Skin	.40	.01	.21	.01	.44	.02	.16	.01	.03	.01
Eyes	.01	.01	.01	.01			.02	.09		
Pituitary	0	0	.01				.01			
Gonads	.01	.01	.01	.01			.01	.05		
Urine	60.0	--	70.0	--	60.9	--	83.7	--	75.9	--
Feces	6.33	--	5.99	--	10.8	--	10.3	--	10.9	--
Tibia					.11	.63				
Tibia Head					.31	1.05				
Femur					.48	.55				
Skel + 1 bone					12.9	.71				

* + Lungs

The U^{230} used for the 1 day, 4 day Group I, 16 day, and 32 day studies was obtained from the Chemistry Division of the Argonne National Laboratories from deuteron bombarded thorium. The U^{230} used on the 4 day Group II studies was prepared in this laboratory from bombardment of thorium to produce Pa^{230} by the d-4n reaction on Th^{232}. The target was allowed to cool so that the short-lived Pa^{232} had decayed to form U^{232}. The Pa^{230} and Pa^{233} were isolated from the fission products, U^{232}, and small traces of U^{233}. This preparation was allowed to decay for 25 days at which time the U^{230} and U^{233} were isolated. The activity, contributed to the preparation by the U^{233} by decay of Pa^{233}, was observed to be less than 2% of the total uranium activity.

Vanadium. A complete study upon the distribution of carrier-free V^{48} has been completed in rats. This element is rather readily obsorbed after intramuscular injection. At 1, 4, 15, and 64 days after administration, 28%, 23%, 9%, and 5% of the V^{48} remained at the injection site. Vanadium is excreted in both urine and feces, the former playing a predominate part in the early time period. A wide distribution of V^{48} occurs in the tissues of the rat at early time periods following intramuscular administration. Clearance from the body is almost complete 64 days after intramuscular administration. When administered orally, V^{48} is not absorbed to any great extent from the gastro-intestinal tract. A summary of the intramuscular studies is presented in Table VI.

Zirconium. Metabolic tracer studies on Zr^{95} have been completed to 128 days after intramuscular administration. The results agree with those obtained at earlier time periods. At 64 days, 15% of the injected Zr^{95} remained at the injection site. The value obtained at 128 days was higher than this, being 21%. It appears that Zr^{95} residue in muscle is poorly mobilized by the body. At these time periods, the skeleton remains the primary depository of the retained Zr^{95}. Measurable amounts were found in the soft tissues. These data are presented in Table VII.

TABLE VI

DISTRIBUTION OF V^{48} IN TISSUES OF THE RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION IN CARRIER-FREE STATE. VALUES CORRECTED FOR ABSORPTION AND RECOVERY, EXPRESSED AS PERCENT OF DOSE

	1 Day		4 Days		15 Days		64 Days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.21	.16	.10	.10	.05	.07	.03	.03
Lungs	.46	.26	.29	.18	.15	.08	.04	.02
Spleen	.68	.53	.63	.65	.45	.38	.15	.17
Blood	4.60	.30	1.52	.11	.20	.01	.01	.01
Liver	8.69	.78	6.23	.64	2.37	.22	.89	.08
Kidney	6.41	2.65	4.35	1.82	1.57	.76	.26	.09
Adrenals	.02		.01		.02		.01	.04
Thyroid	.02		.01		.01		.01	
Lymph Gl		.43		.47		.35	0	0
Pancreas	.21	.20	.19	.15	.10	.10	.01	.02
Brain	.05	.03	.03	.01	.02	.01	.01	.01
Fat	.38	.28		.06		.08		.01
Stomach	.99	.33	.24	.13	.10	.01	.02	.01
Sm Int	3.66	.43	.96	.13	.54	.04	.22	.02
Lg Int	6.12	.66	1.40	.21	.41	.04	.13	.01
Bone	14.1	.68	9.94	.53	8.98	.47	4.58	.23
Muscle	7.65	.07	4.96	.04	4.15	.04	2.19	.02
Skin	5.14	.18	4.46	.18	2.73	.11	.98	.03
Pituitary	.02		.01		.01		0	0
Eyes	.02	.07	.01	.03	.01	.02	.01	.01
Gonads	.36	.12	.57	.17	.38	.13	.29	.09
Urine	32.3	--	39.6	--	44.0	--	54.7	--
Feces	7.82	--	24.3	--	33.7	--	35.4	--

TABLE VII

DEPOSITION OF CARRIER FREE Zr^{95} IN TISSUES OF RAT FOLLOWING INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR ABSORPTION FROM LEFT LEG AND RECOVERY

	64 Days		128 Days	
	% per organ	% per gram	% per organ	% per gram
Heart	.11	.11	.12	.13
Lungs	.36	.22	.31	.16
Spleen	.37	.49	.29	.38
Blood	.26	.01	.16	.01
Liver	2.22	.29	2.12	.20
Kidney	1.49	.75	.98	.37
Adrenals	.04		.04	
Thyroid	.01		.02	
Lymph Gland	.04	.46		.74
Pancreas	.11	.15	.10	.13
Brain	.02	.01	.01	.01
Fat		.09	.06	.02
G.I.	1.59	.06	1.34	.06
Bone	23.0	1.33	21.1	1.04
Muscle	4.10	.03	5.31	.04
Skin	2.99	.10	4.88	.10
Gonads	1.29	.43	1.47	.46
Urine	5.04	--	12.2	--
Feces	56.9	--	49.4	--

Decontamination and Bone Metabolism Studies

Effect of Sodium Citrate and Zirconium Citrate Treatment on Radioactive Strontium Retention and Excretion. Immediate and massive injections of zirconium citrate have proven to be one of the most effective means of removing injected plutonium or radioactive yttrium from the body. There is a tremendous increase in urinary excretion of these elements, and bone retention is decreased.

In the following experiment, the effects of sodium citrate and zirconium citrate treatment on the retention and excretion of radioactive strontium were investigated. Adult female rats, weighing 300-350 grams were injected intraperitoneally with 8 microcuries of carrier-free $Sr^{89,90}$. They were divided into three groups of 5 rats each.

a) Control Group - no treatment

b) Sodium Citrate- received 1.6 ml of a 10% sodium citrate solution by injection intraperitoneally immediately after the dose of radiostrontium.

c) Zirconium Citrate - received 1.6 ml. of zirconium citrate solution (pH 6) containing 40 mg Zr, and citrate ion equivalent to "b" above. This was administered by intraperitoneal injection immediately after the dose of radiostrontium.

The animals were placed in individual metabolism cages and urine and feces were collected separately for three days. At this time the animals were sacrificed and tissues and excreta were analyzed for radiostrontium. The results are shown in Table VIII.

There appears to be no significant effect of sodium citrate. Urinary excretion of radiostrontium by the zirconium citrate treated animals was higher than that in the controls, but the difference was not statistically significant. There was no difference in retention in the carcass.

This decontamination procedure, so effective with radio-yttrium and plutonium, appears to be of no value in the case of radiostrontium. This difference in behavior is in line with the fundamental chemical and biological differences of these elements.

Comparison of the Metabolism of Carrier-free Radiocalcium, Radiostrontium, and Radiobarium in the Young Rat. Because of the significance of calcium in bone metabolism, and the importance of radiostrontium and radiobarium as fission products, a comparison was made of the metabolism of carrier-free radioactive isotopes of all three of these alkaline earth metals. Although the general similarity of these elements is recognized, it was felt that such a study might reveal significant differences in their biological behavior.

The animals used were 48-52 day old young female rats, in which active growth and new bone formation was taking place. They were reared on a normal diet, and maintained on this diet for the duration of the experiment. They were injected parenterally with the radioactive isotopes, and were placed in individual metabolism cages so that urine and feces could be collected separately. After 4 days, they were sacrificed, and the tissues and excreta were analyzed for radioactive isotopes present. The results are shown in Table IX. For direct comparison, the values are expressed as the percent of the administered dose, corrected to 100 percent, and plus or minus the standard deviation. All three elements were concentrated in bone, with very little in the soft

TABLE VIII

EFFECT OF SODIUM CITRATE AND ZIRCONIUM CITRATE TREATMENT ON THE RETENTION AND EXCRETION OF RADIOSTRONTIUM*

Group	Urine	Feces	Femur	Liver	Carcass
Control	45.1 ±5.6	33.6 ±2.2	0.8 ±0.1	0.05 ±0.04	20.5 ±3.4
Sodium Citrate	45.2 ±4.8	33.2 ±4.4	0.9 ±0.1	0.05 ±0.02	20.6 ±1.2
Zirconium Citrate	54.4 ±4.6	26.4 ±2.8	0.6 ±0.3	0.04 ±0.01	18.5 ±5.1

* Values given are expressed as percent of the administered dose, corrected to 100 percent, plus-minus the standard deviation.

TABLE IX

DISTRIBUTION OF CARRIER-FREE RADIOACTIVE BARIUM, STRONTIUM, AND CALCIUM FOUR DAYS AFTER INJECTION INTO THE YOUNG, NORMAL RAT*

	Barium	Strontium	Strontium	Calcium
Injection Route	Intraperitoneal	Intraperitoneal	Intramuscular	Intramuscular
No. of Animals	5	8	6	6
Carcass	57.8 ±6.7	70.3 ±5.1	69.6 ±2.9	80.8 ±2.6
Femur	2.9 ±0.7	3.3 ±0.6	3.2 ±0.5	4.1 ±0.9
Urine	13.1 ±4.4	13.5 ±6.6	13.5 ±3.1	3.9 ±1.7
Feces	23.3 ±3.4	11.3 ±3.4	13.7 ±1.5	11.2 ±2.0

*Values given are expressed as percent of the administered dose, corrected to 100 percent, plus or minus the standard deviation.

tissues.

Comparative distribution studies of Ca^{45} and Sr^{89} in soft tissues as well as bone are as follows. Three groups of animals were given either or both radioisotopes intramuscularly and sacrificed four days later. Although the body handles these two related elements in a similar manner, the comparative deposition does not appear to be identical. Absorption from the injection site was almost complete for both elements, being 2.6% and 4.3% in the two calcium studies and 5.09% in the strontium study. Relatively more calcium than strontium was stored in the bone. The values obtained for the soft tissues were comparable with the exception of skin, in which case relatively more calcium was stored in the skin again than was strontium. Furthermore, it appears that less calcium was excreted in the urine than strontium, although the fecal excretion appears to be comparable. The distribution of Ca^{45} and Sr^{89} in the soft tissues of the rat as well as various calciferous samples are presented on Tables X and XI.

Effect of Fasting on the Absorption and Retention of Radioactive Strontium. Since radiostrontium is one of the few important fission products absorbed from gut, it presents a serious hazard from contamination of food or water supply. Fasting reduces calcium excretion and effects new bone formation. The effect of fasting on radiostrontium absorption, retention and excretion was studied in the following experiment.

Young adult female rats were fasted for two days. Twenty microcuries of carrier-free radiostrontium was administered by stomach tube or by intraperitoneal injection. They were placed in individual metabolism cages, without food, and urine and feces were collected separately. After three days, the animals were sacrificed and analyzed for radiostrontiu. The controls were fed ad libitum both before and during the experiment. The results are shown in Table XII.

It will be noted that the fasted animals absorbed from the gut and stored in the body twice as much radiostrontium as did the controls. This may in part have been due to the prolonged retention of radiostrontium in the gut (almost 1/5 of the dose still remained in the intestinal tract after three days.)

Following intraperitoneal injection, more radiostrontium was retained by the fasted animals and only 1/4 as much was excreted in urine and feces as in the controls. This is no doubt associated with the diminished calcium excretion during fasting.

The results indicate an increased hazard of radiostrontium contamination in fasted individuals. They also indicate the desirability of controlling the dietary condition of the animal in studies on radiostrontium metabolism.

Study of Bone Resorption Produced by Massive Doses of Parathormone: Effect on Bone Histology, and on the Distribution and Excretion of Radiophosphorus and Radiostrontium. Massive doses of parathyroid hormone provide one of the most effective means of producing acute bone resorption. Although the rat is rather resistant to the action of parathormone, dramatic effects are produced if the dose is large enough. This study was undertaken as a preliminary to combining acute bone resorption with such decontamination procedures as zirconium citrate treatment.

Young growing rats of 6 - 7 weeks of age and weighing 125 to 150 grams were injected with parathormone (E. Lilly preparation) at the level of 1 unit per gram

TABLE X

DEPOSITION OF Ca^{45} IN RAT 4 DAYS AFTER INTRAMUSCULAR ADMINISTRATION
VALUES CORRECTED FOR ABSORPTION IN LEFT LEG AND RECOVERY

	% of Dose	
	% per organ	% per gram
Heart	.01	.02
Lungs	.02	.01
Spleen	.01	.02
Blood		
Cells	.20	.07
Plasma	.09	.02
Liver	.07	.02
Kidney	.04	.02
Adrenals	.01	--
Thyroid	.01	--
Lymph Gl	.01	--
Pancreas	.01	--
Brain	.01	.01
Fat	.02	--
Teeth		
I.T.	.47	--
I.R.	1.21	--
Mo	.36	--
Stomach	.08	.05
Sm Int	.19	.03
Lg Int	.32	.08
Int Wash	.78	--
Bone		
Fibula	.29	.92
Tibia Head	1.36)	4.27
Tibia	1.39)	
Scull Cap	1.43	2.73
Femur	3.66	5.26
Total Skeleton	76.3	6.50
Muscle	4.17	.08
Skin	.93	.07
Ovary	.01	--
Eyes	.01	--
Pituitary	.01	--
Urine	2.61	--
Feces	12.1	--

TABLE XI

COMPARATIVE DEPOSITION OF RADIO-CALCIUM AND STRONTIUM IN THE SAME ANIMALS 4 DAYS AFTER INTRAMUSCULAR ADMINISTRATION. VALUES CORRECTED FOR UNABSORBED PORTION IN LEFT LEG AND RECOVERY

	% of dose			
	Calcium		Strontium	
	% per organ	% per gram	% per organ	% per gram
Soft Tissues	.63	.06	.59	.05
Kidney	.01	.01	.01	.01
Teeth				
Mo.	.47	--	.56	--
I.R.	.82	--	1.29	--
I.T.	1.09	--	.78	--
G.I.	1.01	.10	1.13	.12
Int. Wash	1.23	--	1.15	--
Bone				
Tibia	1.39)	4.72	.95)	3.71
Tibia Head	1.12)		1.04)	
Femur	4.55	5.72	3.06	3.83
Fibula	.20	.50	.15	.39
Scull Cap	2.04	5.52	1.24	3.22
Total Skeleton	75.2	6.70	65.0	5.80
Muscle	3.99	.08	3.31	.07
Skin	.34	.02	.15	.01
Urine	5.10	--	15.4	--
Feces	10.1	--	10.5	--

TABLE XII

THE EFFECT OF FASTING ON THE ABSORPTION, DEPOSITION, AND EXCRETION OF CARRIER-FREE RADIOSTRONTIUM*

	Administered by Intraperitoneal Injection		Administered by Stomach Tube	
	Fasted	Control	Fasted	Control
Carcass	81.4 ±5.2	59.1 ±5.3	34.5 ±11.1	18.4 ±6.4
Femur	3.7 ±0.3	2.8 ±0.5	1.3 ±0.6	0.8 ±0.4
Urine	3.1 ±3.3	18.4 ±6.6	1.6 ±1.6	1.0 ±1.4
Feces	4.5 ±3.3	17.8 ±4.9	42.4 ±18.6	77.0 ±8.0
G.I. Tract	7.2 ±8.0	2.0 ±1.0	20.3 ±16.0	0.9 ±1.4

The rats had been fasted 48 hours when the radiostrontium was administered. They were sacrificed three days later.

*Values given are expressed as percent of the administered dose, corrected to 100 percent, plus or minus the standard deviation.

body weight and 5 units per gram body weight by intraperitoneal injection. Six hours later they received carrier-free radioactive phosphorus or strontium by intraperitoneal injection. They were placed in individual metabolism cages and urine and feces were collected separately. Twenty-four hours after injection of parathormone, or 18 hours after injection of the radioactive isotopes, the animals were sacrificed. Femur and tibia were taken for bone histology and radioautographs. The tissues and excreta were analyzed for radiostrontium or radiophosphorus.

a) Effects on bone histology.

At the dose level of 1 unit per gram, only slight differences in bone histology were evident. There was some increase in the number of osteoclasts (associated with bone resorption) and preparations by the Gomorri technique suggested a moderate demineralization of the secondary spongiosa.

At the higher dose level (5 units per gram body weight) dramatic changes were apparent. Great numbers of osteoclasts were seen on the trabeculae and along the endosteal surface. Trabeculae were thin and reduced in number. Osteoblasts on the surface of the remaining trabeculae were flattened and resembled fibroblasts. Loss of bone substance in the zone of provisional calcification and the primary spongiosa next to the epiphyseal cartilage was such, that there was great fragility and a tendency to break in this area during dissection. Gomorri preparations of this area suggested severe demineralization. The general picture was one of intensive bone resorption.

b) Distribution and excretion of radiophosphorus.

The data for radiophosphorus, expressed as percent of the administered dose and corrected to 100 percent, is shown in Table XIII. No significant difference was apparent with the dose of 1 unit per gram. However, the larger dose did increase (about two times) the urinary excretion of radiophosphorus; and reduced the uptake by bone. This is in conformity with the known action of parathormone in effecting bone resorption and increasing urinary phosphate excretion.

c) Distribution and excretion of radiostrontium.

The data for radiostrontium are given in Table XIV. The most remarkable feature of this data is the almost complete lack of effect of even massive doses of parathormone, despite histological evidence of intensive bone resorption. Aside from an increased urinary excretion of radiostrontium in the rats receiving 5 units of parathormone per gram, there is no significant difference in soft tissue or skeletal retention. The high retention of radiostrontium by these animals, corresponding to that of actively growing young controls, suggests that active deposition of radiostrontium is taking place along with the process of bone resorption.

The calcium being deposited, will of course carry with it the high specific activity of the radiostrontium of plasma, accounting for the high apparent uptake of the latter. The calcium liberated by bone resorption, on the other hand, will contain

TABLE XIII

EFFECT OF PARATHORMONE ADMINISTRATION ON THE DISTRIBUTION AND EXCRETION OF RADIOPHOSPHORUS

Group	Urine	Feces	Femur	Liver	Kidney	Muscle*	Carcass
Control	17.8 ±1.0	0.07 ±0.02	2.50 ±0.13	6.0 ±0.2	1.02 ±0.03	18.2 ±1.5	49.8 ±0.8
1 unit PTH/gm	13.8 ±1.2	0.08 ±0.03	2.66 ±0.06	6.2 ±0.1	1.12 ±0.04	19.2 ±1.7	50.9 ±1.8
5 units PTH/gm	32.1 ±1.3	0.08 ±0.03	1.64 ±0.03	6.5 ±0.5	1.20 ±0.04	21.5 ±1.1	33.2 ±1.5

*Values are averages for five animals, expressed as percent of the administered dose plus or minus standard deviation.

TABLE XIV

EFFECT OF PARATHORMONE ON THE DISTRIBUTION
AND EXCRETION OF RADIOSTRONTIUM*

Group	Urine	Feces	Femur	Liver	Kidney	Carcass
Control	0.73	0.81	4.16	0.06	0.03	82.5
1 unit per gram	1.62	0.81	3.52	0.07	0.02	83.6
5 units per gram	7.62	0.87	3.75	0.07	0.04	77.1

*Values are the averages for five animals in each group, expressed as percent of administered dose.

very little radioactive isotope. The higher urinary excretion corresponds to the increased calcium excretion with parathormone.

d) Conclusions.

Massive doses of parathormone in the young rat resulted in histological signs of intensive bone resorption. At the higher dose levels, there was increased urinary excretion of radiophosphorus and radiostrontium, but very little significant differences in skeletal retention. This suggests that active bone deposition is taking place along with bone resorption. Although parathormone appears to have little effect on radiostrontium decontamination, it may be of value, in conjunction with zironium citrate, in contamination of other metals such as plutonium and radioyttrium.

Radio-Chemical Isolation

Protoactinium was separated from a thorium target which had been bombarded with deuterons. A solvent extraction method which has been reported elsewhere was used. About twenty-five millicuries of protoactinium was obtained. This activity was set aside for the growth of uranium for twenty-five days, at which time the uranium was separated. Alphas of the U^{230} series were detected. The protoactinium was removed from a benzene TTA solution in order to prepare it for physiological use by diluting the TTA solution to 0.02 M and extracting with concentrated nitric acid.

Carrier-free radioactive cadmium was obtained from a deuteron bombarded silver target by a method previously reported from this laboratory. Approximately 1.4 millicuries of radio-cadmium was separated from this target.

Work is in progress at this time to separate carrier-free radioactive arsenic from a germanium target which has been bombarded with deuterons. The method, previously reported, involves distillation of the germanium as a tetrachloride while the arsenic is oxidized to its pentavalent state, followed by reduction of the arsenic and distillation of arsenic trichloride.

There is in the laboratory at this time an alpha bombarded cadmium target, from which we expect to separate carrier-free radioactive tin and indium. A previous method, involving distillation of the tin, has proved unsatisfactory because of the low final yields of tin obtained. Part of the loss has been due to the fact that a fraction of the radio-active tin tenaciously adheres to any container in which it is placed. Attempts have been made to remedy this situation by complexing the radio-tin in a solution which is physiologically useful. Glucosi and citric acid solutions seem hopeful for this purpose. It is believed that higher yields could be obtained also if the distillation method could be avoided. Work is progressing on a method of extraction with TTA, and, although incomplete, results indicate that the activities can be separated by this method.

Other activities during this period included preparation of physiological solutions of columbium, lanthanum, and barium. A solution of praseodynium was received from Oak Ridge, which was assayed, identified, and prepared for physiological use. A magnesium target was milled and prepared for shipment from this laboratory to the project at Columbia University.

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II BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge

Project 48A - II

Biological Use of the 184-inch Cyclotron

by

C. A. Tobias, J. H. Lawrence, Paul D. Rosahn, Hal Anger and William Linlor

The 190 Mev deuteron and the 380 Mev alpha particle beams were used in a number of exposures on various biological specimens. A detailed report (Quarterly Progress Report for January-March, 1948) described the physical arrangement for such bombardments. More recently progress was made in the following directions:

(a) A new bombardment table was designed to allow alignment with the beam and remote control selection of various ionizing portions of the beam. A good part of the design work is completed and the main part of the apparatus will go into use during the month of July.

(b) The problem of dosage measurement was investigated and a set of intercomparisons made with G. Failla and his associates. They determined the dose with special tissue wall, tissue gas ionization chambers.

(c) A number of measurements were made to obtain the Bragg curve and the corrections for scattering of the deuteron beam in various materials. With the aid of the data gained it is now possible to administer known doses of deuterons and alpha particles into a given depth of an animal tissue.

(d) A set of experiments was carried out to confirm the previously reported experiments concerning lethal effects on mice. The results indicate that the same dose delivered in a short time interval (15 seconds) is somewhat more effective than when delivered in a long time interval (2 hours). A number of blood counts and some histological studies were obtained. So far these do not show any significant differences from the findings obtained after exposures of similar animals to x-ray or fast neutron beams.

(e) A number of exploratory tests were carried out regarding the effect of the deuteron beam on tumors, using type A mice, and the Strong transplantable mammary carcinoma. This strain of animals was carried in our laboratory for about 10 years. 100% of the transplants usually become takes and close to 100% of the animals having tumors die due to the presence of the carcinomas. In a series of tests attempts were made to determine the minimum dose necessary to achieve complete regression and healing of the tumors. A fold of skin containing the tumors was pulled away from the body of the anesthetized mice and the low energy end of the deuteron beam was directed against the tumor after passing through proper layers of absorbers and diaphragms. The dose levels tried were 500, 1000, 1500, 2000, 2500, 3000, 4000, and 5000 d units. (The d unit is a conventional unit temporarily introduced by us to indicate relative doses of deuterons. 1 d is about equal to 1 rep, but the expression "rep" will not be used until more extensive dosage determinations are made.) Below 3000 d only partial temporary regression of the tumors took place; at and above 3000 d the tumors appeared to regress completely. The regression was in each instance accompanied by severe skin burns and local loss of hair. It is too early to say whether or not the skin lesions will heal. In this instance the skin received about the same dose as the

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tumors since the tumors were implanted right under the skin.

It seemed to be worthwhile to test the action of the deuteron beam on tumors after the beam had passed through a considerable layer of tissue. The shape of the Bragg curve is such that it allows considerable more dose to be given to the tissue near the end of the range of the particles compared to the beginning of their range. (See our previous report.) One could not foretell whether or not the animals themselves would die in such an experiment as the lethal doses were about 10 times smaller than the doses necessary to kill tumors. The animals were placed so that the beam had to go first through their body and then reached the tumors. The peak of the Bragg curve was adjusted to hit the tumor. In addition to this the animals were rotated around an axis perpendicular to the beam and going through the tumors. The rotation was through an angle of about 180°. The dose given to the tumors was 4000 d. In these experiments using 19 animals it was demonstrated that it is entirely feasible to give a large dose of irradiation to the tumor after the beam has crossed the animal's body without causing acute lethal effects in mice. The tumors thus irradiated show rapid regression, but it is too early to tell whether such regression will be complete or temporary and how severe the skin effects may be. Nevertheless, the results are greatly encouraging since they may mean a definite step towards well controlled and effective depth therapy by means of particle beams. The work is being continued.

Radiobiology: Bacterial Cell Radiosensitivity

R. S. Weatherwax and R. L. Dobson

During the past few years a series of papers particularly by C. F. Robinow have shown the existence of discrete chromatinic structures in the bacterial cell. These structures undergo regular divisions closely correlated with the division of the cell. It seems highly probable that these chromatinic bodies represent the bacterial equivalent of the nucleus or chromosome, and are thus carriers of the bacterial genes.

The hit theory of the killing of bacteria by irradiation postulates the existence of a radiosensitive "target", in which one or in some cases more than one hit is sufficient to kill the cell. Lea has calculated the size of such a sensitive area in E. coli, and finds it to be in close agreement with the measured size of the chromatinic body.

A search is now indicated for a correlation between the resistance of a bacterial cell to irradiation at a particular stage of growth and the number of chromatinic bodies that it possesses at that time.

An example of what might be expected follows. An old cell of E. coli usually contains a single dumbbell-shaped chromatinic body. When this cell is transferred to fresh medium it begins to grow in size, and the nuclear structure undergoes division. Just before the first visible cell division this cell may then contain 2, 4, or even 8 chromatinic bodies. If, as Robinow believes, such a cell has already undergone internal septation by the formation of plasma membranes, and is actually 2 or 4 cells not yet separated, then such a structure (which would still be enumerated as a single cell by colony count) should show a marked increase in resistance to irradiation. If, on the other hand, a hit in any one of the chromatinic bodies would kill the entire unit, then the resistance of the unit should be less than that of a cell containing only one chromatinic body.

The discovery of such a correlation would lend support to both the idea that these bodies do carry gene-like entities and to the "one-hit" theory.

Experiments have been carried out to test these ideas. At intervals during the first few hours after inoculation a growing broth culture of E. coli is sampled for a viable cell count and the resistance to a fixed dose of ultraviolet light is determined. It has been found that the percent of the organisms surviving this dose undergoes regular wave-like fluctuations during the growth of the culture.

The period of this fluctuation compares favorably with the generation time calculated from the growth curve run simultaneously. The growth curve frequently shows indications of so-called "fission waves" or jump-like increases in the number of cells at regular intervals which approximate the generation time. If all of the cells of the inoculum could be obtained in the same stage of division at the start of growth, so that they would proceed to divide "in phase", these "jumps" in the growth curve and the waves in the corresponding curve showing the change of resistance would be accentuated and less equivocal interpretations would be possible. So far it has not been possible to obtain such a uniform inoculum.

The organism used has been a radiation-resistant mutant (B/r) of E. coli supplied by Miss E. Witkin.

Similar experiments with the parent strain B indicate that the variation in radioresistance with age of culture does not parallel that found with B/r. This suggests another avenue of approach to an understanding of the fundamental difference between these two related organisms which is reflected in a difference in radiosensitivity.

Less securely established data suggests that while strain B/r shows an overall change of resistance during the growth cycle it does not lose the essentially sigmoid shape of its survival curve (percent survival against changing dose) when such a curve is run at various intervals during growth.

Bone Marrow Transplantation

R. L. Dobson, J. Talbot, and E. Pinson

The marrow transplantation experiments which have been described in previous reports are being continued. These experiments were designed to develop techniques and secure basic information about the behavior of marrow implants, particularly in regard to their survival times. The experimental procedure has consisted of implanting healthy rat bone marrow into various sites such as liver, spleen, muscle and subcutaneous tissue, of rats of the same and of other strains in both the normal state and after having had previous treatment with either radiation or chemical hemopoietic depressant drugs.

Rats of the Curtis-Dunning and Slonaker strains have been used, the pretreated recipients having received daily injections of benzene and olive oil or sublethal doses (500 r total body) of 200 kv x-rays. Control rats have been subjected to mock surgical procedures after previous therapy with either benzene or x-ray.

In the earlier experiments aseptic technique was not used, and the marrow transplants consisted of semi-solid chunks of marrow handled with forceps and trochars. In the later experiments carried out by Drs. Talbot and Pinson strict aseptic precautions have been observed, and the implanted material was a suspension of marrow in normal saline handled in a syringe.

Definite active growth of femoral and tibial marrow in various implant sites has been observed as long as thirty days after operation. These specimens show young forms and mitotic figures. In two animals who received marrow from a different strain and who were autopsied more than a year after implantation no active marrow growth was found. A number of animals have been carried seventy and more days after operation, but all the biopsy and autopsy material has not yet been examined. Peripheral blood count data is being accumulated.

Plans for future experiments include such manipulations as preparation of the donor animals by bleeding or phenylhydrazine etc. to achieve hyperactivity in the marrow, repeated doses of x-ray to the recipients with shielding over the implant sites, alterations in the adrenal and other hormone systems, etc.

Although these experiments have shown definite marrow growth in implant sites several weeks after operation, the data regarding maximum survival time and the various factors which influence it have not been worked out.

Information Division
Radiation Laboratory
University of Calif.
Berkeley, Calif.

Determination of the Rate of Biochemical Reactions

C. A. Tobias

The path of an element A in a series of biochemical reactions may be traced by means of one of its radioactive isotopes A*. The distribution of A* gives some information on the distribution of A but the rate of exchange of A* alone in biochemical reactions does not directly tell the rate of exchange of A. It has been repeatedly pointed out that in order to determine the rates of biochemical reactions, a knowledge of the amount of A present in each of the fractions studied is also necessary in addition to the information furnished by the use of A* (1). Often the determination of the amount of each substance in the various biochemical fractions has encountered difficulty because of the very small quantities present. This difficulty has been removed for a number of elements by the use of the technique of trace analysis by means of induced radioactivity (2). Considerations to be presented here are intended to simplify the calculations involved in the determination of the rate of biochemical reactions where use is made of both techniques, that is, radioactive tracers and the determination of the amount of micro-constituents present.

In the literature, some papers are available which refer to the general problem of the rate of biochemical reactions. Zilversmit et al (3,4) have discussed the criteria for establishing one compound as precursor of another, by the use of radioactive tracers; Branson (5,6) introduced the term "metabolism function" for convenient mathematical description of the metabolism of compounds. These and other special methods have recently been reviewed by Radin (7). The above methods, however, do not consider the general problem of biochemical reaction rates; they refer to somewhat special cases. A very general treatment of tracer methodology has been given by Sheppard (8). In the following the case of steady state systems will be treated in a general way so that the treatment will represent certain special cases of Sheppard's theory.

In many of the problems of metabolism one deals with steady state systems. To illustrate this, let us take as an example the simplified picture of the metabolism of iron in mammals. Iron is taken up into the blood plasma at a rate which may be considered constant. At a fixed rate the plasma transfers the iron into the bone marrow, where in turn it is presumed to be synthesized into hemoglobin. Thus the new iron appears at a steady rate in the blood cells. From these cells through hemolysis, iron appears again in the plasma. Part of the plasma iron disappears at a presumably steady rate into cytochrome and catalase iron. Finally a certain constant rate may go into so-called storage iron which may be excreted from the plasma. In normal individuals one may regard the instantaneous amount of iron in the plasma, bone marrow, and cell fraction as constant and also each of the instantaneous turnover rates are constant independently of time. If a radioactive sample of iron, let us say Fe 59, is added into the metabolic system, one usually assumes that this small amount will not disturb the total rate of metabolism at all. Let us assume that radioactive iron was added to the plasma. It is then possible to observe the rate of appearance of radioactive iron in the bone marrow and in the blood cells; further, in the cytochrome and catalase fractions and in the amount excreted. The rate of appearance of radioactive iron in the above compounds does not in itself tell us the absolute rate of turnover of the inactive iron that was already present in the body. However, using the data collected the absolute turnover rates may be calculated by a method presented below.

One might represent a steady state system as pictured in Diagram 1. Assume n distinct states - these may be different compounds of element A in different (or

identical) locations of the biological system. The concentration, as well as the total amount of element A, is assumed to stay constant in each state throughout the experiment and will be denoted as follows:

Concentrations: $C_1, C_2, \ldots, C_n$ for states 1, 2, . . . , n

The total mass of each element: $M_1 \times C_1 = A_1$, $M_2 \times C_2 = A_2, \ldots, M_n \times C_n = A_n$,

where $M_1, M_2, \ldots, M_n$ are the masses of the tissue in each state.

There is a constant rate of exchange of atoms A between states i and k. The exchange, generally speaking, may go on in both directions simultaneously. Define the rate of flow of atoms A from state i to state k by $\alpha_{ik} A_i$ and the rate from k to i by $\alpha_{ki} A_k$, then the net rate of exchange of A

$$- \alpha_{ik} A_i + \alpha_{ki} A_k$$

and the net change of concentration in states i and k

$$\Delta C_i = \frac{-\alpha_{ik} A_i - \alpha_{ki} A_k}{M_i} = - \alpha_{ik} C_i + \gamma_{ki} C_k \qquad (1)$$

$$\Delta C_k = \frac{\alpha_{ik} A_i - \alpha_{ki} A_k}{M_k} = \gamma_{ik} C_i - \alpha_{ki} C_k$$

where, by definition $\gamma_{ki} = \frac{\alpha_{ki} M_k}{M_i}$ $\qquad i,k = 1,2,\ldots, n$

Some states may take up some of A at a constant rate from an external reservoir, containing A at concentration C_o. The total uptake in state k is:

$$\alpha_{ok} C_o$$

while the change in concentration resulting in state k is $\frac{\alpha_{ok}}{M_k} C_o = \gamma_{ok} C_o$

with the definition $\frac{\alpha_{ok}}{M_k} = \gamma_{ok}$

It is here assumed that some of element A will also be eliminated from some of the states into the reservoir for excretion. The total amount excreted will be: $\alpha_{ko} A_k$

and the change of concentration in state k

$$\alpha_{ko} \frac{A_k}{M_k} = \gamma_{ko} C_k \quad ; \quad \alpha_{ko} = \gamma_{ko}$$

To avoid ambiguity we shall allow only

$$\alpha_{ik} \geq 0 \quad ; \quad \gamma_{i,k} \geq 0 \qquad i,k = 0,1,2,\ldots,n$$

Now the total mass and the concentration of A in each state is preserved; thus a set of linear equations may be written down to reinforce this condition.

$$\alpha_{01}C_0-(\alpha_{10}+\alpha_{12}+\ldots+\alpha_{1n})A_1+\alpha_{21}A_2+\alpha_{31}A_3\ldots+\alpha_{n1}A_n = \frac{dA_1}{dt} = 0$$

$$\alpha_{02}C_0+\alpha_{12}A_1-(\alpha_{20}+\alpha_{21}+\ldots+\alpha_{2n})A_2+\alpha_{32}A_3+\ldots+\alpha_{n2}A_n = \frac{dA_2}{dt} = 0 \qquad (2)$$

$$\vdots \qquad\qquad \vdots \qquad\qquad \vdots$$

$$\alpha_{0n}C_0+\alpha_{1n}A_1+\ldots+\alpha_{n-1,n}A_{n-1}-(\alpha_{n0}+\alpha_{n1}+\ldots+\alpha_{n,n-1})A_n = \frac{dA_n}{dt} = 0$$

From the point of view of measurements it is more direct to work in terms of concentration; thus write

$$\alpha_{kk} = \sum_{\substack{\ell=0 \\ \ell=k}}^{n} \alpha_{k\ell}$$

; define $\gamma_{kk} = \alpha_{kk}$

Divide each equation 1, 2, ... k, ..., n by M_1, M_2, ... M_k, ..., M_n and substitute $A_\ell = C_\ell M_\ell$ to obtain:

$$\begin{aligned}
\gamma_{o1}C_o - \gamma_{11}C_1 + \gamma_{21}C_2 + \dots + \gamma_{n1}C_n &= \frac{dC_1}{dt} = 0 \\
\gamma_{o2}C_o + \gamma_{12}C_1 - \gamma_{22}C_2 + \dots + \gamma_{n2}C_n &= \frac{dC_2}{dt} = 0 \\
\vdots \qquad\qquad \vdots \qquad\qquad \vdots \qquad\qquad & \qquad \vdots \\
\gamma_{ok}C_o + \gamma_{1k}C_1 + \dots + \gamma_{kk}C_k + \dots + \gamma_{nk}C_n &= \frac{dC_k}{dt} = 0 \\
\gamma_{on}C_o + \gamma_{1n}C_1 + \dots + \gamma_{n-1,n}C_{n-1} - \gamma_{nn}C_n &= \frac{dC_n}{dt} = 0
\end{aligned} \qquad (3)$$

We only have a total of n independent relationships. These are naturally not sufficient to determine the n(n+1) unknown rate coefficients α_{ik} or γ_{ik}.

Another set of relationships results, if a radioactive or isotopic tracer experiment is carried out with one of the radioactive isotopes of A, to be denoted A*. This isotope has to be administered without disturbing the steady state conditions in the system in any appreciable way. We shall assume that this is the case if the following conditions hold.

(a) The chemical form of A* is the same as that of A in the state A_k to which the tracer is added. The administered compound should not appreciably disturb the sequence of chemical events.

(b) The mass of A* is negligibly small compared to the mass of A in state k

$$M^* << M_k$$

(c) The length of time τ of administration of A* is small compared to the "turnover time" of A in state k.

$$\frac{A^*}{\tau} << \alpha_{ik} A_k \qquad k = 1, 2, \dots, n$$

If A* is added to the reservoir (K = 0), the radioactivity should distribute there instantaneously.

(d) After administration, the molecules containing A* mix completely with molecules of A_k in a short time compared to the turnover time of A_k. Isotope exchange is permitted provided the position of labeling the molecule remains the same. Mixing time must be of the same order as τ of condition (c).

(e) The radiations emitted from A* in the course of the experiment are not intense enough to appreciably alter the steady state due to their biological action.

Assuming the above four conditions valid, one may proceed to study the information obtainable from such a tracer experiment. We could choose either system of equations, those written for A_k or C_k; however, usually experimentally it is easier to determine M_k and C_k, that is to determine the mass of tissue and the concentration of A and A* per unit mass of tissue. Let us assume that the density of tracer material A* is denoted by: X_1 (t), X_2 (t), ... X_n (t) in the various states as functions

of time and by X_o = constant in the external reservoir. Since A^* will be carried along with the atoms of A in each exchange at the same relative rate as A, one may write:

$$
\begin{aligned}
\gamma_{o1} X_o - \gamma_{11} X_1(t) + \gamma_{21} X_2(t) + \ldots + \gamma_{n1} X_n(t) &= \frac{dX_1}{dt} \\
\gamma_{o2} X_o + \gamma_{12} X_1(t) - \gamma_{22} X_2(t) + \ldots + \gamma_{n2} X_n(t) &= \frac{dX_2}{dt} \\
\vdots \qquad \vdots \qquad \vdots \qquad \vdots \qquad & \vdots \\
\gamma_{on} X_o + \gamma_{1n} X_1(t) + \ldots + \gamma_{n-1,n} X_{n-1}(t) - \gamma_{nn} X_n(t) &= \frac{dX_n}{dt}
\end{aligned}
\tag{4}
$$

By measuring X_i and $\frac{dX_i}{dt}$ at frequent time intervals, one would be able to get enough data for setting up and remaining n^2 linear equations needed to determine γ_{ik}. One may now proceed to solve the above system of linear differential equations since the general solution will give more insight into the nature of the problem. One may remark here that usually in experiments one of two boundary conditions are encountered. First:

At $t = o$ $\quad X_o \neq o$ but $X_i(0) = 0$ for $i = 1, 2, 3, \ldots, n$

at $T > 0$ $\quad X_o$ = constant

This is the case when the experimental objects are placed in an environment of constant radioactivity or are fed with food containing constant density of radioactive material.

Second: At $t = 0$ $\quad X_o = 0$ but $X_1(0)$ = constant, $X_2(0) = X_3(0) = \ldots, X_n(0) = 0$.

$t > 0$ $\quad X_o(t) = 0$

This is the case when a given amount of radioactivity is administered instantaneously to one of the available states. One may notice that in the latter case the first column in (4) would vanish: one would deal with a system of homogenous linear differential equations.

In either case one may show that the general solution of (4) is of the form:

$$
\begin{aligned}
X_1(t) &= A_{11}e^{\lambda_1 t} + A_{21}e^{\lambda_2 t} + \ldots + A_{n1}e^{\lambda_n t} + A_{o1} \\
X_2(t) &= A_{12}e^{\lambda_1 t} + A_{22}e^{\lambda_2 t} + \ldots + A_{n2}e^{\lambda_n t} + A_{o2} \\
\vdots \qquad & \vdots \qquad \vdots \qquad \vdots \qquad \vdots \\
X_n(t) &= A_{1n}e^{\lambda_1 t} + A_{2n}e^{\lambda_2 t} + \ldots + A_{nn}e^{\lambda_n t} + A_{on}
\end{aligned}
\tag{5}
$$

and, as is well known, the system of funtions $X_1(t)$, $X_2(t) \ldots X_n(t)$ are also solutions of a differential equation:

$$\rho_n \frac{d^n X}{dt^n} + \rho_{n-1} \frac{d^{n-1} X}{dt^{n-1}} + \dots + \rho_2 \frac{d^2 X}{dt^2} + \rho_1 \frac{dX}{dt} + \rho_0 X = \text{Constant} \tag{6}$$

where $\rho_0, \rho_1, \dots, \rho_n$ are constant coefficients, functions of γ_{ik} only; the coefficients $\lambda_1, \dots, \lambda_n$ are solutions of equation:

$$\rho_n \lambda^n + \rho_{n1} \lambda^{n-1} + \dots + \rho_2 \lambda^2 + \rho_1 \lambda + \rho_0 = 0 \tag{7}$$

The n (n + 1) constants a_{ik} are determined by the boundary conditions of any given problem; in actual experiments a_{ik} and λ_i are to be determined from the data taken.

By direct substitution of (5) into (4) one then finds very convenient relations between the experimentally determined exchange constants of the radioactive tracer: λ_k and a_{ik} and the exchange constants γ_{ik}. These are as follows

$$\left.\begin{array}{l}
\left.\begin{array}{l}
\gamma_{o1} X_o - \gamma_{11} A_{o1} + \gamma_{21} A_{o2} + \dots + \gamma_{n1} A_{on} = 0 \\
\gamma_{o2} X_o + \gamma_{12} A_{o1} - \gamma_{22} A_{o2} + \dots + \gamma_{n2} A_{on} = 0 \\
\vdots \qquad \vdots \qquad \vdots \qquad \vdots \\
\gamma_{on} X_o + \gamma_{1n} A_{o1} + \dots + {}_{n-1,n} A_{o,n-1} - \gamma_{nn} A_{on} = 0
\end{array}\right\} n \\
\\
\left.\begin{array}{l}
-\gamma_{11} A_{11} + \gamma_{21} A_{12} + \dots + \gamma_{n1} A_{1n} = A_{11} \lambda_1 \\
\gamma_{11} A_{21} - \gamma_{21} A_{22} + \dots + \gamma_{n1} A_{2n} = A_{21} \lambda_2 \\
\vdots \qquad \vdots \qquad \vdots \qquad \vdots \\
\gamma_{11} A_{n1} + \gamma_{21} A_{n2} + \dots + \gamma_{n-1,1} A_{n,n-1} - \gamma_{n1} A_{nn} = A_{n1} \lambda_n
\end{array}\right\} n \\
\\
\qquad \vdots \\
\\
\left.\begin{array}{l}
-\gamma_{1n} A_{11} + \gamma_{2n} A_{12} + \dots + \gamma_{nn} A_{1n} = A_{1n} \lambda_1 \\
\gamma_{1n} A_{21} - \gamma_{2n} A_{22} + \dots + \gamma_{nn} A_{2n} = A_{2n} \lambda_2 \\
\vdots \qquad \vdots \qquad \vdots \qquad \vdots \\
\gamma_{1n} A_{n1} + \gamma_{2n} A_{n2} + \dots + \gamma_{n-1,n} A_{n-1,n} - \gamma_{nn} A_{nn} = A_{nn} \lambda_n
\end{array}\right\} n
\end{array}\right\} n(n+1) \text{ equations} \tag{8}$$

The above system of equations thus give a complete answer to the problem of determining the rate of turnover of elements in "steady state". The significance of the above derivation lies in the fact that it gives the general form of the solution. In practice the functions X_1 (t), X_2 (t) . . . . X_n (t) may be obtained by direct measurement of the radioactivity of the tracer as a function of time. One may then analyze the data in terms of exponential functions and obtain the values a_{ik} and λ_k. Having obtained these, the coefficients of transfer γ_{ik} may be calculated directly from the linear system of equations (8).

If one also knows the concentrations C_k in each state, as well as the masses M_k, the net turnover rate between each of the states as well as the exchange turnover rates will become known, according to the definitions given in equations (1), (2), and (3).

The above treatment becomes invalid if the biochemical processes involving A do not represent a steady state. To obtain the constants of such a process, it is necessary to measure, in states k the concentrations C_k of the stable element in function of time, along with the information obtained by the use of the radioactive isotope A*.

Summary:

Theoretical relationships are given to calculate the rates of biochemical reactions of an element in a biochemical system involving steady states and using data obtained with radioactive tracers. The general form of solution is given for n different states.

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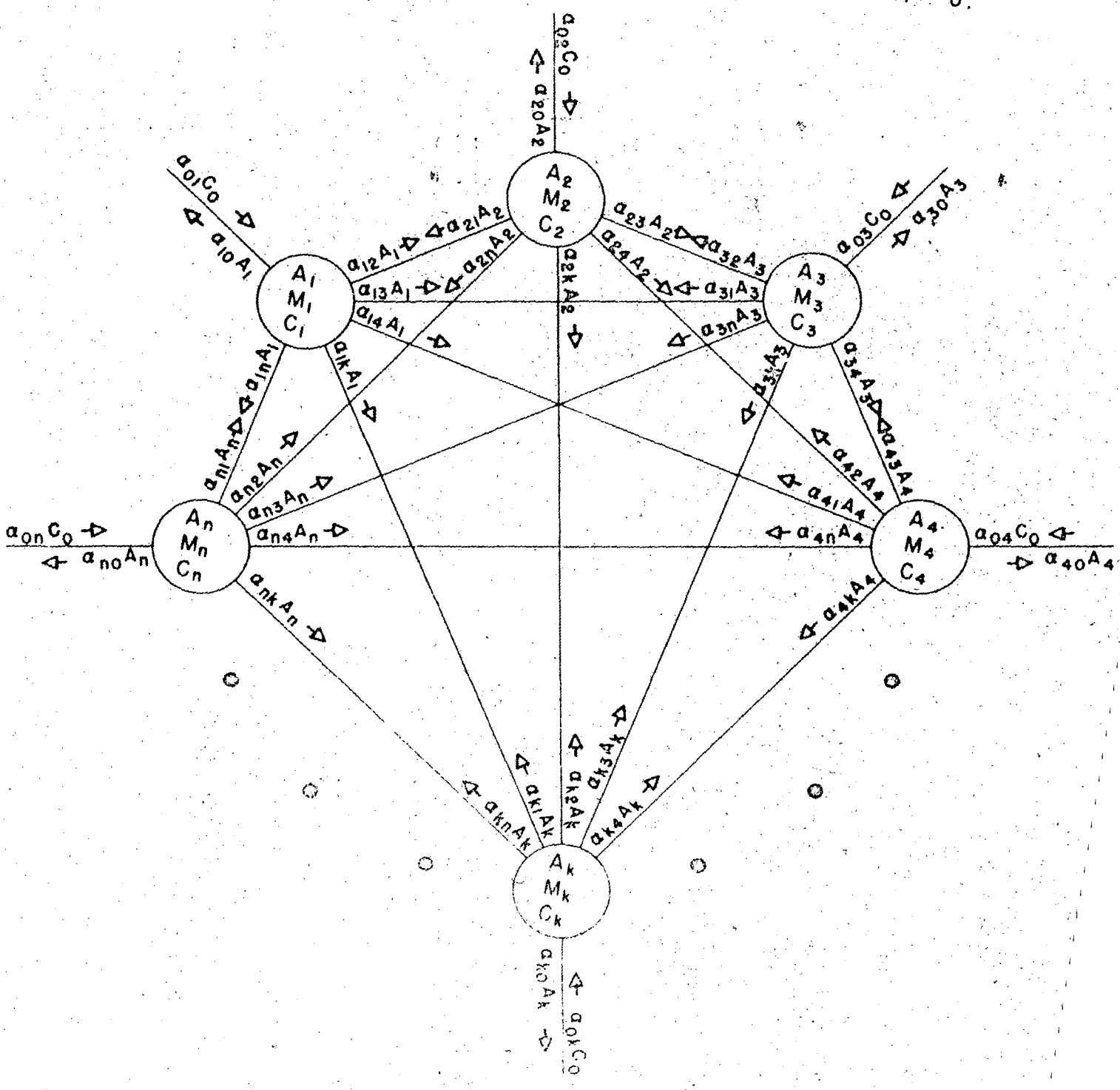
DIAGRAM 1. Schematic representation of a steady state system consistin of n states, with amounts A_k, in mass of tissue M_k, and with con centration C_k in each state. The constant rate of exchange of A from state k to state i is denoted by $a_{ki}A_k$. An external reservoir contain A with concentration C_o, and is denoted by subscript o.



Other Experiments in Progress

Activation analysis. Long life radioactive iron and zinc have been separated from a set of neutron irradiated tissue ash samples in an effort to study their distribution in the animal body.

Metabolism of simple carbon compounds. The work is being continued as outlined in the previous quarterly progress report.

The study of sodium ion exchange in the body. A series of tests have been completed on a set of rabbits, studying the distribution of sodium ions prior to and following irradiation by x-rays. Detailed reports covering the above subjects will be submitted at a later date.

The rate of biochemical reaction. A theoretical analysis is being made on the determination of the rate of biochemical reactions using data obtainable in radioactive tracer experiments. The first part of the treatment is now completed and is given in the preceding chapter.

III BIOLOGICAL EFFECTS OF RADIATION FROM EXTERNAL AND INTERNAL SOURCES

R. S. Stone - in charge

Project 48 C

University of California Medical School

Hematological Effects of Total Body Irradiation

B.V.A. Low-Beer

Hematological studies on patients who have been treated by doctors of the University of California Out-Patient Department have been continued during this period. The findings during this period have not been sufficiently different from those previously reported to warrant further discussion.

Metabolism and Effects of Radio-Iodine (I^{131})

Earl R. Miller and Nadine Foreman

Uptake of Radioiodine Before and After Treatment. During the past three months, twelve patients have been studied with tracer doses of I^{131} who previously had received larger doses of radioiodine for the treatment of Graves' disease. Before their treatment the uptake of radioiodine by their thyroid glands had been high (greater than 40%), but after treatment it was found to be within normal limits (less than 30%) in all but three patients. All of these patients had reached normal metabolic levels before the present tracer study was done.

Table I lists the percentages of uptake of I^{131} before and after treatment.

TABLE I

Patient	% Uptake of I^{131} by thyroid before treatment	% Uptake of I^{131} by thyroid after treatment
M.C.	90	10
E.D.	73	20
E.E.	45	28
A.F.	57	18
H.H.	80	10
E.H.	49	12
H.L.	80	18
V.M.	77	8
R.P.	79	12
M.S.	69	46
E.N.	85	75
C.M.	58	49

The last three patients listed in Table I are the three whose uptake was still high in spite of the fact that they had recovered from their hyperthyroidism as judged by clinical and laboratory evidence. In each, the thyroid gland was barely palpable and it was thought that the relatively high uptake of radioiodine might be explained by the fact that so small a gland would have to have a more rapid turnover of iodine in order to maintain the metabolism at normal levels.

Relationship Between Size of Dose and Percent Uptake of I^{131}. Further observations have been made upon the relationship between the ability of the thyroid to concentrate radioiodine and the dose administered. In general, the percentage uptake of a tracer dose (250 μc) and a therapeutic dose (2000 μc or more) are very nearly the same.

TABLE II

Patient	Date	Dose μc	% Uptake
1. E.C.	5-5-48	250	90
	5-10-48	2850	90
	6-28-48	246	80
	6-29-48	2900	75-80
2. W.D.	3-15-48	238	30
	3-16-48	1390	38
	5-12-48	171	38
	5-13-48	2015	40
3. E.E.	3-22-48	250	45
	3-24-48	2000	46
4. J.M.	5-3-48	250	72
	5-5-48	1070	73
5. E.P.	4-5-48	238	60
	4-19-48	1000	50
6. E.K.	6-22-48	250	40
	6-24-48	7940	51
7. V.M.	4-12-48	238	60
	4-14-48	2700	77
8. R.P.	4-12-48	246	67
	4-14-48	2977	79

Comparison Between In Vivo and In Vitro Measurement of I^{131} Uptake. Additional studies have been made upon the accuracy of the method of measuring in vivo the ability of the thyroid gland to concentrate I^{131}. Seven patients were given tracer doses of radioiodine 24 to 48 hours prior to thyroidectomy and the amount in the thyroid was measured just before operation. The entire surgical specimen was measured by the same method after its removal and the two values were compared. In only three of the seven cases were the data complete enough to warrant analysis.

The discrepancy between the amount of I^{131} calculated to be in the gland from the preoperation measurement and that from measurement of the surgical specimen, (Table III #7) is partially due to the method of measurement, and partially to the estimation by the surgeon of the amount of thyroid which has been left in the neck. Further, the geometrical variations between the intact thyroid and the surgical specimen are difficult to estimate and control.

TABLE III

	I (L.M.)	II (O.A.)	III (J.L.B.)
1) Wt. of removed specimen - gm.	270	40.4	9.6
2) Estimated wt. of tissue left in situ	2	3	0.5
3) Estimated total wt. of thyroid	272	43.4	10.1
4) Total μc measured in neck pre-operatively	57	12	46
5) Total μc measured in surgical specimen	60	11.7	41
6) Calculated μc in total gland based upon 1, 3, and 5	63	12.6	48
7) % difference between observed and calculated totals, 4 and 6	9.5%	5.0	15.2

Radioiodine in Carcinoma of the Thyroid. Three patients with advanced carcinoma of the thyroid have been given large doses of radio-iodine; the first received 100, the second 89.1, and the third 53.9 millicuries.

CASE I: A 19 year old male in whom the diagnosis of carcinoma of the thyroid was made by biopsy June 1947. In October 1947 a left neck dissection was carried out, but the adherent thyroid left in situ. The patient was given 2 millicuries of I^{131} prior to this procedure and the tumor was found to take up 0.2% per gram of the administered dose. Study of the thyroid revealed an uptake of 20% of a tracer dose of radioiodine.

In December 1947, the patient was given 25 millicuries of I^{131} which altered his thyroid metabolism in no demonstrable way. On April 16, 1948 the patient received 100 millicuries of I^{131}. When the patient was seen two months later, signs of early myxedema were evident.

CASE II: A 31 year old female with carcinoma of the thyroid which had been treated both with surgery and with x-ray in 1945. Because of tracheal obstruction, a tracheotomy had been performed in January 1948. She was normal with respect to thyroid metabolism at the time she was first seen. Her thyroid concentrated 17% of a tracer dose of I^{131} while there was apparently no selective uptake by the tumor. On May 14, 1948, the patient received 53.9 millicuries of radioiodine. At the end of two months definite clinical evidence of myxedema has appeared.

CASE III: A 59 year old female with advanced carcinoma of the thyroid, with both local and pulmonary metastases, who also has required a tracheotomy for relief of progressive respiratory obstruction. Preliminary tracer studies revealed that her thyroid concentrated 8% of the administered dose while the tumor had no significant content of radioiodine. On April 19, 1948, the patient received 89.1 millicuries of radioiodine and developed signs of myxedema 2 1/2 months later.

Each of the above patients complained of local tenderness over the thyroid, and of pain on swallowing, 24 to 48 hours after administration of the radioiodine. These symptoms lasted only for 2 days and were not accompanied by systemic symptoms. In the first case there was pooling of secretions within the pyriform fossae at the time of the local soreness, but there was no redness or swelling of the laryngeal structures. In the third patient it was impossible to view the larynx directly because of the infiltrating tumor tissue.

Dental films were placed in contact with the neck in two patients (1 and 3) in an effort to see whether or not the thyroid could be localized. The films were left in place for from 30 to 60 minutes, at hourly intervals after the patients had received the large amounts of radioiodine. There was very definite blackening of the films in this length of time, however, it was so diffuse that only a general idea of localization of the thyroid could be obtained.

Further studies are being carried out using a Geiger counter close to the skin in an attempt to localize the thyroid gland and functional metastases from thyroid carcinomas, and to determine, if possible, the frontal area of the thyroid. In the first experiments the counter tube was surrounded by a thin lead shield with a one inch aperture. By decreasing the aperture to a half inch diameter it was possible to determine the frontal area of the thyroid gland somewhat more accurately. In order to improve the technique still further, a heavily-shielded counter is being constructed in which there will be a one-eighth inch window through a one inch thickness of lead. The counter is to be mounted in such a way that its movement over the anterior surface of the neck can be easily and carefully controlled.

IV HEALTH CHEMISTRY AND PHYSICS

Health Chemistry

N. B. Garden

During this quarter laboratory facilities of Bldg. 5 were completed to provide working space for twelve chemists; most of these chemists have moved in and started work. There has been concentrated in this building all the restricted chemistry from Bldg. 4, so that the latter is now unrestricted. Considerable time and work was devoted to special planning, designing and materials testing so that laboratories and their services and equipment could be somewhat standardized. The immediate reaction of chemists moving into the new quarters indicates that very favorable progress has been made.

The actual moving of the active work in progress was accomplished without difficulty, since all material was confined in closed systems in the gloved boxes and the latter could be moved with ease.

Special protective processes and devices were designed and a number completed during the last three months:

1. The special lead-shielded box for beta-gamma protection, as well as alpha, was completed.

2. The preliminary steps of setups and test runs for the spinner column extraction of americium from plutonium were completed.

3. A simple 60-inch cyclotron target for the bombardment of alpha-active samples was designed, built and used successfully.

4. Special parabolic miniature heat lamps for microchemical work were built.

5. An electric stirring unit for remote use in gloved boxes was developed.

6. The canvas containers for alpha meters were replaced with more satisfactory compact aluminum boxes.

7. The more elaborate Webb target assembly for bombardment of alpha-active samples in the 60-inch cyclotron was developed to the point where dummy runs could be made.

8. Development of a special box to enable Dr. Gofman to process and bottle yttrium without exposure or contamination took place.

9. A shielded box to permit milling targets on the milling machine was developed.

The usual activities of monitoring, disposal of radioactive materials, the transportation and supervision of incoming and outgoing isotopes, cyclotron target handling, decontamination and storage have continued in increasing amounts, especially with regard to target transportation and monitoring. The quantity of material dumped at sea was unusually large, not only from routine laboratory pickups but also from

various cleanup operations, such as at the Army 2001 Warehouse.

Unusual and increasing interest has been shown in the Berkeley-type gloved box by personnel at other atomic installations, and complete box assemblies, plus accessories, have already been shipped to Los Alamos. Hanford has also ordered one, and drawings of the boxes and their accessories have been sent to Brookhaven. Drawings of the major portion of the Health Chemistry equipment, such as gloved boxes, caves, manipulators, tongs, shields, containers, capsules, etc., have been requested by other installations. Conducting visitors has consumed no small part of the time during the last quarter.

Health Physics

B. J. Moyer

General Remarks on Personnel Monitoring. There are now approximately 600 film badges regularly in use, covering all who have even incidental entry into proximity radiation fields.

Crew members of both 184-inch and 60-inch cyclotrons are equipped with the following items: gamma pocket chamber, gamma pocket electroscope, slow neutron pocket chamber and film badge. Members of the following groups are equipped with gamma pocket chambers and gamma pocket electroscopes, as well as film badges: linear accelerator operators, electrical maintenance, inspection technicians, accelerator technicians and electronics installation. Other persons are issued pocket chambers and electroscopes as occasion demands. This includes experimenters, plumbers, carpenters, riggers, welders, etc.

Beginning with April 1, a graphical record of dosages as recorded on all these devices has been maintained, allowing a quick estimate of accumulated dosage by individuals whose work dictates the use of equipment other than a film badge.

Tissue-Wall Chamber Surveys. During a portion of April and May, Drs. G. Failla and H. Rossi from Columbia University made measurements with their ionization chambers constructed with "tissue-equivalent" walls and filled with gas having chemical elements in the same proportions as those found in tissue. Comparative measurements were made on equipment used locally. Final results have not yet been obtained from them as to their interpretation of data, but on-the-spot observations yielded the following results:

(1) Radiation field in typical region outside shielding (10 ft. walls, 2 ft. roof, at this time) for deuteron beam of about 1 microampere on a Be target at 81" was:

Their tissue-equivalent chamber	Our polystyrene chamber
.698 m rep/hr.	.77 mr/hr.
.702 m rep/hr.	.77 mr/hr.
.722 m rep/hr.	.78 mr/hr.

(2) Comparison of dosage measured by a tissue-equivalent thimble chamber, with our 25r thimble chamber for a region within 3" of paraffin in the high-energy neutron beam.

Their tissue-equivalent chamber	Our 25r thimble chamber
14.8 m rep/hr.	16.8 mr/hr.
12.9	14.9
13.2	15.1
11.4	13.9
11.7	14.1
12.2	14.5
---- etc.	----

As a result of these measurements it appears that we are not underestimating the ionization produced by the cyclotron radiation fields in so far as health protection is concerned.

Slow Neutron Flux Densities in the Shielding Wall of the 184-inch Cyclotron. Figure 1 shows the result of indium foil measurements of slow-neutron flux in the concrete, and in the region just outside the concrete shielding. The foils were calibrated by means of a known Ra-Be source with a water tank.

The data were taken thru a 6" diameter access hole, filled with wooden cylinders interspersed by foils. The cyclotron was operating on deuterons at about 0.7 microamperes with a 1/2" Be target. The access hole employed was on the east side near the southeast corner.

The increase in intensity upon emerging from the concrete is interpreted as due to the neutrons which escape thru the 2 ft. roof, and are subsequently scattered downward. Other data support this interpretation.

Radiation from the Cyclotron Dee. Figure 2 shows the beta-gamma intensity pattern of the dee and deflector channel when the tank was opened on 6-11-48 for internal work.

The last operation was 11 hours preceding the measurement. A beta-gamma survey meter was employed, with a .002" Al window, and the figures given are mr/hr at about 6" from the surface of the object.

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Information Division

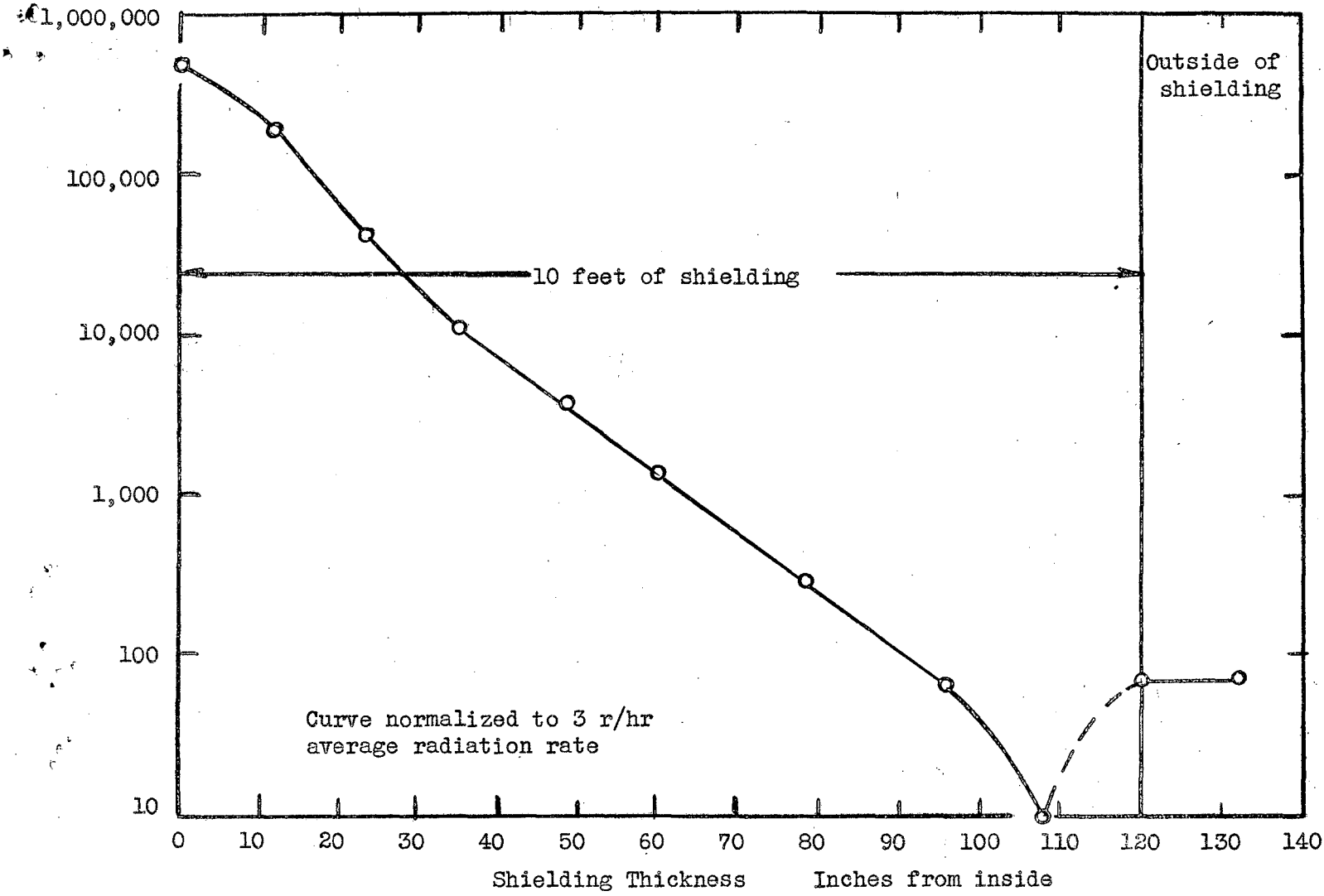

Figure 1

Slow Neutron Flux Distribution in Concrete shielding in 184" Cyclotron

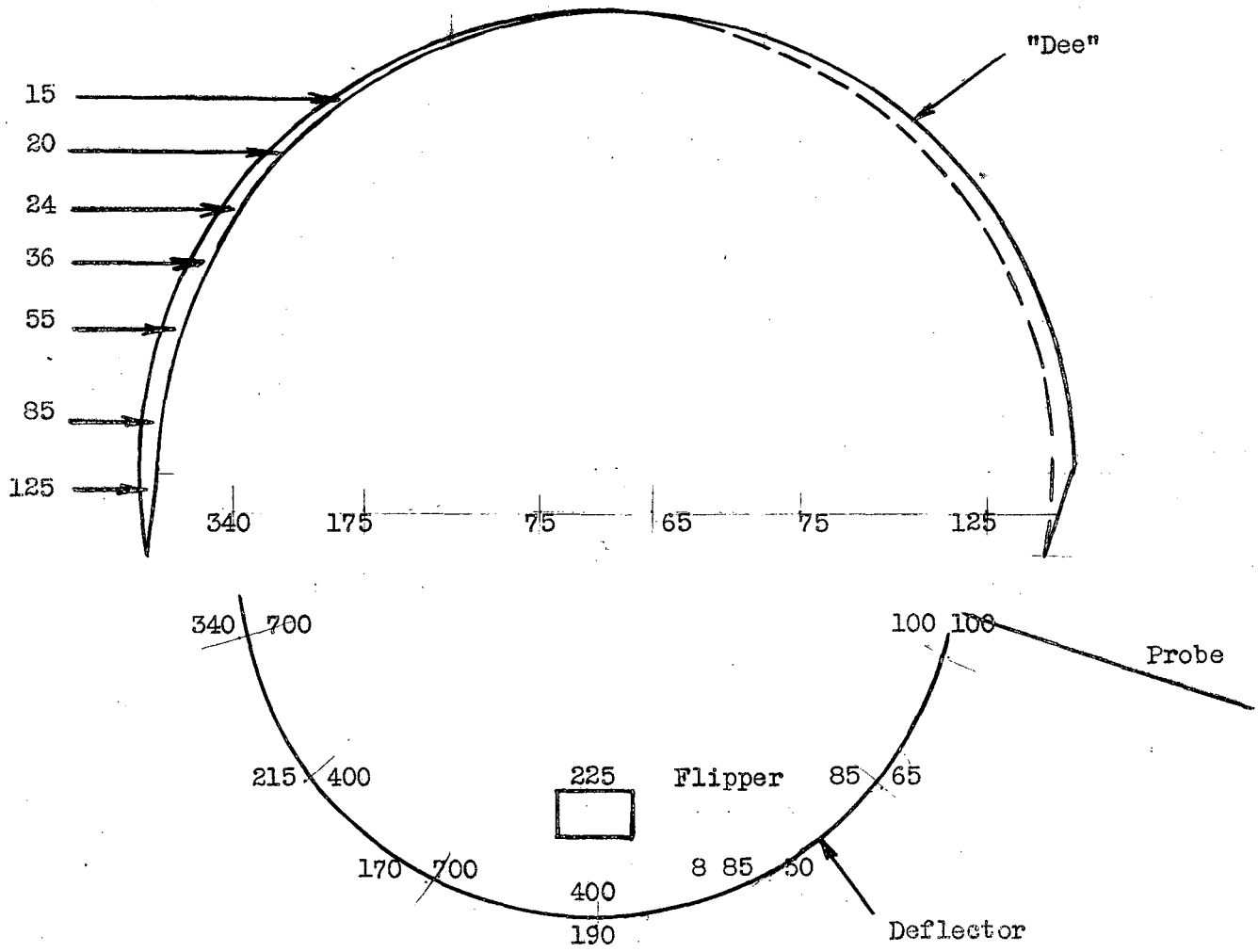

Figure 2

Pattern of Intensity on Cyclotron Dee and Deflection Channel.
(Numbers indicate mr/hr.)

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