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Radiation Laboratory
Berkeley, California

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MEDICAL AND HEALTH PHYSICS QUARTERLY REPORT

October, November, December 1954

February 28, 1955

MEDICAL AND HEALTH PHYSICS QUARTERLY REPORT

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STUDIES OF RADIOACTIVITY AND IRRADIATION

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TRACER STUDIES AND EFFECTS OF IONIZING RADIATION

LANTHANIDE RARE EARTHS

Patricia W. Durbin, Joseph G. Hamilton, Marilyn H. Williams,
Ruth H. Newman, and Margaret Gee

Tracer studies in the rat employing either carrier-free or high-specific-activity radioisotopes of lanthanum, promethium, gadolinium, terbium, and erbium are presented in Tables I through V. In each table the standard error of mean of the liver and skeleton is presented at the bottom of the table.

The procedure employed--namely, the injection by the intramuscular route of the rare earth complexed with sodium citrate--is the same as was presented in earlier quarterly reports.

Only 1- and 4-day studies were possible with La^{140} in view of its short half life. Interestingly enough, the highest concentration at the site of injection was observed for La^{140} . It may be noted that the liver is the principal organ of accumulation, and the skeletal concentration is less than one-third that of the kidney; however, by the fourth day, the concentration in the skeleton remained almost unchanged while that of the kidney had decreased and was exactly equal to that of the skeleton.

The data presented for Pm^{147} include 1-, 4-, 64- and 238-day time intervals. In this instance, it may be noted that the amount of retention at the site of injection was initially smaller than for La^{140} . With Pm^{147} a considerably greater portion was excreted in the urine in the first 24 hours. The liver uptake, while still greater than that of the skeleton, is much less than was observed in the La^{140} studies, and the concentration in the skeleton at the 1- and 4-day time intervals is higher than for La^{140} . Another notable observation is the fact that the skeletal retention, expressed as percent per organ, remains almost constant throughout the 238-day time interval while the percent per gram shows a decrease at the longer times. This presumably is because the animals continued to grow after they had received the Pm^{147} , so that this decrease in concentration was simply a function of increase in skeletal mass. The kidney concentration, while still well below that of the skeleton, expressed as percent per gram, still remained relatively high.

Hamilton

Table I

The deposition of lanthanum in the rat 1 and 4 days after intramuscular administration using La^{140} as a tracer. Values are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100 percent. Each rat in the 1-day group received $28.8 \mu\text{C}$ of La^{140} , $1.2 \mu\text{g}$ of lanthanum, and 6.0 mg of sodium citrate. Each rat in the 4-day group received double these amounts. The standard error of the mean for the liver and skeleton is shown at the bottom of the table.

	1 day		4 days	
	%/organ	%/g	%/organ	%/g
Spleen	0.11	0.21	0.10	0.19
Blood	0.08	0.01	0.02	<0.01
Liver *	65.4	8.45	64.2	7.94
Kidney	2.50	1.59	1.35	0.83
G.I. Tract	0.78	0.12	0.45	0.08
G.I. Contents	0.75	-	2.63	-
Muscle	1.62	0.02	1.21	0.01
Skeleton **	18.5	0.84	18.4	0.83
Balance	2.92	-	2.55	-
Skin	1.60	0.04	0.99	0.03
Urine	4.56	-	5.62	-
Feces	1.20	-	2.60	-
Injection Site	33.0	-	22.5	-
Av. Recovery	102	-	101	-
Std Error of Mean	*	± 0.9	± 1.6	± 0.60
	**	± 0.15	± 0.70	± 0.02

Table II

The deposition of carrier-free promethium-147 in the rat 1, 4, 64, and 238 days after intramuscular administration. Values are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100 percent. Each rat in the 1- and 4-day groups received 10 μ c of Pm^{147} and 3.0 mg of sodium citrate. Each rat in the 64- and 238-day groups received double these amounts. The standard error of the mean for the liver and skeleton is shown at the bottom of the table.

	1 day		4 days		64 days		238 days	
	%/organ	%/g	%/organ	%/g	%/organ	%/g	%/organ	%/g
Spleen	0.09	0.19	0.07	0.15	0.04	0.07	0.03	0.05
Blood	0.05	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Liver*	43.8	6.37	41.4	6.12	1.70	0.19	0.97	0.11
Kidney	1.76	1.17	1.44	1.04	0.46	0.26	0.37	0.19
G.I. Tract	1.36	0.20	0.63	0.09	0.25	0.04	0.12	0.01
G.I. Contents	1.75	-	1.45	-	0.09	-	0.02	-
Muscle	1.98	0.02	0.73	0.01	0.86	0.01	0.28	<0.01
Skeleton**	34.3	1.82	36.4	2.13	28.6	1.28	26.7	1.02
Balance	2.55	-	2.32	-	1.01	-	0.50	-
Skin	1.63	0.05	0.73	0.03	0.45	0.01	0.21	<0.01
Urine	9.79	-	9.61	-	14.5	-	17.3	-
Feces	0.86	-	5.07	-	49.8	-	53.5	-
Injection Site	4.24	-	4.75	-	3.21	-	1.75	-
Av Recovery	97.6	-	94.0	-	91.2	-	91.3	-
Std Error	*	± 1.95	± 0.35	± 2.4	± 0.32	± 0.03	± 0.40	± 0.04
of Mean	**	± 1.6	± 0.12	± 2.3	± 1.19	± 0.08	± 0.65	± 0.05

Table III

The deposition of gadolinium in the rat 1 and 4 days after intramuscular administration using Gd^{159} as a tracer. Values are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100 percent. Each rat in the 1-day group received $3.8 \mu\text{C}$ of Gd^{159} , $2.03 \mu\text{g}$ of gadolinium, and 2.2 mg of sodium citrate. Each rat in the 4-day group received 5.5 times these amounts. The standard error of the mean for the liver and skeleton is shown at the bottom of the table.

	1 day		4 days	
	<u>%/organ</u>	<u>%/g</u>	<u>%/organ</u>	<u>%/g</u>
Spleen	0.10	0.18	0.15	0.27
Blood	0.32	0.03	0.14	0.01
Liver *	25.1	2.82	12.1	1.48
Kidney	1.63	1.06	1.87	1.16
G.I. Tract	1.06	0.16	0.71	0.12
G.I. Contents	2.18	-	0.95	-
Muscle	2.49	0.02	2.89	0.03
Skeleton **	45.0	2.07	41.4	1.82
Balance	4.37	-	3.81	-
Skin	2.20	0.06	1.76	0.04
Urine	14.8	-	26.9	-
Feces	0.79	-	7.24	-
Injection Site	23.4	-	15.4	-
Av Recovery	120	-	88.5	-
Std Error	*	± 1.0	± 0.3	± 0.10
of Mean	**	± 0.6	± 1.2	± 0.09

Table IV

The deposition of terbium in the rat 1, 4, 64, and 256 days after intramuscular administration using Tb^{160} as a tracer. Values are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100 percent. Each rat in the 1-, 4-, and 64-day groups received $3.0 \mu c$ of Tb^{160} , $3 \mu g$ of terbium, and 2.8 mg of sodium citrate. Each rat in the 256-day group received four times these amounts. The standard error of the mean of the liver and skeleton is shown at the bottom of the table.

	1 day		4 days		64 days		256 days		
	%/organ	%/g	%/organ	%/g	%/organ	%/g	%/organ	%/g	
Spleen	0.12	0.24	0.13	0.24	0.09	0.17	0.03	0.06	
Blood	0.20	0.02	0.06	<0.01	<0.01	-	<0.01	<0.01	
Liver*	15.8	2.23	6.83	0.85	1.09	0.12	0.24	0.03	
Kidney	2.75	1.68	2.05	1.36	0.78	0.42	1.55	0.80	
G.I. Tract	1.43	0.22	0.84	0.13	0.34	0.04	0.17	0.02	
G.I. Contents	2.47	-	0.73	-	0.06	-	0.02	-	
Muscle	2.91	0.03	2.31	0.02	1.0	0.01	1.00	<0.01	
Skeleton**	53.3	2.44	60.5	2.96	57.1	2.52	48.5	1.84	
Balance	4.66	-	2.70	-	1.70	-	1.50	-	
Skin	2.44	0.08	2.10	0.06	0.76	0.02	0.66	0.01	
Urine	11.5	-	15.6	-	21.0	-	25.7	-	
Feces	2.48	-	6.17	-	16.1	-	20.6	-	
Injection Site	27.2	-	15.2	-	10.5	-	5.97	-	
Av Recovery	113	-	116	-	109	-	98.0	-	
Std Error	*	±0.6	±0.11	±0.85	±0.11	±0.26	±0.03	±0.03	<±0.01
of Mean	**	±1.0	±0.11	±1.6	±0.08	±0.8	±0.05	±1.6	±0.08

Table V

The deposition of erbium in the rat 1, 4, and 16 days after intramuscular administration using Er^{169} as a tracer. Values are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100 percent. Each rat in the 1- and 4-day groups received 2.4 μC of Er^{169} , 1.9 μg of erbium, and 2.8 mg of sodium citrate. Each rat in the 16-day group received double these amounts. The standard error of the mean for the liver and skeleton is shown at the bottom of the table.

	1 day		4 days		16 days	
	%/organ	%/g	%/organ	%/g	%/organ	%/g
Spleen	0.09	0.16	0.06	0.13	0.07	0.13
Blood	0.19	0.02	0.05	<0.01	<0.01	<0.01
Liver*	3.12	0.40	1.15	0.14	0.60	0.07
Kidney	1.31	0.80	0.76	0.48	0.35	0.20
G.I. Tract	0.90	0.15	0.57	0.09	0.31	0.04
G.I. Contents	1.60	-	0.31	-	0.11	-
Muscle	2.39	0.02	1.75	0.02	1.44	0.01
Skeleton**	60.0	2.70	56.4	2.49	56.6	2.51
Balance	3.96	-	2.66	-	1.07	-
Skin	2.08	0.06	1.76	0.06	0.90	0.02
Urine	19.6	-	27.4	-	30.8	-
Feces	4.79	-	7.09	-	7.69	-
Injection Site	3.76	-	3.92	-	1.56	-
Av Recovery	116	-	113	-	97.5	-
Std Error of Mean	* ± 0.13	± 0.04	± 0.09	± 0.02	± 0.09	± 0.01
	** ± 0.42	± 0.12	± 0.80	± 0.13	± 0.90	± 0.07

The experiments with Gd^{159} were conducted only for the 1- and 4-day time periods because of the short half life of this isotope. The hepatic uptake in the 1- and 4-day periods is very much less than that of Pm^{147} , and there is a considerable increase in the skeletal accumulation. Another interesting observation is the high urinary excretion in the 1- and 4-day time intervals.

Although terbium is the next member of the 4f-type rare earths, comparison of the Tb^{150} tracer studies at 1 and 4 days with the same intervals for the Gd^{159} studies shows that there is a very marked decrease in the uptake by the liver and increase in accumulation by the skeleton. When the data for the 64-day and 256-day time intervals are examined, it is seen that the total quantity in the skeleton does not decrease significantly, though the percent per gram did, as also noted in the case of Pm^{147} . Here again this may be ascribed to the effect of growth. At 256 days it may be seen that the concentration per gram of the liver is very much smaller and is exceeded by that of the spleen. Kidney values appear quite high, and suggest that for rare earths with long half lives the kidney should be considered as one of the primary target organs.

Unfortunately, it was possible to do only 1-, 4- and 16-day tracer studies with Er^{169} . Erbium is one of the heavier members of the rare earth group, and here may be seen a very minimal uptake by the liver as contrasted with the skeleton. There is also, as with terbium, a rapid initial rate of urinary excretion.

These represent the last five tracer studies on the rare earths and lanthanum. This material is now being compiled for publication.

TRACER STUDIES WITH CALCIUM AND STRONTIUM

Patricia W. Durbin, Joseph G. Hamilton, Marilyn H. Williams,
Nylan Jeung, and Margaret Gee

Series of tracer studies with Ca^{45} and the Sr^{90} - Y^{90} mixture have been done in both rats and monkeys.

Four time intervals were employed for the rats, namely, 4, 16, 70, and 264 days after injection of $4 \mu c$ of high-specific-activity Ca^{45} and $0.5 \mu c$ of Sr^{90} . The mixture of these radioisotopes was given by intravenous injection in the presence of 0.5 mg of calcium and 7.8 mg of sodium citrate. The Sr^{90} was carrier-free. Differential beta counting was employed, and all beta activity was counted after Y^{90} had reached full equilibrium. (The method of preparing the thin samples is presented immediately after this portion of the report.) A filter was then employed to absorb all Ca^{45} particles. Most of the Sr^{90} beta particles were also absorbed, but the filter permitted the majority of the energetic Y^{90} beta particles to be counted. The reliability of this procedure appears evident from the consistency of both rat and monkey data.

Seven rats were used for each of the time intervals; data are presented in Table VI. The data for the content for Ca^{45} and Sr^{90} are expressed as percent per organ and percent per gram. The ratio of Sr^{90} to Ca^{45} is also included in Table VI.

Hamilton

Table VI

The deposition of Ca^{45} and Sr^{90} in the skeleton of the rat 4, 16, 70, and 264 days after intravenous administration. Mean values, expressed in percent of administered dose, are shown with their standard errors. Each rat received $4 \mu\text{c Ca}^{45}$, $0.5 \mu\text{c Sr}^{90}$, 0.5 mg of calcium, and 7.8 mg of sodium citrate.

	Leg Bones		Mandibles		Vertebrae*		Total Skeleton		Teeth	
	%/organ	%/g	%/organ	%/g	%/organ	%/g	%/organ	%/g	%/organ	%/g
<u>4 days</u>										
Ca^{45}	5.95 ± .18	4.76 ± .17	3.37 ± .17	3.66 ± .34	3.13 ± .15	2.62 ± .11	70.0 ± 2.3	5.08 ± .27	2.74 ± .16	
Sr^{90}	3.85 ± .14	3.08 ± .09	2.58 ± .11	2.81 ± .81	2.12 ± .11	1.79 ± .16	50.1 ± 1.8	3.62 ± .15	2.01 ± .08	
$\text{Sr}^{90}/\text{Ca}^{45}$	0.65 ± .01	-	0.77 ± .03	-	0.68 ± .03	-	0.72 ± .02	-	0.73 ± .02	
<u>16 days</u>										
Ca^{45}	5.25 ± .20	3.53 ± .11	3.55 ± .09	3.70 ± .07	2.89 ± .13	2.35 ± .10	66.2 ± 3.1	3.72 ± .10	3.33 ± .14	
Sr^{90}	3.72 ± .14	2.50 ± .10	2.50 ± .10	2.61 ± .10	2.06 ± .11	1.60 ± .03	48.9 ± 1.8	2.75 ± .09	2.26 ± .09	
$\text{Sr}^{90}/\text{Ca}^{45}$	0.71 ± .01	-	0.71 ± .02	-	0.69 ± .04	-	0.74 ± .03	-	0.68 ± .02	
<u>70 days</u>										
Ca^{45}	4.16 ± .25	2.51 ± .16	3.05 ± .19	2.75 ± .18	2.31 ± .09	1.64 ± .07	66.7 ± 2.8	3.08 ± .14	1.08 ± .05	
Sr^{90}	2.75 ± .20	1.65 ± .12	2.03 ± .14	1.84 ± .13	1.38 ± .06	.98 ± .04	39.6 ± 1.9	1.83 ± .09	0.55 ± .04	
$\text{Sr}^{90}/\text{Ca}^{45}$	0.66 ± .02	-	0.67 ± .04	-	0.60 ± .02	-	0.59 ± .01	-	0.50 ± .03	
<u>264 days</u>										
Ca^{45}	3.26 ± .06	1.71 ± .04	2.00 ± .05	1.45 ± .04	1.09 ± .08	0.85 ± .07	44.7 ± 1.8	1.69 ± .06	0.44 ± .02	
Sr^{90}	2.17 ± .10	1.13 ± .04	1.37 ± .03	0.99 ± .03	0.62 ± .05	0.48 ± .04	31.0 ± 1.4	1.16 ± .06	0.24 ± .02	
$\text{Sr}^{90}/\text{Ca}^{45}$	0.66 ± .03	-	0.68 ± .02	-	0.57 ± .01	-	0.69 ± .05	-	0.54 ± .03	

* Only 3 vertebrae

The most important observation to be made from the data in Table VI is that $\text{Sr}^{90}\text{-Ca}^{45}$ ratios were consistently less than unity and averaged approximately 0.65.

A similar experiment was performed with two monkeys. Each received by intravenous injection $134\text{ }\mu\text{c}$ of Ca^{45} with 16 mg of calcium and $35\text{ }\mu\text{c}$ of carrier-free Sr^{90} in the presence of 70 mg of sodium citrate. The excretion data are given in Table VII. The female, "Rosie," was pregnant at the time this experiment was performed. However, the $\text{Ca}^{45}\text{-Sr}^{90}$ mixture was given presumably before there was any appreciable ossification of the skeleton of the fetus. The male, "Tony," who was sacrificed six months later, apparently had chronic arthritis, of undetermined origin, which was confirmed by x-ray examination. The kidneys were the principal channel of elimination in both animals. The total urinary excretion for the 10-day time intervals employed for both animals was quite similar, as was also the fecal excretion. The total excretion by both routes of elimination was very similar. The Sr^{90} excretion was consistently higher than that of the Ca^{45} .

Detailed survey of various portions of the skeleton of the male monkey sacrificed six months later is to be found in Table VIII. Here again the calcium and strontium content are expressed as percent per organ and percent per gram. The fifth column gives the ratio of Sr^{90} to Ca^{45} , and perusal of this column leads to a number of interesting observations. In the skeleton the ratio is lowest for the shaft of the femur. This may be because the femur contains a relatively large amount of compact bone, whereas in the ribs, for example, there is a relatively large amount of trabecular bone. Only two soft tissues were included, namely, "balance" and muscle. The balance includes skin, fat, viscera, fluids, and blood. An interesting point is that the ratio for muscle was high, although the total content of both alkali earths in muscle was low.

Table VII

The excretion of Ca^{45} and Sr^{90} by an adult female rhesus monkey, "Rosy," and an adult male rhesus monkey, "Tony," for the first 10 days after intravenous injection. Values are expressed in percent of administered dose. Each monkey received $35 \mu\text{c}$ Sr^{90} , $134 \mu\text{c}$ Ca^{45} , 16 mg Ca, and 70 mg sodium citrate.

Feces

"Rosie"			"Tonie"		
Days	% Ca	% Sr	Days	% Ca	% Sr
0-1	0.72	0.90	0-1	0.31	0.35
1-2	2.07	2.76	1-2	2.48	3.55
2-3	1.65	1.91	2-3	1.76	2.25
3-5	0.68	1.50	3-4	2.37	2.23
5-7	0.71	0.77	4-5	0.93	1.19
7-10	<u>0.85</u>	<u>1.34</u>	5-6	0.64	0.50
Total	6.68	9.18	6-8	0.92	0.91
			8-10	<u>0.68</u>	<u>0.49</u>
			Total	10.09	11.47

Urine

0-1	16.91	31.38	0-1	7.12	29.30
1-2	7.80	12.72	1-2	7.16	12.60
2-3	1.14	2.52	2-3	4.54	6.06
3-5	1.25	2.28	3-4	3.26	4.05
5-7	1.98	2.37	4-5	4.37	3.22
7-10	<u>1.20</u>	<u>3.21</u>	5-6	0.53	0.95
Total	30.28	54.48	6-8	1.05	1.62
			8-10	<u>0.31</u>	<u>0.50</u>
			Total	28.30	58.30

Table VIII

The deposition of Ca^{15} and Sr^{90} in an adult male monkey 6 months after intravenous administration. Values are expressed in percent of administered dose. The animal was given $35 \mu\text{c Sr}^{90}$, $134 \mu\text{c Ca}^{45}$, 16 mg Ca, and 70 mg sodium citrate. Excretions were collected for the first 10 days after injection.

	Ca		Sr		Sr/Ca
	%/organ	%/g	%/organ	%/g	
Skull	5.91	0.039	2.96	0.020	0.501
Mandible	2.30	-	1.31	-	0.569
Sternum and C. C. j.	0.72	0.028	0.35	0.012	0.486
Clavicles	0.54	0.051	0.31	0.030	0.574
Scapulae	2.07	0.056	1.28	0.034	0.618
Ribs	1.43	0.045	0.90	0.029	0.629
Cervical and Thoracic Vert.	5.14	0.039	2.80	0.021	0.544
Lumbar Vert., Pelvis, Tail	16.8	0.038	8.74	0.020	0.520
Hands and Feet	3.40	0.027	2.05	0.016	0.602
Patellas	0.70	0.035	0.35	0.018	0.500
Tibia Shafts	1.38	0.067	0.90	0.042	0.652
Tibia Heads	1.72	0.047	0.77	0.021	0.448
Femur Shafts	1.67	0.053	0.52	0.017	0.311
Femur Heads	2.20	0.049	1.04	0.023	0.472
Ulna Shafts	0.93	0.074	0.48	0.038	0.516
Ulna Heads	1.47	0.067	0.66	0.030	0.449
Radius and Fibula Shafts	1.38	0.092	0.56	0.037	0.406
Radius and Fibula Heads	1.45	0.063	0.64	0.028	0.441
Humerus Shafts	1.56	0.076	0.80	0.039	0.513
Humerus Heads	3.03	0.071	1.59	0.037	0.524
Teeth	0.55	-	0.27	-	0.490
Muscle	0.11	-	0.09	-	0.818
* Balance	0.18	-	0.11	-	0.611
Feces	10.09	-	11.46	-	1.135
Urine	28.30	-	58.3	-	2.060

* Balance includes skin, fat, viscera, and blood.

A METHOD FOR UNIFORM MOUNTING OF SAMPLES EMITTING SOFT RADIATIONS

George Barr

This method was developed for preparing evenly distributed samples of alpha emitters and soft-beta emitters dissolved in salt solutions with dry weights of the order of 5 to 50 mg per ml. It avoids the clumping otherwise encountered during direct drying, which changes the self-absorption factor considerably and leads to an erroneous estimate of activity in the sample. The method was developed especially for the radioactive assay of solutions of animal tissue.

The preparation is as follows: The samples to be mounted are first dissolved in enough 4 N nitric acid so that the final solution contains no more than 50 mg of solids per ml. In this case, suitable aliquots are pipetted onto rimmed gold plates, 4 cm in diameter. They are then placed on a hot plate and completely dried to get rid of excess nitric acid. The samples are transferred to a hot plate at about 80°C, and redissolved in water and a minimal amount of dilute HNO₃. Dilute NH₄OH (less than 10%) is added dropwise, with continual stirring by blowing across the samples through a micropipette. When a permanent precipitate is formed, stirring is continued until the samples are as finely divided as possible, in order to produce smooth surfaces on the final preparations. The precipitated samples are taken to dryness at 80°C. When dry, they are transferred to a hot plate at about 200°C, and drying is completed.

The final preparation may be hygroscopic, in which case the samples are stored in a desiccator. If the original sample is dissolved in dilute HCl, precipitated, and dried as above, it is less likely to be hygroscopic, but may creep out of the dish during drying.

Figure 1 is a self-absorption curve for Ca⁴⁵ prepared by the above method.

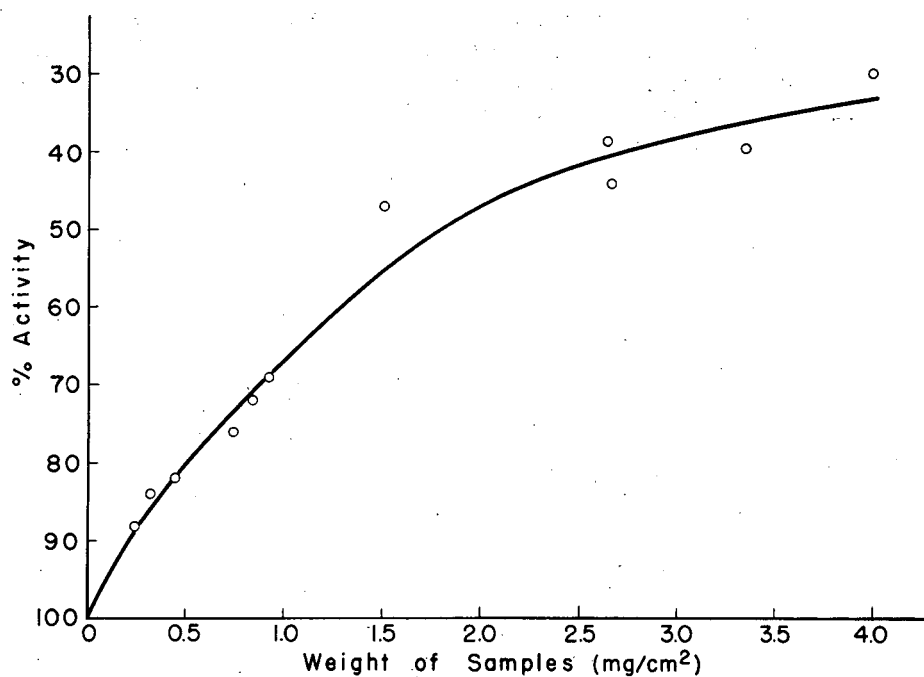
ASTATINE STUDIES

REPORTS ISSUED

Joseph G. Hamilton, Patricia W. Durbin, Marshall W. Parrott,
and Muriel Johnston, associated with C. J. Shellabarger*

For six weeks during the preceding quarter we had the pleasure of collaborating with Dr. Claire J. Shellabarger, who was on leave from Brookhaven National Laboratory. Dr. Shellabarger has been involved for the past year in the study of astatine in the thyroid gland. During the six weeks that he was associated with us, a number of experiments were performed with the purpose of determining what might be the chemical state of astatine in the thyroid gland of the rat and the effect of known thyroid stimulants and anti-thyroid compounds. One paper, "Effects of Thyroxine and KSCN on Capacity

*Brookhaven National Laboratory

Ca⁴⁵ SELF-ABSORPTION CURVE

MU-8845

Fig. 1. The self-absorption of Ca⁴⁵ in bone ash. Samples of rat bone ash, Ca₃(PO₄)₂, were dissolved in 4 N HNO₃ and plated on rimmed gold dishes (4 cm i.d.). They were counted on G-M counter with 1.23 mg/cm² mica window at a distance of 0.5 cm from the tube.

of Rat Thyroid Gland to Accumulate Astatine-211," by C. J. Shellabarger, P. W. Durbin, M. W. Parrott, and J. G. Hamilton has already appeared as a UCRL Report, UCRL-2793, and has been accepted for publication in Proceedings of the Society for Experimental Biology and Medicine. A second paper, entitled, "The Codetermination of Iodine-127, Iodine-131, and Astatine-211 in Tissue," by P. W. Durbin, J. G. Hamilton, and M. W. Parrott, has also appeared as UCRL-2792. Another paper is in preparation, part of which follows.

EFFECTS OF PROPYLTHIOURACIL AND THYROXINE ON CAPACITY OF RAT THYROID GLAND TO ACCUMULATE ASTATINE-211

P. W. Durbin, C. J. Shellabarger, M. W. Parrott, and J. G. Hamilton

It has been shown that the thyroid gland accumulates At^{211} but to a lesser degree than I^{131} , and that thyroid-stimulating hormone (TSH) increases the thyroidal accumulation of both radiohalogens, whereas iodide and thyroxine lower the thyroidal accumulation of both.^{1,2,3} The results of chronic treatment with propylthiouracil or thiouracil increased the thyroidal uptake of At^{211} in contrast to the depression of I^{131} uptake.^{4,5} It is the purpose of this work to show that thyroxine inhibits the propylthiouracil effect and that withdrawal of propylthiouracil following chronic treatment with this drug increased thyroidal uptake.

Methods and Materials

The animals employed were female Sprague-Dawley rats weighing approximately 200 grams that had been maintained on the Radiation Laboratory stock diet and distilled water for at least two weeks prior to use. The propylthiouracil-treated animals received 0.1 percent PTU in their drinking water for eleven days, and off-PTU rats received 0.1 percent for nine days, after which they were returned to distilled water. L-thyroxine was given to PTU and non-PTU rats by daily subcutaneous injections of 23 micrograms per 100 g body weight for seven days. The number of rats used in each group is indicated in Table IX. Following the treatment described above, all rats were given 10 μc of At^{211} intravenously and the thyroidal accumulation of At^{211} was determined 18 hours later by methods previously described.⁵

¹J. G. Hamilton and M. H. Soley, Proc. Nat. Acad. Sci. 26, 483 (1940)

²J. G. Hamilton, C. W. Asling, W. M. Garrison, and K. G. Scott, Univ. Calif. Publ. Pharmacol. 2, 283 (1953)

³P. W. Durbin, C. J. Shellabarger, J. G. Hamilton, and M. W. Parrott, Proc. Soc. Exptl. Biol. Med. In Press (1955)

⁴C. J. Shellabarger and J. T. Godwin, J. Clin. Endocrinol. and Metabolism 14, 1149 (1954)

⁵P. W. Durbin, J. G. Hamilton, and M. W. Parrott, Proc. Soc. Exptl. Biol. Med. 86, 369 (1954)

Table IX

The results of 18-hour uptake studies on female Sprague-Dawley rats. Control rats received distilled water, PTU rats received 0.1% propylthiouracil in distilled water for 11 days. Off-PTU rats received 0.1% PTU for 9 days, then were returned to distilled water and L-thyroxine was given by daily subcutaneous injection (23 μ g/100 g) for 7 days. Each rat received 10 μ c At²¹¹ intravenously. Mean values are presented with standard error.

Treatment	No. of Rats	Body weight (g)	Thyroid weight (mg)	Mg thyroid per 100 g. body wt.	% Admin. At ²¹¹ in thyroid	% At ²¹¹ per g thyroid
Control	8	234 $\pm$ 14	<u>20.8</u> $\pm$ 1.7	8.9 $\pm$.6	0.24 $\pm$.02	11.6 $\pm$ 1.1
Thyroxine	7	218 $\pm$ 11	<u>14.9</u> $\pm$ 1.1	6.8 $\pm$.4	0.022 $\pm$.002	1.5 $\pm$.1
PTU	9	209 $\pm$ 12	<u>23.8</u> $\pm$ 1.4	11.4 $\pm$.9	0.58 $\pm$.07	24.4 $\pm$ 1.9
PTU + Thyroxine	9	200 $\pm$ 10	15.5 $\pm$.6	7.8 $\pm$.3	0.010 $\pm$.001	0.6 $\pm$.1
Control	7	209 $\pm$ 6	<u>15.4</u> $\pm$ 1.6		0.24 $\pm$.01	16.1 $\pm$ 1.5
PTU	7	174 $\pm$ 3	32.4 $\pm$ 1.5		1.07 $\pm$.07	23.4 $\pm$ 2.9
Off-PTU	6	197 $\pm$ 4	28.6 $\pm$ 2.0		1.95 $\pm$.31	68.7 $\pm$ 10.5

* When the mean is underlined this indicates that when this mean was tested against the mean immediately below, the t-test gave values beyond the 1% level of confidence.

Results

The data presented in Table IX verify previous findings that chronic PTU treatment increases thyroidal accumulation of astatine. Withdrawal of PTU further increased the accumulation of At^{211} by a factor of approximately eight over the controls. The combination of treatment with L-thyroxine and PTU produced thyroidal At^{211} uptakes that were lower than either PTU or control values.

It does not seem likely that the observed changes in thyroidal accumulation of At^{211} were due to changes in thyroid size, since correction for thyroid weight by presenting the data as percent At^{211} per gram of tissue results in values that are still significant.

Discussion

An analysis of the interactions of the thiouracils and TSH and their action on the thyroid gland has been reported by Halmi and Spirtos,⁶ and their conclusions may well be applied to the problem at hand, i. e., the ability of PTU to enhance the thyroidal accumulation of At^{211} . The ability of the thyroid gland to trap iodide appears to be controlled by two opposing factors--TSH, which increases the thyroidal iodide trap,⁶ and an intrinsic thyroid principle (probably the total iodine content of the thyroid gland or more especially thyroid hormone).^{7, 8}

It has been amply demonstrated that chronic PTU or thiouracil treatment increases the thyroidal uptake of At^{211} .^{4, 5} Since it remains to be established whether or not At^{211} is organically bound by the thyroid gland, it does not seem necessary to invoke the explanation that the goitrogenic compounds act directly on the behavior of the thyroid gland toward At^{211} , but rather to assume that the increased level of TSH stimulation has increased the "astatide trap." The increased astatide trap would be adequate to explain the enhancement of At^{211} uptake observed with chronic PTU or thiouracil treatment. The observation that exogenous thyroxine abolishes the enhanced At^{211} uptake in PTU-treated rats, indeed, lowers it to about the level observed in the thyroxine-injected control rats, further substantiates the hypothesis that TSH is a major factor governing the thyroidal accumulation of At^{211} . Work in progress at Brookhaven National Laboratory indicates that when thiouracil is administered just prior to the administration of At^{211} , there is no increase in the thyroidal accumulation of At^{211} . This has been tentatively ascribed to the fact that no increase in TSH stimulation occurred. Further work will be necessary to provide a fully valid explanation for the further increase in the thyroidal accumulation of At^{211} observed upon the withdrawal of PTU.

⁶N. S. Halmi and B. N. Spirtos, *Endocrinology* 55, 613 (1954)

⁷E. B. Astwood, *Harvey Lectures* 195 (1944-45)

⁸W. P. Vanderlaan and R. Caplan, *Endocrinology* 54, 437 (1954)

THE INDUCTION OF MAMMARY TUMORS FOLLOWING ADMINISTRATION OF ASTATINE-211

It has been previously reported⁹ that at an early age there is a notable increase in the occurrence of spontaneous mammary tumors in rats following administration of At²¹¹. Complete pathological study of sections of these tumors is now in progress. Preliminary diagnosis revealed "wild-type" epithelial cells, large numbers of mitotic figures, and several lung metastases. An attempt is being made to determine the primary cause of these neoplasms, whether they are due to direct radiation effect or to a disturbance in the endocrine balance following radiothyroidectomy. A group of 20 female Sprague-Dawley rats 55 days old were given daily subcutaneous injections of 23 micrograms per 100 g body weight of L-thyroxine for seven days. This dosage of thyroxine has been found adequate to reduce the thyroidal accumulation of At²¹¹ to 0.02 percent of the administered dose, and effectively protects the thyroid from severe radiation damage. A similar group were given sham saline injections. On the seventh day, each rat was given 0.5 μ c per g of At²¹¹ intravenously. These animals have now been under observation for three months. To date, one animal in the sham-injected control group has developed a mammary tumor, and none has been observed in the thyroxine-treated group.

It has been reported previously that an anemia has been observed in rats several months after the administration of At²¹¹ at this level. Consequently, all the rats in this experimental group are being subjected monthly to routine hematological study, i. e., red-cell count, white-cell count, and hemoglobin determination. In order to estimate the functional state of the reproductive system, a 10-day series of vaginal smears from both groups is now in progress.

OTHER STUDIES WITH ASTATINE-211

Halogen Uptake in Rats

During the course of our recent studies on the thyroidal accumulation of At²¹¹ and I¹³¹, it was found that the thyroidal uptake of these radiohalogens had dropped to extremely low levels. Since dietary iodine intake is the most easily manageable factor involved, it was decided that the type of diet employed be changed. In view of the fact that we are now collaborating with Brookhaven National Laboratory on these experiments and that the diet employed in that installation is Purina Laboratory Chow, this was the diet chosen. The diet previously fed contained 2.5 micrograms per g of added iodide, whereas Purina Chow contains 0.38 μ g per g of iodide. These iodide concentrations amount to daily iodine intakes of 25 μ g and 3.8 μ g micrograms per rat per day respectively, based on a daily intake for the rat of 10 g of food. It has been fairly well substantiated that for rapidly growing rats (50 to 150 g) 3.5 to 4 μ g per day of iodide represents an adequate intake and that for adult rats 1 to 2 μ g of iodide per day is adequate to protect against enlargement of the thyroid gland.¹⁰

⁹J. G. Hamilton, P. W. Durbin, and M. W. Parrott, J. Clin. Endocrinology and Metabolism 14, 1161 (1954).

¹⁰E. J. Farris and J. Q. Griffiths, "The Rat in Laboratory Investigation," J. B. Lippincott Co., Philadelphia, 2nd Edition, 1949, Ch. 5, pp. 76-77.
Hamilton

Experiments are now in progress to determine the extent of the effect of both dietary iodine content and early astatine alpha-particle radiation damage on the shape and magnitude of the curve for At^{211} uptake vs time.

Rhesus Monkeys

In earlier quarterly reports mention has been made of the four monkeys that received astatine by intraperitoneal injection. The first pair, which were males, were given $0.36 \mu\text{c}$ per gram on February 12, 1953, and the second pair, which were females, received $0.8 \mu\text{c}$ per gram on May 10, 1953. All the animals weighed between 2.5 and 3 kilograms at the time they received the astatine. The best data that we have available are that the males were approximately eight months of age when injected and the females approximately 11 months.

The astatine-injected animals have continuously deteriorated, as has been indicated earlier by the evidence of anemia and leukopenia, as well as by changes that are attributed to simian myxedema resulting from almost complete destruction of the thyroid gland due to the astatine accumulated by that organ. The most seriously affected of the four is shown in Fig. 2, in which the puchiness under the eyes is very evident. In Fig. 3 there may be noted the loss of hair on the back and almost complete lack of hair on the tail. This female monkey, interestingly enough, weighed 4.5 kilograms on December 22, 1954, which is only one-half a kilogram less than the controls, and appears to be markedly edematous. Several months ago her appearance suggested that she might have a breast tumor with a metastasis in the axilla. Accordingly, the animal was anesthetized and examined by several of us with great care. There was no evidence of breast tumors or fluid in the peritoneal cavity. For the past three months she has been in rather poor physical condition, although there is no evidence of infection, and her dietary intake is reasonably good. However, this particular monkey lacks any aggressiveness as compared to the other three monkeys treated with astatine, who are somewhat less aggressive than the controls.

Figure 4 shows the appearance of another of the animals that received astatine. After receiving the astatine, the animal failed to grow and develop sexually and, as can be seen from the photograph, also has considerable pouchiness under the eyes. Figure 5 indicates that there has been some loss of hair; in particular, the tail is almost naked. A normal control is shown in Fig. 6. Here may be seen the pointed face and deep-set eyes, which are characteristic of a healthy male rhesus monkey. This photograph was taken several months before the preceding photographs were made, and thus a comparison of the size is not justified.



ZN-1179

Fig. 2. Close-up of a 2.5-year-old female rhesus monkey, "Karen," 20 months after the intraperitoneal injection of $0.8 \mu\text{c}$ of At^{211} per gram of body weight. The animal shows a marked degree of simian myxedema. Her present weight is 4.5 kilos and she appears to be quite edematous.



ZN-1180

Fig. 3. Rear view of the same animal shown in Fig. 2. Note the sparseness of hair in the neck region and the nearly hairless tail.



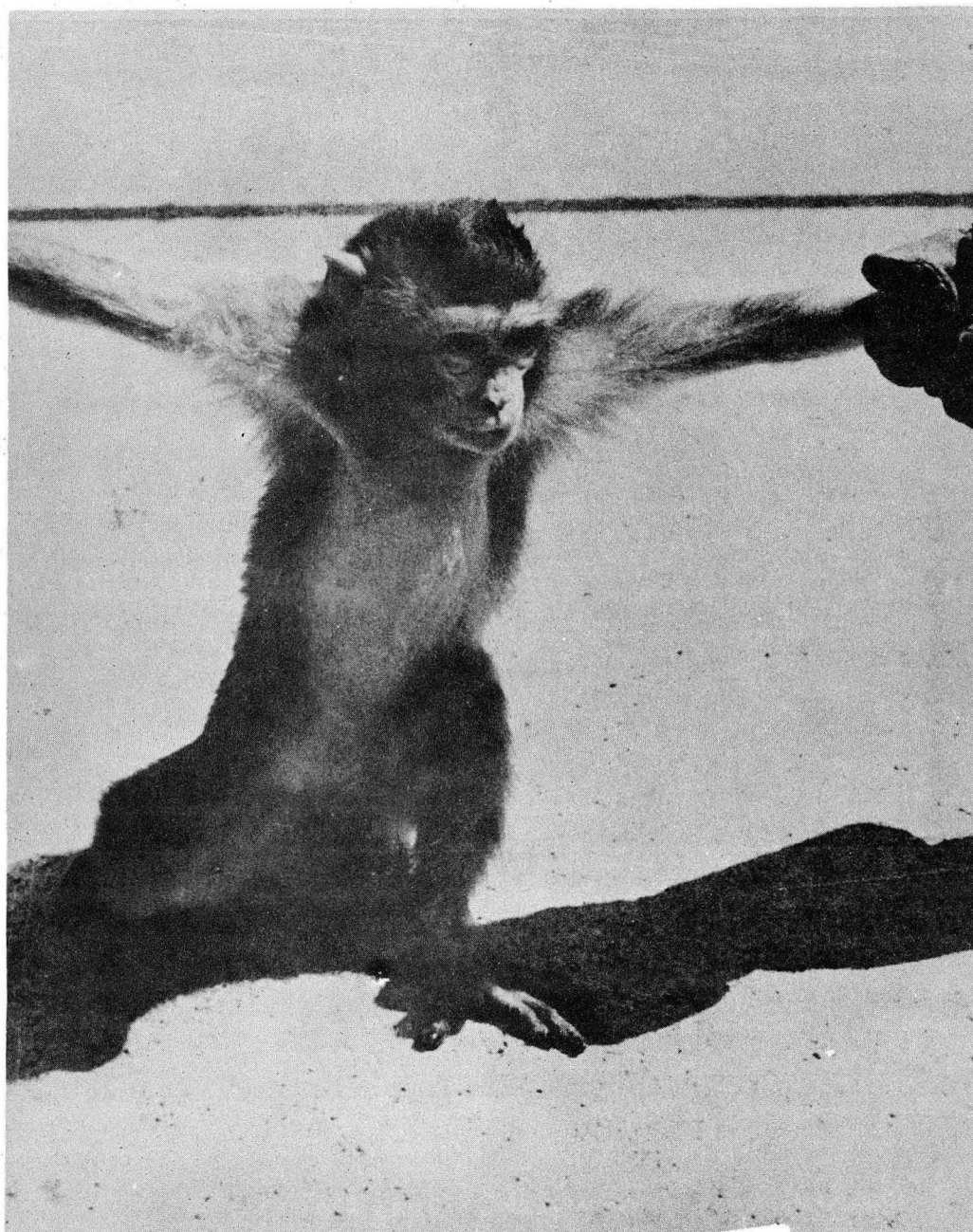
ZN-1181

Fig. 4. Front view of a 2.5-year-old male rhesus monkey, "Squeaky," 23 months after the intraperitoneal injection of $0.36 \mu\text{c}$ of At^{211} per gram of body weight. Note the emaciated appearance, sparseness of hair, and lack of sexual development. At the present time the animal weighs 2.7 kilos.



ZN-1182

Fig. 5. Rear view of a 2.5-year-old male rhesus monkey, "Mike," 23 months after the intraperitoneal injection of $0.36 \mu\text{c}$ of At^{211} per gram of body weight. Note the naked tail and the ruffled appearance of the hair. The animal weighs 3.0 kilos at the present time.



ZN-1183

Fig. 6. Front view of normal male rhesus monkey approximately the same age as those shown in Figs. 2-5. Note the general lithe appearance, the smooth coat and the sharpness of the facial features. Currently, the animal weighs 5.1 kilos.

RADIATION CHEMISTRY

REPORTS ISSUED

During this quarter, the following papers have been published:

"Indirect and Direct Action of Heavy-Particle Radiation on Acetic Acid in Aqueous Solution," by Warren M. Garrison, Winifred Bennett, Sibyl Cole, Herman R. Haymond, and Boyd M. Weeks, issued as UCRL-2631.

BIOLOGICAL STUDIES OF RADIATION EFFECTS

John H. Lawrence, M. D., in charge

Donner Laboratory of Biophysics and Medical Physics
University of California, Berkeley, California

IN VIVO DETERMINATION OF TWO ISOTOPES SIMULTANEOUSLY:

Its Application to the Study of Regional Blood Flow,
Transcapillary Exchange, and Intracellular Penetration Rates

Ernest L. Dobson, George F. Warner, Frank T. Upham,
Caroline R. Finney, and Dorothy M. Anderson

A method for calculating regional blood flow from the rate of disappearance of intra-arterially injected ionic radiosodium has been described previously. Briefly, it consists of monitoring the region supplied by the injected artery with an external counter. Following the injection of a rapidly diffusible ion such as sodium into the brachial artery, a large portion of the labeled sodium has been shown to be temporarily localized in the arm owing to the large sodium pool of the muscle. This is gradually washed out by the blood, and the rate of washing out is a function of blood flow.

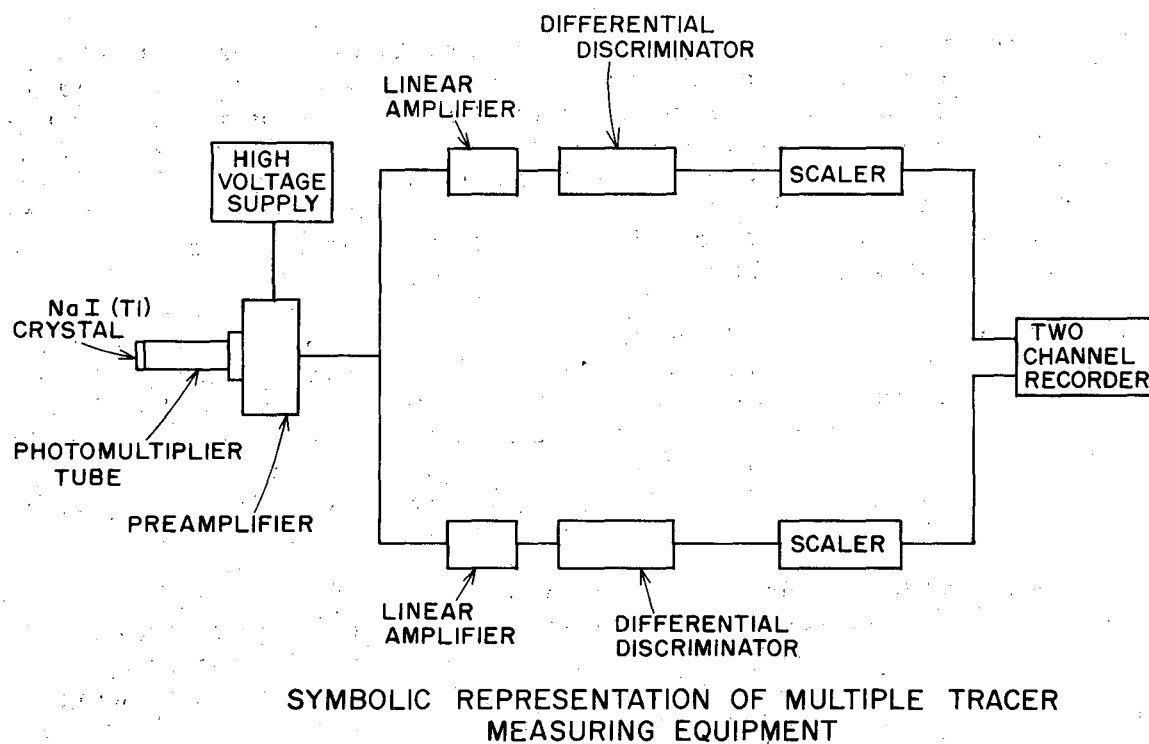
If blood and tissue have the same sodium concentration and a sample of tissue containing radiosodium ion is bathed in an equal amount of blood, one-half of the activity is found in the blood, and therefore, one-half is left in the tissue. If the blood is constantly renewed at a rate such that its volume is replaced once each minute, the activity in the muscle is reduced not to 50% in a minute, but to 37% or $1/e$ of its original level, owing to the logarithmic nature of the process.

In working with this method, it seemed of interest to try to observe more than one isotope simultaneously. Attempts were made to count positron-annihilation radiation from Na^{22} in the hope that this could be observed simultaneously with $\text{I}^{-}(\text{I}^{131})$. The iodide should behave differently following its injection owing to its different distribution in the tissue. (Na^{+} is found principally outside of cells, and I^{-} can penetrate the cell membrane quite readily.) Also the I^{131} can be attached to albumin and thus be kept within the confines of the capillaries themselves. However, the counting efficiency for the positrons was so low that the method was temporarily discarded.

Recently the use of the differential discriminator has been applied to this problem. The apparatus as used is illustrated in Fig. 1. Because of the difference in gamma-ray energies of Na^{24} and I^{131} , the pulse heights generated in a scintillator are different for the two disintegrations. If pulse-height differential discriminators are used the Na^{24} and I^{131} disintegrations observed by the same crystal scintillator can be recorded simultaneously and independently.

In preliminary studies, this technique has been applied to differentiate between the behavior of sodium ion and iodinated albumin. The sodium ion diffuses so rapidly through the capillary membrane that blood flow rather than the diffusion coefficient is the rate-limiting factor in its equilibration between

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MU-8299

Fig. 1. Symbolic representation of multiple-tracer measuring equipment.

blood and body tissues. Iodinated albumin, on the other hand, is such a large molecule that it cannot, except in very limited amount, get out of the confines of the capillary wall.

Figure 2 illustrates the physical picture and the expected character of the disappearance curves if the area supplied by the injected artery is uniform. However, if the capillary bed is not uniform, the disappearance curve is not a simple exponential but a multicomponent logarithmic curve of the form

$$A = A_1 e^{-k_1 t} + A_2 e^{-k_2 t} + A_3 e^{-k_3 t} + \dots$$

Figures 3a and 3b illustrate such a physical setup for two simultaneous labels and the curves derived from it. The curve for the albumin, which is confined to the smaller volumes representing the blood vessels, has the equation

$$A = 70e^{-2t} + 70e^{-1t} + 7e^{-a_1 t}.$$

The curve for the sodium, which mixes in the larger volume, has the equation

$$A = 140e^{-0.1t} + 7e^{-0.01t}.$$

In order to observe a disappearance curve in an animal, one must make a correction for recirculated activity. This can be accomplished by observing the appearance of the recirculated activity in the opposite leg. By subtracting this activity from the observed activity in the injected leg, a difference curve is obtained which represents the net disappearance from the injected side. The appearance and disappearance curves as recorded by the counters is presented in Fig. 4, while the difference curves or net disappearance curves for both the intravascular iodinated albumin and the extravascular iodinated albumin and the extravascular sodium iodide are presented in Fig. 5.

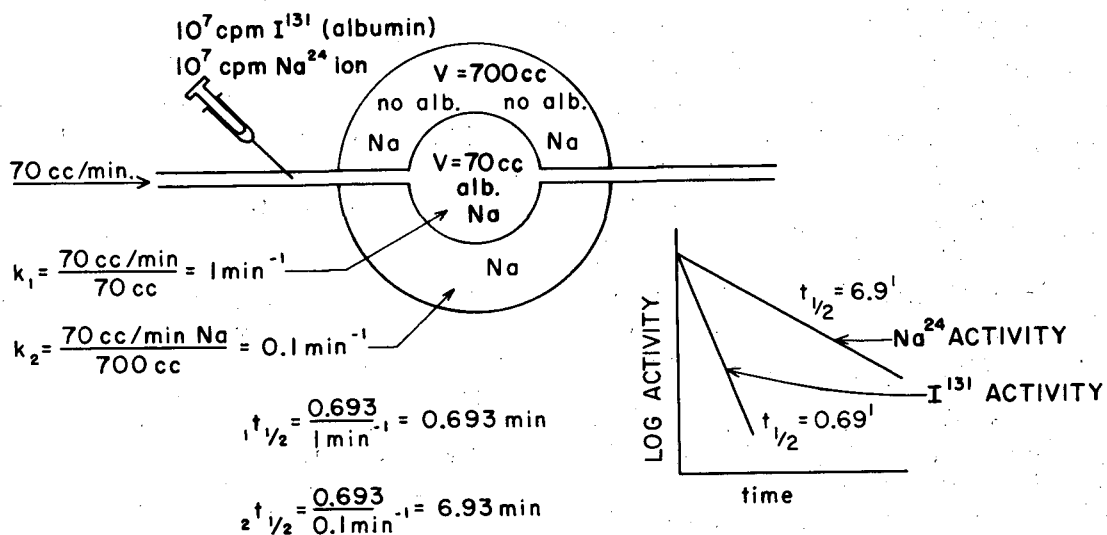
The net disappearance curves can be resolved into their respective components. The magnitudes of these components indicate the relative proportions between poorly and highly vascularized areas within a given tissue, as well as the total blood supply to that tissue.

It is hoped that the comparison of such simultaneous curves of intravascular substances, extracellular substances, and intracellular substances will yield valuable information on transcapillary exchange and intracellular penetration of important metabolites as well as on the regional blood flow.

HUMAN STUDIES WITH RED CELLS LABELED WITH CHROMIUM-51

William E. Siri, Enrique Strajman, and Samuel I. Berlin

These studies were performed during the last three months with three main purposes in mind. First, to study the dynamic aspects of the blood-mixing process for substances nondiffusible into the interstitial fluid. Second, to determine the blood volume in lean human bodies, or in other words the blood volume corrected for total body fat. Third, to determine the life of the red cells.



MU-8297

Fig. 2. A geometrical model of a simple wash-out system in which blood is simultaneously washing iodinated albumin out of a small vascular compartment and sodium-24 out of a larger extravascular compartment. The inset shows the difference between the two wash-out curves for this system.

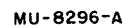
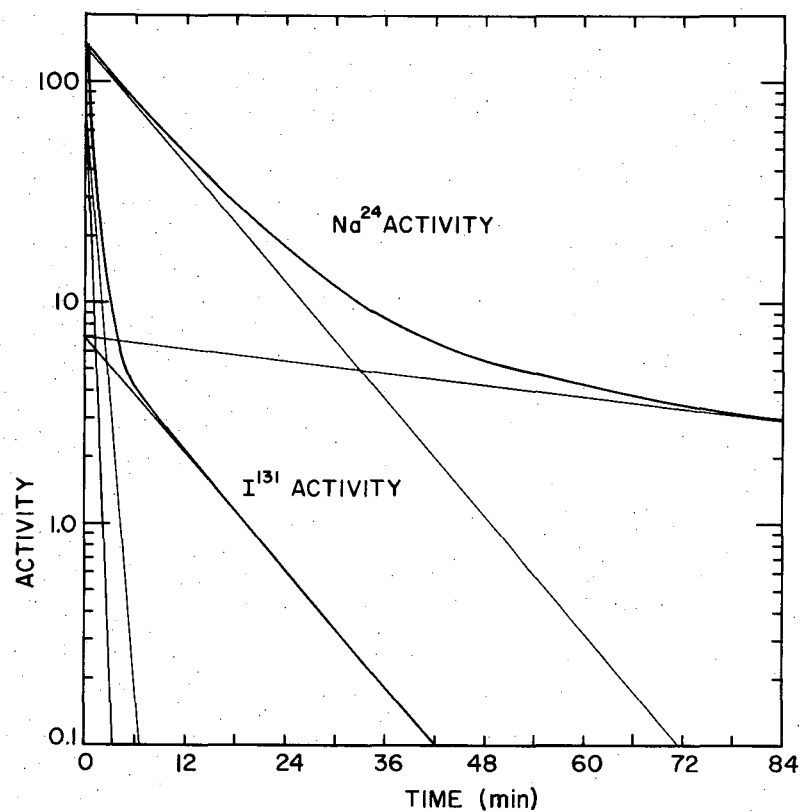


Fig. 3a. A geometrical model of greater complexity than that illustrated in Fig. 2. This model closely approximates the situation that would be encountered in actual muscle.



MU-8296

Fig. 3b. The multicomponent curves derived from the geometrical model of Fig. 3a as they would be recorded by a counter that could see the entire model. These curves have been resolved into their component parts corresponding to the different perfusion areas represented in Fig. 3a.

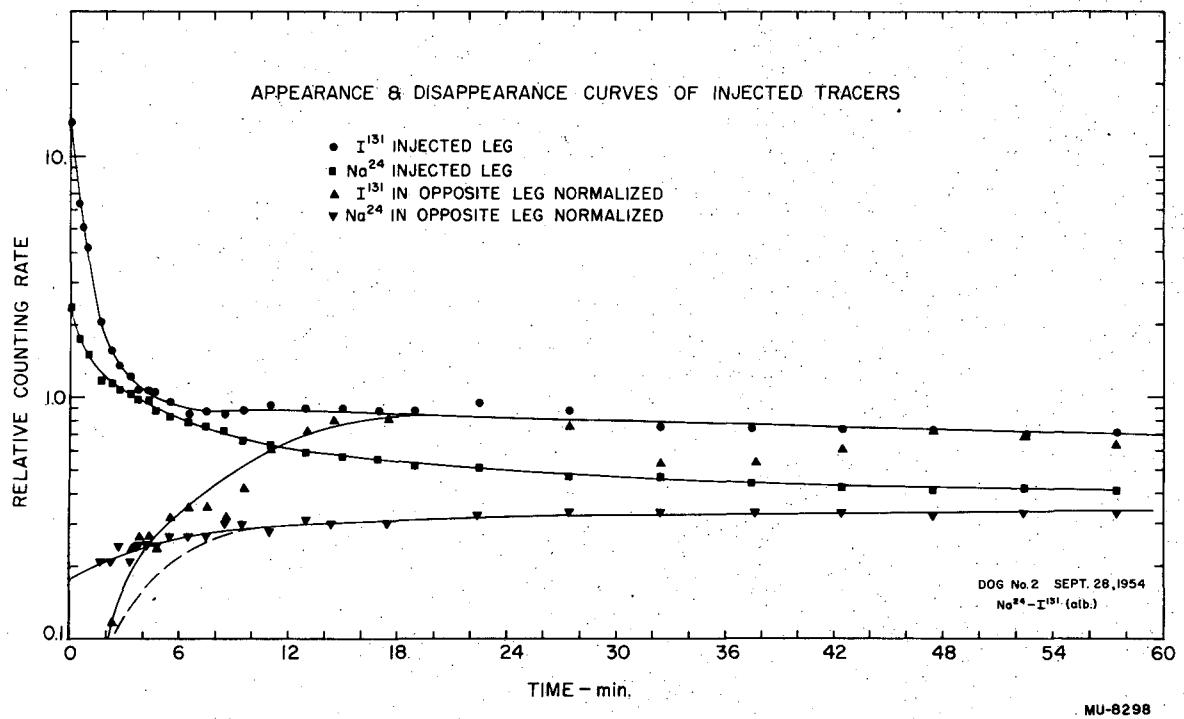


Fig. 4. Appearance and disappearance curves of injected tracers.

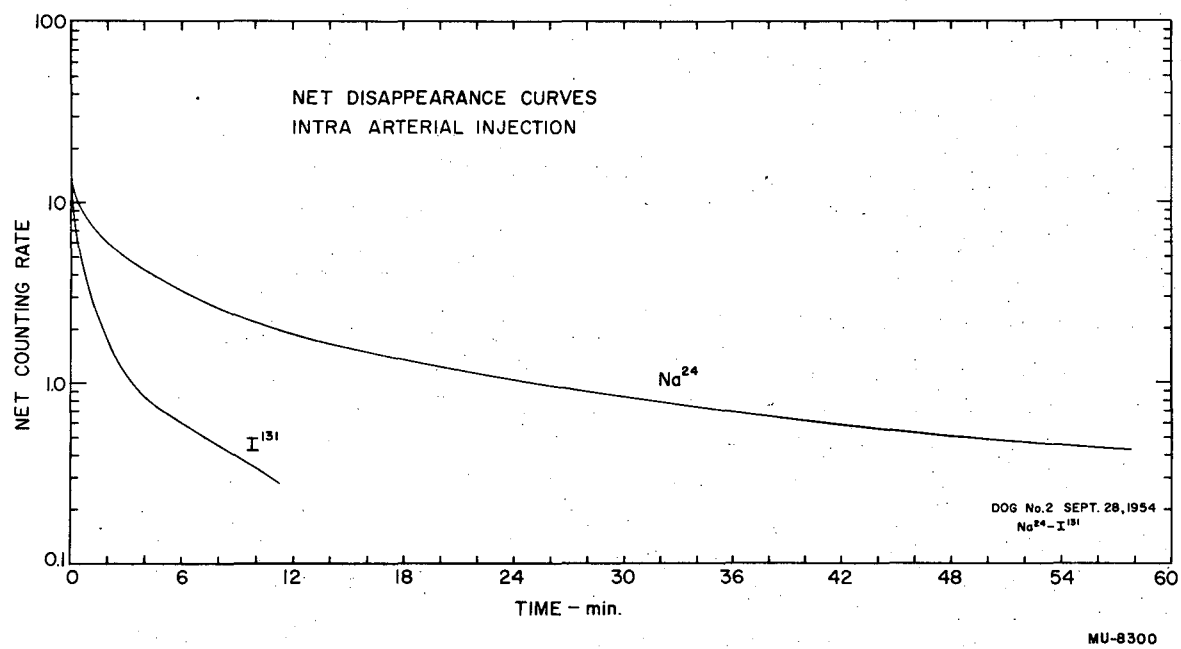


Fig. 5. Net disappearance curves intra-arterial injection.

Subjects

A group of more than 40 young and old normal men and women were studied.

Technical procedure

Ten cc of blood was withdrawn from the subjects and incubated with Cr^{51} . Eight cc of the labeled blood was then injected intravenously into the subject, who was resting in a recumbent position. As many as four scintillation counters were placed around the subject's feet to measure the rates of accumulation in the extremities until mixing was completed. Approximately 90 minutes after injection, a blood sample was taken to determine the blood volume by using the dilution principle. Radioactive water was also injected to determine the total body water, and density measurements were performed in the chamber to determine the percent of body fat. Blood samples were taken weekly to follow the percent of labeled red cells remaining in the circulation.

Results

These studies are practically completed at present. However, the analysis of the data is not finished yet. Only the dynamic studies are reported here.

The mixing of labeled red cells within the blood compartments follows three components. The rates of these components are of about the same order of magnitude as the components found in previous studies with substances diffusible and nondiffusible into the interstitial fluid. Although the statistical analysis has not been completed, it can be postulated that the second component is slowed quite markedly by the aging of the subjects. The slope with aging seems to be very close to the slope obtained with substances such as sodium diffusing into the interstitial fluid. However, it has not been determined yet whether this similarity is statistically significant.

THE RELATIONSHIP OF AGE AND SEX TO THE EARLY MIXING OF SODIUM-24 IN HUMANS

Enrique Strajman

The influence of age and sex on the early dynamic processes of the mixing of Na^{24} in humans observed after the intravenous injection of Na^{24} was determined in the studies reported here.

Na^{24}Cl was injected intravenously in recumbent humans and measured with a scintillation counter over the heart. A total of 133 subjects, men and women, whose ages ranged from 22 to 90 years, were studied. The study was circumscribed to the evaluation of what has been called the second component. This component follows an exponential function whose half time ranged from 15 to more than 100 seconds.

It was observed that the second component is slowed down quite markedly with increased age of subjects. The correlation coefficient r between age

Lawrence

and rate was 0.65, and the variance was 11 seconds. In general, faster rates were observed in women than in men of the same age. This sex difference is statistically significant. The regression line for each sex shows a sex difference of about 5 seconds at the level of 22 years and about 10 seconds at the level of 85 years. The correlation coefficient for each sex separately was better than for both sexes together, 0.79 for men and 0.88 for women.

The interpretation and mechanism of the second component is not as yet well established. However, it might be pointed out that the second component is one of the three components observed in the process of mixing within the blood by a substance that has been intravenously administered. What part of the circulatory system is responsible for slowing down the second component is not very clear at the present time.

At present, a series of measurements is in progress; red cells labeled with chromium-51 are injected intravenously in humans to find out whether any difference is observed in the second component as compared to the sodium, and to determine whether the aging process affects sodium diffusion into the interstitial fluid.

THE INCORPORATION OF PHOSPHORUS-32 INTO DNA OF HYPOPHYSECTOMIZED RATS

Lola S. Kelly

Considerable attention has been devoted recently to the possible role of the anterior pituitary hormones in the cancer process. It therefore seemed of interest to measure the effect of hypophysectomy on the rate of cell renewal in normal tissues.

The incorporation of P^{32} into desoxyribonucleic acid (DNA) has been shown previously to be a convenient measure of cell renewal in a tissue. In this preliminary survey Long-Evans rats were hypophysectomized at about 30 days of age and the incorporation of injected P^{32} into DNA of various tissues was measured one to two months after the operation. Two groups of control rats were included in the experiments. The rats in one group (heavy controls) were the same age as the hypophysectomized animals at the time of measurement (i. e. two to three months old). Those in the other group (light controls) were the same weight as the operated rats (approximately 30 days old).

DNA was isolated from liver, kidney, lung, thymus, spleen, small intestine, and "carcass."* The specific activity of DNA and inorganic phosphate was measured 2, 12, and 24 hours after the intraperitoneal injection of P^{32} .

*"Carcass" was prepared by skinning and decapitating the rat, removing all the internal organs, and grinding in a Waring Blendor. The high figure for incorporation of P^{32} into DNA of this heterogeneous fraction is primarily due to bone marrow.

SPECIFIC ACTIVITIES OF DNA AND INORGANIC PHOSPHATE IN
HYPOPHYSECTOMIZED AND NORMAL RATS

Time after P ³²	2 HOURS			12 HOURS		24 HOURS		
	Light Controls	Heavy Controls	Hypophysectomized	Heavy Controls	Hypophysectomized	Light Controls	Heavy Controls	Hypophysectomized
LIVER								
DNA spec. act.	0.566 ± 0.06 (10)	0.375 ± 0.018 (11)	0.221 ± 0.028 (9)	1.99 ± 0.52 (8)	1.53 ± 0.08 (10)	2.37 ± 0.48 (4)	1.66 ± 0.14 (4)	1.95 ± 0.25 (4)
Inorganic spec. act.	194 ± 8 (10)	426 ± 29 (9)	456 ± 60 (9)	120 ± 6 (7)	150 ± 11 (10)	33.5 ± (2)	74.9 ± 3.2 (4)	76.1 (2)
DNA % Inorganic	0.303 ± 0.04 (10)	0.092 ± 0.006 (11)	0.0624 ± 0.006 (9)	1.63 ± 0.46 (8)	1.04 ± 0.07 (10)	7.11 ± 0.95 (4)	2.24 ± 0.26 (4)	2.04 ± 0.26 (4)
SPLEEN								
DNA spec. act.	13.2 ± 2.3 (3)	8.73 ± 1.07 (14)	3.78 (2)	16.0 ± 2.0 (7)	16.2 ± 2.04 (5)	16.6 (1)	14.6 ± 4.6 (3)	11.7 (2)
Inorganic spec. act.	141 ± 6 (3)	258 ± 9 (7)	279 ± 36 (6)	116 ± 2.2 (6)	121 ± 11 (4)		65.3 (1)	
DNA % Inorganic	7.57 ± 2.5 (3)	3.79 ± 0.7 (7)	1.60 (2)	14.1 ± 1.9 (6)	13.4 ± 1.55 (5)		23.4 (1)	
SMALL INTESTINE								
DNA spec. act.	4.68 ± 0.18 (12)	6.88 ± 0.42 (11)	6.11 ± 0.54 (10)	37.8 ± 2.3 (8)	37.6 ± 2.1 (10)	23.8 ± 0.18 (3)	42.4 ± 2.5 (4)	39.3 ± 3.0 (5)
Inorganic spec. act.		188 ± 17 (6)	309 ± 9 (3)	51.5 ± 3.3 (6)	77.3 ± 12 (6)		67.5 ± 6.6 (4)	
DNA % Inorganic		3.55 ± 0.27 (6)		71.0 ± 2.5 (6)	50.8 ± 4.7 (6)		73.5 ± 9.6 (6)	
CARCASS								
DNA spec. act.	5.24 ± 0.23 (12)	7.91 ± 0.13 (9)	2.48 ± 0.55 (9)	26.9 ± 1.5 (8)	21.3 ± 1.66 (10)	12.5 ± 0.73 (4)	21.4 ± 1.06 (4)	17.7 ± 0.87 (5)
LUNG								
DNA spec. act.	0.474 ± 0.07 (4)	0.934 ± 0.18 (5)	0.786 ± 0.09 (3)	6.52 ± 1.3 (4)	7.53 ± 0.68 (5)	1.32 (1)	6.67 (1)	9.08 (2)
KIDNEY								
DNA spec. act.	0.269 ± 0.03 (6)	0.207 ± 0.013 (5)	0.154 (2)	0.562 ± 0.042 (4)	0.382 ± 0.033 (5)	0.798 (2)	1.04 (1)	0.292 (2)
THYMUS								
DNA spec. act.	6.37 ± 0.33 (4)	9.38 ± 0.44 (11)	8.14 (2)	36.0 ± 2.6 (3)	37.0 ± 1.0 (3)	23.1 (1)	39.0 (1)	43.0 (1)

Specific activities are expressed as counts per mg P divided by counts injected per gm rat. All values have been multiplied by 10². Numbers in parenthesis represent number of determinations. Errors are one standard error of the mean.

The results of this preliminary experiment have been summarized in the table. Specific activities are expressed as counts per mg phosphorus divided by counts injected per gram rat.

It can be seen from the table that there are no major differences in the DNA specific activities among the three groups of rats measured. With the exception of the 2-hour carcass and spleen values the hypophysectomized animals match their age controls very well. However, since there are known to be differences in the metabolism of inorganic phosphate after hypophysectomy, it will be necessary to make a careful study of the specific-activity time curves of DNA precursors for each tissue.

THE TOTAL DNA CONTENT OF LIVERS AND SMALL INTESTINE AFTER WHOLE-BODY X-IRRADIATION

Lola S. Kelly

Paigen and Kaufmann (J. Cell and Comp. Physiol. 42, 163, 1953) reported a marked alteration in the desoxyribose nucleic acid (DNA) content of mouse livers after 600r of x-rays. Eighteen hours after irradiation, the DNA content per mg dry weight was 40% of normal; and 48 hours after irradiation, it was 130% of normal. Since they found only slight changes in dry weight, these results indicated a drastic loss and rapid recovery of DNA per liver. In view of the well-established constancy of DNA per cell, these experiments would imply (a) loss of destruction of over half the cells in the liver, for which there is no histological evidence, or (b) a marked loss of DNA from individual nuclei, which is conceivable in liver cells, since they are known to be polyploid. Furthermore, if the very rapid recovery of DNA content (doubling between 18 and 48 hours) were to occur, one should see a turnover of DNA similar to that found in regenerating liver. We have not seen such an effect on turnover (UCRL-2661, July, 1954), but considered it worth while to repeat the total DNA measurements.

Two experiments were run, using A-strain mice weighing 20.5 to 21.5 g. In each experiment half the mice were irradiated with 800r, and total DNA of livers and small intestines was determined by the method of Schneider. In Experiment I the time interval between irradiation and sacrifice was 17 hours, and in Experiment II it was 24 hours. All mice were fasted for 18 hours before sacrifice. The tissues from control and irradiated mice were carried through all procedures together.

The results are expressed as mg DNA phosphorus and were calculated from the optical densities in the diphenylamine reaction, using a DNA standard of known phosphorus content.

Mg DNA P per liver or small intestine after 800r x-rays

	Time, irradi. to sacrifice	Number of mice	Liver	Small Intestine
Exp. I	controls	7	0.430 ± .014	1.08 - .03
	17 hours	8	0.414 ± .010	0.886 - .019
Exp. II	controls	6	0.351 ± .006	1.07 - .01
	24 hours	6	0.344 ± .006	0.688 - .025

The results of this experiment do not confirm the observations of Paigen and Kaufmann. In both Experiments I and II the DNA content of the irradiated livers is very slightly lower than the control livers, but the differences are not statistically significant. We have no explanation for this except that these experiments were not performed on the same group of mice nor at the same time.

The DNA content of the small intestines dropped markedly after irradiation. This was to be expected from histological observations and earlier measurements of other chemical constituents.

QUANTITATIVE CONCEPT OF THE PATHOGENESIS OF CORONARY DISEASE

John W. Gofman

Extensive statistical calculations have been made in the effort to determine the major operative mode by which serum lipoproteins are related to coronary atherosclerosis and coronary disease. The conclusions reached indicate that whereas serum lipoprotein measurements provide an excellent discrimination between individuals with coronary disease and those without overt coronary disease if the populations are controlled with respect to the age variable, the discrimination cannot be directly extended to groups of variable ages without specifically taking the age variable into account. Consideration of how this age variable may be taken into account has led to evaluation of the following concept of the origin of coronary disease. The disease is being regarded as an accumulative process that involves two major factors, the rate of accumulation and the time over which any particular rate of accumulation operates. The rate factor may be considered as proportional to an "effective" serum lipoprotein concentration, the term "effective" indicating that cognizance must be taken of differential significance of the various lipoprotein classes. This effective concentration may be represented as a term α , which accounts for the differential significance of the lipoproteins. Then we may write:

$$\text{accumulated coronary disease} = k \int_{t_1}^{t_2} \alpha dT.$$

If we regard t_1 as birth and t_2 as the time in years elapsed since birth, the integration yields the total accumulated coronary disease. The validity of this concept has been checked in two ways, (a) comparison of predicted accumulation of coronary disease with autopsy-measured accumulation, (b) comparison of predicted mortality rates from coronary disease with those to be obtained from vital statistics.

Such comparisons have been calculated now and provide excellent confirmation of the validity of the concept, at least as a first-order approximation to the evolution of coronary disease. The implications of the integral approach to the problem of coronary disease are great, in that we are led to the conclusion that potential prophylaxis and therapy must be directed toward suppression of growth of the integral itself, rather than merely to immediate suppression of the α value. This means early recognition of individuals with elevated lipoprotein, and hence elevated α values, and effective suppression of the α values to prevent rapid growth of the integral of coronary disease accumulation. It renders more imperative the understanding of the basic disorders of fat and sterol metabolism that lead to faulty lipoprotein transport patterns. Our studies of the metabolism of these substances, utilizing tritium and C^{14} labeling, are being directed toward understanding the metabolic basis for disturbed lipoprotein transport. Some of the results obtained with tritium-labeled cholesterol have been reported previously.

Analogous studies with tritium-labeled fatty acid are in progress and will be reported later.

HEMATOLOGICAL EFFECTS OF LOW-LEVEL IRRADIATION

R. Lowry Dobson

Additional blood counts and films were obtained from cyclotron personnel for analysis of the hourly and daily variation of unusual cell types in response to known "subtolerance" doses of ionizing radiation. The data examined so far suggest a biphasic rise in double nucleated lymphocytes following an exposure. Details of this response are being worked out.

RADIATION INJURIES

R. Lowry Dobson

Two chemists who sustained radiation burns to the fingers earlier in the year have been followed, and periodic photographs of the hands have been taken. The lesions have healed well. However, in one area of finger skin which received a particularly large dose, a small horn has developed. It is planned to have this surgically removed and examined.

CIRCULATION STUDIES

R. Lowry Dobson

Abnormal circulation dynamics involving the spleen are being investigated in a number of patients. The circulatory mixing rates and blood volumes of one such patient, a candidate for splenectomy, were determined before and after x-ray therapy to the spleen. The mixing picture improved after treatment. This patient has now had a splenectomy and will be studied further after convalescence.

BACTERIAL RADIOBIOLOGY

R. Lowry Dobson

Escherichia coli, strain B/r, can partially recover from the lethal effects of x-rays if incubated in the presence of nutrient broth subsequent to irradiation. This effect is enhanced by incubating the irradiated cells at temperatures below those which are optimum for growth as shown by Stapleton. It has been found in this laboratory that if organisms are grown in a synthetic medium the ability of the cells to utilize the nutrient broth for recovery is markedly reduced. The synthetic medium was composed of inorganic salts with glucose as an energy source. The organisms do show a slight recovery with the maximum effect at 18° C. This recovery is independent of the presence of the special substance required in cells grown in nutrient broth. Recovery under these conditions is essentially the same whether the irradiated cells are subsequently grown in synthetic medium or nutrient broth. The magnitude of recovery in synthetic-medium-grown cells is considerably less than that shown by nutrient-broth-grown cells. X-ray survival curves of cells from 24-hour cultures from both types of medium are of the exponential type. The ratio of slopes of the survival curves of nutrient-broth cells incubated at 18° C and 38° C is 1.5. The ratio of the slopes of synthetic-medium-grown-cell curves is of the order of 1.1 under the same temperature conditions. Therefore, it appears that some essential factor is missing from the synthetic medium that would enable the cells to develop the capacity for recovery. Further studies are being carried out to determine the nature of this factor.

EARLY CARDIOVASCULAR DISTURBANCES
FOLLOWING THERMAL INJURY

Ernest L. Dobson and George F. Warner

Immediately following severe thermal injury in the anesthetized dog, a marked decrease in cardiac output has been observed. This marked decrease, to as low as 1/7 of the prescald value, occurs within a few minutes and does not result in a consistent decrease in pulse rate or mean arterial pressure. The EKG and pulse-pressure contours show erratic but marked changes. The severe drop in cardiac output is accompanied by a decrease in the circulation to the liver. It seems of importance that the circulation to the liver--which normally represents a large part of the cardiac output--is reduced less than

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the cardiac output itself, with the consequence that the circulation to other areas such as the brain and kidney is probably reduced by a still larger fraction. The physiological effects of the prolonged anoxia which must accompany such a marked decrease in blood flow may be responsible for some of the later derangements seen in severely burned patients, which have been attributed to toxemias and other unknown factors. Infusion of plasma or dextran has served to return cardiac output to normal, at least temporarily, which indicates why a great advantage may be gained by the very early preshock transfusion treatment of severely burned patients.

HEALTH CHEMISTRY

Nelson B. Garden

The quarterly progress report for the period October, November, December 1953 described a large-scale operation which took place in Bldg. 106, Livermore, with equipment designed and assembled by Health Chemistry, for processing material that contained both multicurie quantities of fission products and multicurie alpha-emitting substances. As noted at that time, an operation of this type consumes a great part of the effort of the Equipment Development and Airborne Activity Control groups and places an extra burden on the other Health Chemistry groups. During the quarter covered by this report a similar run was made in Bldg. 99B, Livermore. For this recent operation new equipment was built, incorporating improvements that had become obvious from the first run; among them was a modified ventilation system, which allowed the enclosed air in the processing boxes, at slightly negative pressure, to have a slow leak rather than to completely confine it and accumulate it in expandable receptacles.

Three chemistry boxes and associated equipment were set up and tested and the actual run was completed during this period. Significant points of interest are: the chemical operation was highly successful and the yield and purity of the desired product were excellent; there were no appreciable personnel exposures, and the air and surface contamination were negligible; the cost of equipment and time required were greatly reduced from the similar operation of a year ago; the flowsheet, cave design, operator technique, and process equipment were of sufficient excellence to warrant development of standard equipment and procedure from the results of the run. It should be particularly noted that the cave front was redesigned to accommodate a new type of manipulator unit known as the castle manipulator; this new tong-holder system replaced the previously used ball-socket accommodation for tongs, and it certainly appears that the castle manipulator offers advantages over the ball-socket arrangement.

A major portion of the effort of the whole Health Chemistry group has been in moving all chemistry work on the Hill (including the entire work in Bldgs. 4 and 5 and that on the third floor of Bldg. 50) to the newly completed chemistry building, Bldg. 70, and in setting up Health Chemistry facilities in that building. The critical feature that determines the completion of the ultimate relocation is the fitness of the ducting manifold system to which the gloved boxes and hoods are connected, and this feature is rapidly being worked out. The conception of and plans for a general box laboratory for processing alpha emitters was made some two and a half years ago, and a reappraisal of the requirements has been necessary, for during this period the number of boxes in use has increased far more than was anticipated. Furthermore, present experiments with transplutonium materials are extremely sensitive (because of the small quantities worked with) to the presence of any emanation, so it is possible that an "emanation box" laboratory and "nonemanation" one may have to be set up separately.

A modification of the heating and ventilating system may have to be effected, for the large number of hoods presently required overloads the system. A possible solution being considered is to put a larger percentage of

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the hoods on a two-speed system--high and low.

Plans are being made or being executed to provide protective plastic coverings of various sorts to certain furniture surfaces and to all porous surfaces, such as cement, so that should some untoward incident make it necessary, decontamination may be done with ease.

For the 60-inch cyclotron bombardment work on transplutonium elements, an internal beam probe has been developed, with improved collimation features. Beam modification over the recent months has resulted in very highly gamma-active targets, necessitating further consideration to the safety aspect of this work. Features have been achieved which allow quicker disassembly of both this internal probe and the more commonly used pistol-grip target holders.

The Idaho Falls Materials Testing Reactor napkin-ring-type irradiation (so called because of the cylindrical features of this capsule, incorporated for the dissipation of heat during irradiation), processed primarily during the previous quarter and described in the report for that period, was completed, the work having taken place in the 6-inch lead cave in Bldg. 5. The final scavenging operations were finished, and the researchers concerned were highly gratified at the excellent yield obtained in this experiment. Members of the Health Chemistry group effected the decontamination of salvageable equipment and the 6-inch lead cave area and readied them for subsequent work.

The Health Chemistry group created a gloved-box setup, plus auxiliary equipment, for use in synthesizing organic sulfur-35 compounds, wherein quantities of the order of 100 millicuries of sulfur-35 were handled; previously only very small quantities of this isotope have been worked with. While the work was accomplished successfully, it was found that the sulfur tended to leak through the gloves, a difficulty meriting attention before subsequent work of a similar nature takes place.

Health Chemistry members acted as consultants and assistants in the packaging, loading, and shielding of a 1,000-curie barium-lanthanum source received from Los Alamos by a Physics group. They also prepared a source to be used for calibration in this work.

Active targets from the Bevatron appeared for the first time during this quarter; Health Chemistry has been involved only in the transportation of these targets to the laboratories; no special target holder or probe design has been indicated as yet.

Successful encapsulation of multicurie quantities of transuranic materials for pile irradiation was accomplished through the efforts of the Equipment Development group in setups at Livermore.

The very desirable requirement that liquid active waste be solidified in some form before incorporating it in concrete has been met with present satisfaction through the use of commercial gels, and the liquid wastes are now treated as they accumulate, at weekly intervals, and made ready for disposal at sea. Several thousand gallons have been processed and disposed of in this manner.

The Health Chemistry source-preparation group (preparing radioactive sources to specifications on request) has been employing with success a vacuum-flashing method of creating even layers of uranium, titanium, and other metals desired for source material; this method is an improvement over electroplating and other techniques used previously. Approximately twenty-five special sources were made to order for chemists and physicists during this period.

In the work on the testing of materials for potential use as protective coatings, one material in particular was found to be at least comparable to 4A Plastic, which has been in use at Berkeley for some time for gloved-box coatings. Its dull color, however, is an adverse feature, as white is the most desirable color in gloved boxes for visibility reasons.

The Airborne Activity Control Group was mainly concerned during this period with the Livermore operation, mentioned in the first paragraph, and the preparation and assessment of the ventilation system in Bldg. 70. Routine air sampling and analysis, and equipment installation and refurbishing continued, as did the training program for new personnel in this group. Members of the group were also engaged in collection, analysis, interpretation, and reporting presence of toxicologic material in the NPG tests during this period, and gave recommendations for its control.

HEALTH PHYSICS

Burton J. Moyer

STATISTICAL SUMMARY OF MONITORING PROGRAM

Survey Instruments Maintained

β - Ionization Chamber	105
I. D. L. Portable Survey Instruments	23
Cutie Pies	3
Recording - Intensity Meters	32
Victoreen Proteximeters	3
Fast-Neutron Proportional Counters	8
Slow-Neutron Proportional Counters	15
Fast-Neutron Proportional Counters (Portable)	21
Slow-Neutron Portable Units	16
Balanced Chamber--Fast Neutron--Portable.	3
Special Tissue Wall Survey Instrument.	1

Personnel Meters in Use

Total Personnel Covered with Film Badges	3,256
Total Man-Days Coverage with Pocket Chamber	8,331
Total Man-Days Coverage with Pocket Dosimeters.	8,331
Total Man-Days Coverage with Pocket Chambers (S. N.)	8,168

Cases of Weekly Exposure Above 0.3r

<u>Weekly film expos. above</u>	<u>184" Area</u>	<u>60" Area</u>	<u>Lin. Acc.</u>	<u>Chem.</u>	<u>Other</u>	<u>Total</u>
0.3	0	19	0	17	7	43
0.5	0	6	0	6	3	15
1.0	0	0	0	2	0	2
1.5	0	0	0	1	0	1
2.0	0	0	0	1	0	1
2.5	0	0	0	1	0	1
3.0	0	0	0	0	0	0