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October 8, 1954

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I. THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

J. G. Hamilton

Project 48A-I

Radioautographic Studies

Radioautographic studies of the long-lived fission products and the actinide elements are being continued. Some excellent radioautographs of actinium (Ac^{227}) in adult rats have been obtained following the adequate aging of the bone sections to permit the establishment of full equilibrium of the actinium with its two long-lived decay products, notably radio-actinium (Th^{227}) and Ac(X) (Ra^{223}). At the same time, of course, the radioactive atoms of these two descendants of actinium which were present in the original solution injected into the animals, had fully decayed when the radioautographs were set up. Thus the radioautographic pattern seen after 100 days of aging of the specimens is a true picture of the distribution of actinium in bone. As might be predicted both on the basis of similarity of chemical properties and certain metabolic characteristics, deposition was confined to the region of the osteoid matrix and in the immediate vicinity of the small blood vessels of the cortical bone. It will be recalled that this characteristic of deposition in the region of the small blood vessels of the cortical bone has been observed with cerium, element 61, americium, and curium.

Earlier and quite unsatisfactory radioautographic studies with zirconium (Zr^{95}) were repeated using normal adult rats and the distribution of this radio-element in bone was observed to be essentially indistinguishable from that found with thorium and plutonium in tha' deposition was limited exclusively to the superficial coverings of the bone and the region of the trabeculae. There was no discernible degree of deposition about the small blood vessels of the cortical bone that has been seen in the group of five elements listed above. A number of quite satisfactory radioautographs of columbium (Cb^{95}) have been obtained and here the pattern appears to be very much like that of zirconium as well as thorium and plutonium. This finding was not predicted inasmuch as columbium behaves rather differently than these other radio-elements in that its deposition in bone is not prolonged as compared to yttrium, zirconium, the lanthanide rare earths, and all of the actinide series with the exception of uranium. Unfortunately, the relatively short half-life of this radio-isotope of columbium does not make possible longterm studies to investigate possible changes of its distribution in the bone as this radio-element leaves the skeleton.

We have secured a sample of Eu^{154} of very high specific activity which is to be employed to investigate the distribution of this radio-element in the skeleton by means of the radio-autographic technique. At the same time, the studies are now underway with yttrium (Y^{88}) in order to secure some satisfactory distribution patterns of this substance in bone. A preparation of Pa^{233} for radioautographic experiments is under way.

Tracer Studies

Actinium. The 1 and 4 day intramuscular tracer studies with Ac^{227} have been completed, the samples having been counted 113 and 126 days respectively after the sacrifice of the animals. Table I. This was done to permit the radio-actinium and Ac(X) present in the injected solutions of actinium at the time of administration to decay away and for these two radio-isotopes to grow into full equilibrium from the actinium in the various tissues and excreta. The significant observations to be made are that the behavior of actinium following parenteral administration is essentially the same as that noted with the four lanthanide rare earths studied to date, namely, lanthanum, cerium, praseodymium, and element 61; and the last two members of the actinide series, americium and curium. These common metabolic properties have also been demonstrated in the radio-autographic studies described in the preceding sections. Absorption from the digestive tract of actinium administered as a solution of $AcCl_3$ was found to be less than .01 percent of the dose given.

Radio-Zirconium. The early parenteral studies with carrier-free radio-zirconium have been repeated in view of the relatively unsatisfactory results obtained in the experiments done several years ago. It will be seen that the skeleton is the chief organ of accumulation both on a per gram and per organ basis and that up to the 32 day interval, there is relatively little loss from that structure. In this particular series of experiments the carrierfree preparation of Zr^{95} was prepared with the addition of a small amount of citric acid in order to keep the zirconium in solution. Table II.

Technetium. The tracer studies with technetium have been completed. The isotope employed for these experiments was the 110 day period, as yet not assigned and produced by the deuteron transmutation of molybdenum. In view of the volatile characteristics of most technetium compounds, the short half-life, and the soft electron radiation, the samples were counted wet using the gamma rays as an index of the quantity of technetium present and providing a filter to cut out all of the electrons. The 1, 2, and 4 day intramuscular studies and the 4 day stomach tube experiments are shown in Tables III and IV. It will be seen that technetium is excreted with extraordinary speed, the kidneys being the chief channel of excretion and that most of the excretion is completed within the first 24 hours. The kidney demonstrates the highest degree of concentration in any of the soft tissues; the one high value noted at 2 days in the gastro-intestinal tract was probably due to technetium in the feces present in the large intestine. It will be noted that the material leaves the kidney with a fair degree of rapidity and the 4 day value is approximately one-half that on the 1 day value. The oral administration of technetium is followed by the absorption of the significant fraction of this radio-element. On the basis of the content in the liver and kidney, as well as the fraction in the urine, an estimate can be made that something of the order of 25 per cent to 50 per cent of the administered dose was absorbed by way of the digestive tract.

Radio-Rubidium. Preliminary tracer studies with carrier-free radio-rubidium have been undertaken. Rb^{86} was the isotope employed and it was prepared by the Sr-d-α reaction. The distribution of this radio-element at 4 days and 16 days, following intramuscular injection resembles quite closely the behavior of cesium. In most

TABLE I

THE METABOLISM OF Ac^{227} IN THE RAT 1 AND 4 DAYS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF A SOLUTION OF $AcCl_3$ IN ISOTONIC SALINE

	1 Day		4 Days	
Tissue	% per organ	% per gram	% per organ	% per gram
Heart	.38	.53	.16	.18
Lungs	.34	.25	.19	.13
Spleen	.09	.19	.14	.19
Blood	1.34	.09	.14	.01
Liver	46.5	6.46	46.7	6.58
Kidney	2.87	1.72	.64	.40
Adrenals	<.01	<.4	<.01	<.4
Thyroid	<.01	<.5	<.01	<.5
Lymph Gland	.03	.48	--	--
Pancreas	.06	.18	.02	.03
Brain	.03	.01	<.01	<.01
Fat	--	.06	--	--
Stomach	.41	.28	.18	.08
Small Intestine	1.15	.22	.83	.10
Large Intestine	1.09	.25	.82	.11
Bone	26.8	2.34	34.7	2.05
Muscle	7.52	.06	4.40	.03
Skin	2.28	.06	1.77	.06
Urine	1.06	--	.24	--
Feces	7.86	--	9.13	--

TABLE II

THE METABOLISM IN THE RAT OF CARRIER-FREE Zr^{95} 1, 4, AND 32 DAYS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF A SOLUTION OF ZIRCONIUM IN ISOTONIC SALINE

	1 Day		4 Days		32 Days	
Tissue	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.56	.71	.23	.32	.15	.21
Lungs	1.42	.90	.88	.65	.63	.33
Spleen	.43	.47	.65	.73	.50	.58
Blood	18.2	1.46	6.35	.45	.47	.04
Liver	8.17	.99	6.57	.89	2.88	.30
Kidney	2.14	1.14	4.31	2.37	2.34	1.13
Adrenals					.04	.54
Thyroid					.04	.33
Pancreas	.16	.25	.15	.24	.22	.22
Brain	.06	.04	.02	.02	<.01	<.01
Fat		.15		.21	.09	.09
G.I.	9.97	.85	3.52	.16	1.52	.12
Bone	20.8	1.39	34.9	3.53	36.1	1.68
Muscle	16.5	.18	13.7	.13	6.54	.06
Skin	14.8	.46	8.88	.24	7.27	.21
Testis	1.83	.64	1.69	.76	1.63	.57
Urine	2.70		2.37		6.86	
Feces	2.04		15.4		32.7	

TABLE III

THE METABOLISM OF THE 110 HOUR Tc IN THE RAT 1, 2 AND 4 DAYS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF A CHLORIDE SOLUTION OF Tc IN ISOTONIC SALINE

	1 Day		2 Days		4 Days	
Tissue	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	<.004	<.007	<.001	<.002	<.005	<.009
Lungs	.085	.056	.087	.057	.074	.049
Spleen	.011	.010	<.005	<.007	<.005	<.005
Blood	.072	.007	.051	.005	<.009	<.001
Liver	.31	.041	.25	.046	.13	.016
Kidney	.59	.35	.47	.33	.32	.19
Adrenals	<.002	<.032	<.002	<.030	<.005	<.10
Lymph Gland	<.001	<.020	<.002	<.040	--	--
Pancreas	.007	.008	<.005	<.006	<.005	<.006
Brain	.005	.003	<.002	<.001	<.005	<.003
Fat	--	.009	--	.006	--	.003
G.I.	.92	.056	6.44	.45	.097	.006
Bone	.20	.008	.16	.006	.060	.002
Muscle	.21	.003	.27	.003	.082	.001
Skin	.49	.019	.67	.026	.74	.026
Fetus	.037	.009				
Urine	83.1	--	79.4	--	70.9	--
Feces	14.0	--	12.2	--	27.6	--

TABLE IV

THE METABOLISM OF THE 110 HOUR Tc IN THE RAT 4 DAYS FOLLOWING THE ORAL ADMINISTRATION OF A CHLORIDE SOLUTION OF Tc IN ISOTONIC SALINE

Tissue	% per organ	% per gram
Heart	.003	.003
Spleen	.003	.003
Blood	.012	.001
Liver	.075	.009
Kidney	.160	.087
Pancreas	.005	.008
Brain	.005	.009
G.I.	.054	.003
Bone	.06	.003
Muscle	.11	.001
Skin	.89	.030
Urine	20.7	--
Feces	77.2	--

chemical properties rubidium and cesium are very much alike and it is to be expected that their metabolic characteristics would be similar. The distribution of the radio-rubidium following administration by stomach tube was essentially the same as was observed for the intramuscular studies at the same time interval. I appears that the absorption of rubidium from the digestive tract is essentially 100% of the administered radio-element. See Tables V and VI.

Radio-Germanium. A rather extensive series of tracer studies have been completed with carrier-free radio-germanium which was made by the transmutation of gallium by 20 Mev deuterons. The 40 hour Ge^{71} was the isotope employed for these studies. The outstanding characteristic of germanium is its extraordinarily high rate of elimination following intramuscular injection there being approximately 75 per cent eliminated within 4 hours and with the kidneys acting as the chief channel of elimination. The only organ to show any appreciable concentration is the kidneys and here the retention remained fairly constant between the first and fourth days. The relatively short half-life of the germanium isotopes employed does not make it possible to continue the experiments for significantly longer time intervals. It is of interest to note that the metabolism of germanium and technetium are very much alike although their chemical properties differ to a considerable degree. No appreciable absorption of germanium took place from the digestive tract following administration of this material by stomach tube and in this regard it behaves very differently from technetium. Judging from very low concentration of Ge^{71} in the kidney following stomach tube administration, it would appear that absorption from the digestive tract was less than 1% in this experiment. See Table VII.

Beryllium. It will be recalled that a number of tracer studies were done in the past with carrier-free Be^7. This radio-element is made either by the deuteron or proton transmutation of lithium. Due to the fact that Be^7 decays by orbital electron capture and that only 10 per cent of the total disintegrations result in the release of gamma rays, the problem of radioactive contaminants is of a serious nature. It should be recalled that the average Geiger counter has about a 1 per cent efficiency for counting gamma rays as compared to beta radiation and on top of this factor, only 10 per cent of the Be^7 disintegrations result in the emission of gamma rays; the remaining 90 per cent of the disintegrations are associated with presumed neutrino emission and are hence not detectible. The usual methods for chemical purification of beryllium from other elements, such as the chloroform extraction of the basic acetate, do not work well with carrier-free beryllium. Hence, in the past we were troubled with unknown amounts of radioactive contaminants which obviously would prejudice the result of the experiments. In the last series of Be^7 studies recently initiated, spectroscopically pure lithium metal was bombarded with 10 Mev protons instead of deuterons and the target was subjected to a very carefully executed series of radio-chemical procedures. The net result of this was isolation of the preparation of a specimen of carrier-free Be^7 in which a lower limit of 1 per cent of radioactive impurities was estimated. A decay curve gave a figure of 52 days for the half-life which has been recently quoted as the most exact figure for this value. In addition, absorption curves of the gamma rays in lead agreed with published values within 5 per cent. Table VIII shows the results of the 1 and 4 day intramuscular studies in which it is apparent that roughly one-third of the Be is fixed in the skeleton and most of the remainder is rather rapidly eliminated chiefly by way of the urine. In complete data at the 16 and 64 day intervals indicates that retention by the skeleton of this radio-element is prolonged.

Cadmium. The results of the carrier-free tracer studies with carrier-free Cd^{109} are given in Table IX. The outstanding characteristics of the metabolism of this element in the carrier-free state, following intramuscular administration, is the high degree of localization and prolonged retention in the liver and kidney. The degree of deposition in other soft tissues and the skeleton is considerably less but in general retention is also prolonged. It is of interest to note that the

TABLE V

THE METABOLISM OF CARRIER FREE Rb^{86} IN THE RAT FOLLOWING THE INTRAMUSCULAR INJECTION OF A SOLUTION OF RbCl IN ISOTONIC SALINE

	4 Days		16 Days	
Tissue	% per organ	% per gram	% per organ	% per gram
Heart	.29	.34	.13	.15
Lungs	.56	.32	.31	.15
Spleen	.41	.48	.19	.21
Blood	3.04	.20	1.47	.09
Liver	4.84	.50	2.84	.23
Kidney	.68	.35	.36	.16
Lymph Glands	--	--	.04	.21
Pancreas	.33	.77	.17	.26
Brain	.29	.19	.15	.10
Fat	--	--	--	.03
Teeth	.03	.11	<.01	<.06
Stomach	.43	.14	.41	.06
Small Intestine	3.48	.43	1.02	.10
Large Intestine	1.20	.19	.84	.08
Bone	14.4	.98	7.90	.12
Muscle	43.6	.35	22.5	.18
Skin	4.09	.10	2.73	.07
Eyes	.06	.15	.02	.06
Gonads	1.21	.43	.66	.18
Urine	16.5	--	48.9	--
Feces	4.30	--	9.34	--

58.24
41.76

TABLE VI

THE METABOLISM OF CARRIER-FREE Rb^{86} IN THE RAT 4 DAYS FOLLOWING THE ORAL ADMINISTRATION OF A SOLUTION OF RbCl IN ISOTONIC SALINE

Tissue	% per organ	% per gram
Heart	.30	.33
Lungs	.74	.35
Spleen	.58	.51
Blood	3.01	.20
Liver	4.41	.42
Kidney	.87	.37
Pancreas	.39	.45
Brain	.37	.23
Fat	--	.03
Teeth	.04	.14
Stomach	.68	.22
Small Intestine	2.17	.26
Large Intestine	1.74	.18
Bone	14.9	.81
Muscle	41.1	.37
Skin	5.79	.13
Eyes	.08	.19
Gonads	1.32	.43
Urine	15.3	--
Feces	6.03	--

TABLE VII

THE METABOLISM OF CARRIER-FREE Ge^{71} IN THE RAT 4 HOURS, 1 DAY, AND 4 DAYS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF A SOLUTION OF $GeCl_4$ IN ISOTONIC SALINE

	4 Hours		1 Day		4 Days	
Tissue	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.06	.06	.03	.04	< .01	< .01
Lungs	.17	.09	.03	.02	< .01	< .01
Spleen	.09	.12	.04	.06	.02	.03
Blood	.76	.04	.15	.01	.15	.01
Liver	2.39	.23	.81	.09	.46	.05
Kidney	2.67	1.16	1.76	.86	1.09	.61
Pancreas	.06	.12	< .01	< .02	< .01	
Brain	.04	.03	< .01	< .01	< .01	
Fat	--	.03	--	< .01	--	< .01
Stomach	.27	.08	.17	.08	.03	.02
Small Intestine	3.78	.30	.63	.07	.05	.01
Large Intestine	1.34	.33	.45	.19	.04	.01
Bone	5.40	.27	2.73	.13	.37	.01
Muscle	5.81	.04	2.75	.02	.50	.005
Skin	2.49	.05	.88	.02	.49	.02
Caecum	.30	.15	.59	.21	.04	.03
Gonads	.06	.03	.02	< .01	.02	< .01
Urine	71.2	--	73.8	--	90.1	--
Feces	2.94	--	15.1	--	6.75	--

TABLE VIII

THE METABOLISM OF CARRIER FREE Be^7 IN THE RAT 1 AND 4 DAYS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF A SOLUTION OF $BeCl_2$ IN ISOTONIC SALINE

	1 Day		4 Days	
	% per organ	% per gram	% per organ	% per gram
Heart	.08	.08	.08	.10
Lungs	.56	.20	.39	.16
Spleen	.11	.17	.23	.31
Blood	1.99	.14	2.00	.13
Liver	5.04	.64	9.58	1.09
Kidney	3.14	1.65	1.95	.96
Lymph Gland	<.01	<.03	.05	.16
Pancreas	.08	.11	.16	.13
Brain	<.03	<.01	.03	.03
Fat	<.01	<.01	.03	.08
Stomach	.17	.06	.21	.05
Small Intestine	1.12	.11	.52	.05
Large Intestine	1.76	.22	.60	.08
Bone	29.4	1.90	32.0	1.61
Muscle	1.88	.01	2.26	.02
Skin	.67	.01	.70	.02
Eyes	<.05	<.2	.08	.21
Gonads	.11	.06	.16	.05
Urine	42.0	--	38.0	--
Feces	11.9	--	10.9	--
	100.0		100.0	

TABLE IX

THE METABOLISM OF CARRIER FREE Cd^{109} IN THE RAT 1, 4, 15, AND 64 DAYS FOLLOWING THE INTRAMUSCULAR ADMINISTRATION OF A SOLUTION OF $CdCl_2$ IN ISOTONIC SALINE

	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	.24	.34	.24	.37	--	--	.06	.10
Lungs	.23	.13	.25	.17	.21	.16	.19	.15
Spleen	.24	.45	.37	.57	.27	.44	.33	.72
Blood	.27	.021	.86	.07	.29	.024	.10	.01
Liver	77.8	10.2	73.5	9.31	74.0	10.2	62.1	10.5
Kidney	3.93	2.50	6.12	4.22	7.24	4.76	11.3	7.97
Adrenals	.049	.96	.03	.60	.039	.472	.03	.65
Thyroid	.011	.38	.02	1.0	< .005	< .25	.01	.42
Lymph Gls.	.053	.49	.07	.56	.058	.46	.08	.79
Pancreas	.77	.98	.81	1.45	.81	1.30	.97	1.56
Brain	.019	.011	.02	.02	.023	.013	.02	.01
Fat	--	.041	--	.03	--	.030	--	.03
Teeth	.019	.15	.05	.25	--	--	--	--
Stomach	.43	.30	.32	.12	.44	.16	.21	.15
Sm. Int.	4.23	.64	2.82	.40	.98	.15	.64	.13
Lg. Int.	2.50	.56	1.43	.20	.98	.17	.21	.05
Bone	2.42	.15	3.34	.10	2.60	.14	1.77	.09
Muscle	1.00	.011	1.38	.02	1.37	.016	1.49	.02
Skin	2.50	.092	2.65	.08	2.42	.082	1.05	.04
Ovaries	.073	.714	.07	1.12	.044	.33	.02	.33
Eyes	.011	.038	--	--	.011	.034	--	--
Urine	.21	--	< .1	--	.15	--	.52	--

content of the radio-cadmium in the blood, muscle, brain, and skeleton is very low. Excretion is almost entirely by way of the digestive tract and very possibly the liver acts as the source for most of the radio-cadmium excreted. The absorption following oral administration was observed to be .25 percent of the amount given by stomach tube. This is not a lower value but is believed to actually represent true absorption for this quantity is based on the radio-cadmium found in the liver and kidney in the stomach tube experiments. Toxicological work done in the past with cadmium using macroscopic quantities indicates that the liver and kidneys are the principal organs of deposition and retention of this element. The available data is not as complete and also the amounts of cadmium employed approached and often exceeded, the toxic level of this very poisonous element.

Other Tracer Studies. Tracer studies with carrier-free radio-vanadium have been initiated as well as a series of tracer experiments with carrier-free U^{230}, which has been obtained through the cooperation of the Chemistry Division of the Argonne National Laboratories, from a thorium target bombarded with 20 Mev deuterons at Berkeley. The purpose of this is to obtain data on the distribution of uranium at a level which can be considered carrier-free as compared to the studies done both here and elsewhere using U^{233}. We now have available a preparation of very high specific activity Eu^{154}, which is in the range of 2 to 5 microcuries per microgram and we plan to do tracer experiments with this element shortly. In addition, we have a target of tantalum which has been bombarded with 200 Mev deuterons from the 184 inch cyclotron. From this sample we hope to isolate sufficient amounts of long-lived radioactive isotopes of thulium and lutecium in order to make some preliminary tracer studies with these two heavy rare earths in the carrier-free state. This is an issue of considerable importance since the chemical and physical properties of the heavy rare earths are much closer to those of yttrium than the lighter members of the rare earth series, such as lanthanum, cerium, praseodymium, neodymium, and element 61. It will be of interest to see whether the metabolic characteristics of the heavy rare earths fail to demonstrate, as does yttrium, the striking and characteristic properties of the lighter members which accumulate to such a high degree in the liver and are deposited in the region of the small blood vessels of cortical bone.

Decontamination and Bone Metabolism Studies

Kinetics of Skeletal Uptake and Urinary Excretion of Radioactive Strontium. Because of its long half-life and ease of absorption from the intestinal tract, radioactive strontium is one of the most dangerous products of fission from the point of health hazard. Because of its close similarity to calcium in biological behavior it provides an excellent tool for studying basic calcium and bone metabolism.

In this experiment, the kinetics of skeletal uptake and urinary excretion of radioactive strontium were studied during the critcal first hour following intraperitoneal injection of a carrier-free dose of Sr^{90}. Three groups of rats were compared.

1. Mature adult females - in which skeletal growth had ceased.
2. Young normal rats - in which active bone formation was taking place.
3. Young rachitic rats - (reared according to specifications of USP XII for standard vitamin D test animals)

In the rachitic animals new organic bone matrix is being formed, but

this matrix does not calcify. The rats were sacrificed at 5, 10, 15, 30, and 60 minutes following injection, and the percent of the dose of radioactive strontium in bone, blood, soft tissues, urine and feces was calculated. The urine figure included bladder washings. The average value for each organ was plotted against time following injection to give the radioactive strontium uptake curves.

The skeletal uptake curves for all three groups are shown in Figure 1. It will be noted that the uptake by adult bone occurs at a slow and steady rate throughout the hour. The initial uptake by both normal and rachitic young rats is very rapid, but tapers off sharply towards the end of the hour. Tangents drawn to these curves at the different points give a measure of the rate of radioactive strontium uptake at that time. This figure, divided by the total plasma strontium at the same time gives a measure of the specific uptake of radio-strontium, expressed as percent of the total plasma "cleared" of strontium by the bone per minute. These specific uptake values are shown, plotted against time, in Figure 2.

The specific uptake by adult bone is almost constant, indicating that the radioactive strontium is passing steadily from blood into bone during this one hour period. This may be explained by a simple adsorption and exchange of strontium with the non-radioactive calcium of the bone salt.

In both the normal and rachitic young animals, the uptake is initially very high, but falls off very rapidly. This may best be explained by a very rapid uptake by bone in a labile combination from which radioactive strontium is actively released towards the end of the hour. Since this effect is equally prominent in the non-calcifying rachitic rats, it is not due to calcification per se, but is probably associated with the organic osteoid matrix present in both young groups. This labile combination with the organic bone matirix may be the first step in the normal calcification process. The greater overall uptake by the normal young animals is probably due to fixation of the radioactive strontium in the depositing bone salt.

The curves for urinary excretion with time are shown in Figure 3. When the specific excretion is calculated (as above) as percent of the plasma "cleared" by urinary excretion per minute, it is found that this remains constant in all three groups throughout the experiment. The clearance in the rachitic rats was almost ten times as great as that in young and adult normal animals, indicating a specific effect of rickets on the excretion of radio-strontium. This ten fold increase in excretion rate may be of some interest from the point of view of decontamination.

Effect of Zirconium Citrate Treatment on the Distribution and Excretion of Radioactive Yttrium. Intraperitoneal injection of large doses of zirconium citrate has been found to increase the urinary excretion and decrease the bone deposition of plutonium following intramuscular or intravenous injection. Because of the metabolic similarity of plutonium and yttrium, it was felt that a similar effect should be obtained with the latter. Radioactive yttrium is not only an important product of nuclear fission, but as a beta emitter, it is much easier to measure. For both reasons, the following experiments were carried out using radioactive yttrium as a "stand-in" for plutonium, and the effect of the timing of the treatment on the effect obtained was investigated.

Skeletally mature adult female rats were used. They were injected intravenously in the right jugular vein with 40 microcuries of Y^{90} in isotonic

saline at pH 5 - 6. Treatment consisted of 40 mg. Zr as zirconium citrate complex in 1.6 cc. administered by intraperitoneal injection either:

1. 48 hours prior to the injection of radio-yttrium (pre-treatment)
2. at the same time as the dose of radio-yttrium (immediate treatment)
3. 48 hours after the injection of radio-yttrium (post-treatment)
4. controls - no treatment

Urine and feces were collected daily and the animals were all sacrificed after 3 days. The results obtained are given in Table X.

Treatment with zirconium citrate at the same time as the injection of radio-yttrium had a profound effect on the distribution of the yttrium. Urinary excretion was increased almost ten fold (from 8.8 to 68.4 percent), deposition in liver was markedly reduced less than half that of the controls (44.9 to 20.3 percent). This tremendous effect was not produced when the treatment was given 48 hours before or following the injection of radio-yttrium. In the latter cases, the figures did not differ significantly from those in the control animals.

This remarkable effect of immediate treatment with zirconium citrate may be explained as a "carrier" action of the massive amount of zirconium citrate complex. Blockage of receptive bone groups by Zr is unlikely, since in that case there would be more effect in the pre-treated group. Ionic exchange of Zr with radio-yttrium already deposited in bone does not appear to be the main effect, since in that case more response would be expected from the post-treated group.

It remains to be seen whether bone resorption by physiological means may free chronic deposits of radio-yttrium or plutonium in bone so that zirconium citrate treatment may be effective in removing it from the body.

Severe Phosphate Deficiency as a Means of Demineralization. Severe phosphate deficiency has been found to be one of the most potent means of producing bone resorption, the severity of the deficiency. A method has been developed for purifying the fibrin used in this diet by iso-electric precipitation so that a synthetic diet is not available containing less than 0.005 percent P. This is less than one third that of the lowest diet hitherto reported. The effects of this diet are now being investigated.

Comparison of the Metabolism of the Alkaline Earth Metals. A comparison of the metabolism of calcium, strontium, and barium has been made using the radioactive isotopes. All three are quite similar in their general behavior, but the excretion increases as the atomic weight increases. The general results substantiate the similarity of calcium and strontium, (carrier-free) and the validity of radio-strontium as a "stand-in" for calcium.

TABLE X

EFFECT OF TIME OF ZIRCONIUM TREATMENT UPON THE UPTAKE, DISTRIBUTION, AND EXCRETION OF INTRAVENOUSLY INJECTED Y^{90}*

	Controls	Immediate Treatment	Pre-Treatment	Post-Treatment
Carcass	44.9	20.3	44.4	43.0
Femur	2.1	0.8	1.2	2.0
Liver	28.5	1.7	29.5	25.0
Kidney	2.4	0.3	2.0	2.0
Urine				
0-1 day	8.8	68.4	7.3	7.7
1-2 days	2.4	1.6	2.7	2.5
2-3 days	1.3	1.2	1.7	2.3
Feces				
0-1 day	3.7	2.2	4.9	3.6
1-2 days	3.5	2.7	2.9	7.4
2-3 days	2.4	0.8	3.4	4.5

*Values equated to 100% (actual recovery 89-98%)

TOTAL EXCRETION

	Urine	Feces
Controls	12.5	9.6
Immediate Treatment	71.2	5.7
Pre-treatment	11.7	11.2
Post-treatment	12.5	15.5

Radio-Chemical Isolation

Carrier-free yttrium was obtained from a strontium target, following deuteron bombardment, by a method previously reported. Carrier-free rubidium was also prepared from this target and the strontium activity, though not carrier-free, was obtained free of other contaminants.

Following deuteron bombardment on a molybdenum target, carrier-free technetium was obtained by a method reported earlier. A method was developed for obtaining carrier-free vanadium from a titanium target bombarded with deuterons. The titanium powder is dissolved in H_2SO_4, taken to dryness, and fused with Na_2CO_3. Vanadium and scandium are extracted with water from the fused mass. Excess salt is removed by repeatedly evaporating to a small volume and saturating the solution with HCl. Sc is removed by extraction with T.T.A. in benzene at pH 5. Ca is removed by extracting with T.T.A. at pH 7.9, using Ca carrier. As a final precaution, small amounts of Sc, Ti, and Ca carriers are added and removed by precipitating the hydroxides from boiling 1N NaOH. It is believed that carrier-free scandium will also be obtained from this target, though this work has not been completed. The decay of a small amount of Ca activity is being followed.

Carrier-free radio-silver was obtained from a palladium target by a method previously reported.

A Cb-Zr solution was received from Oak Ridge and from this solution, carrier-free Zr was separated. The columbium was removed by carrying with MnO_2 in 10N HNO_3. This method was taken from the project literature. During this period a solution of Eu^{154} was also received from Oak Ridge.

Work is progressing on obtaining carrier-free protoactinium from a thorium target by methods from the project literature. Carrier-free germanium has been obtained from a gallium target by distillation of the bromide.

The activity of a Be^7 sample is being followed. The half-life obtained is about 52 days which agrees closely with the latest reported values.

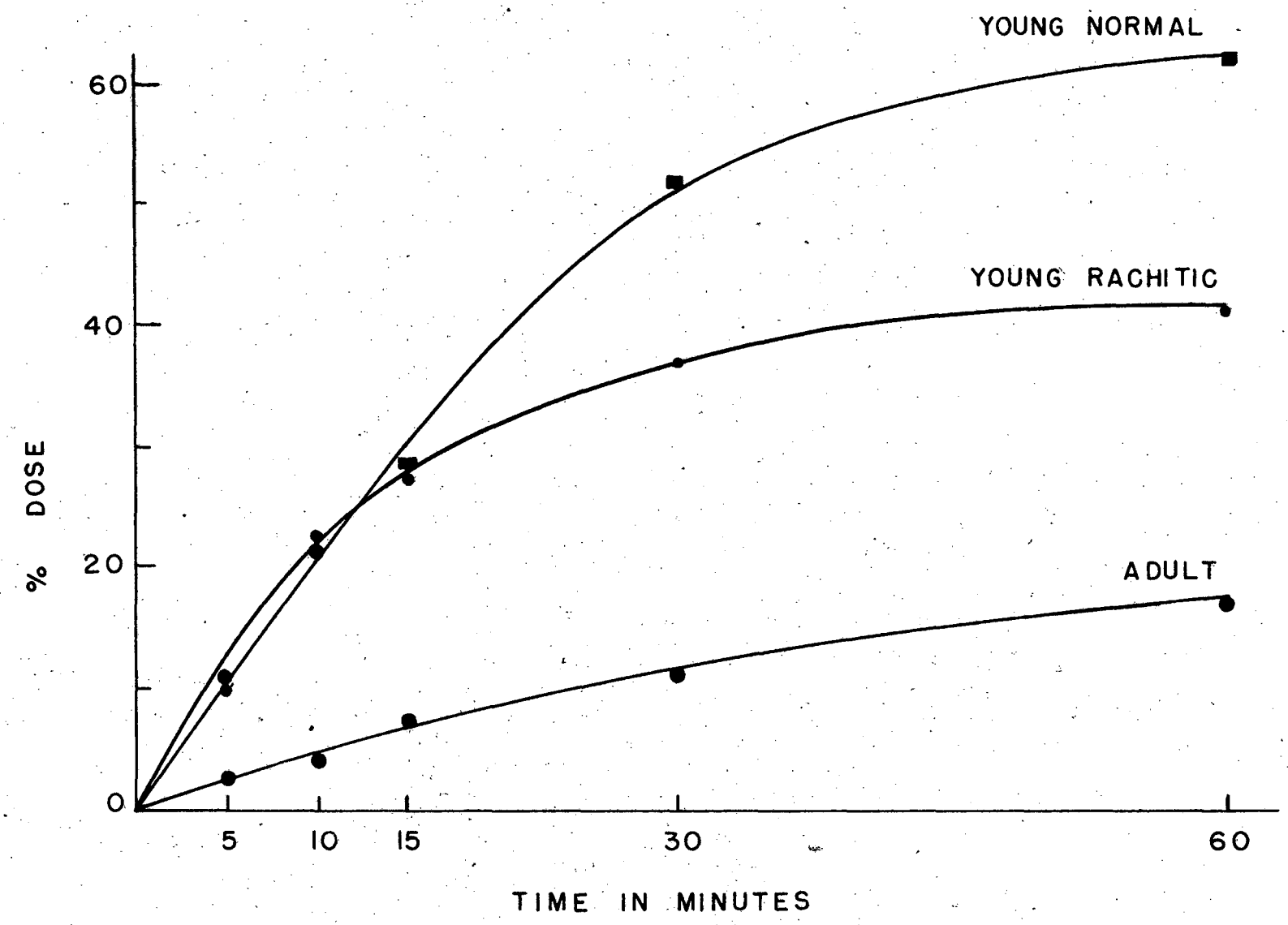
YOUNG NORMAL
YOUNG RACHITIC
ADULT
% DOSE
60
40
20
0
5
10
15
30
60
TIME IN MINUTES

FIG. I

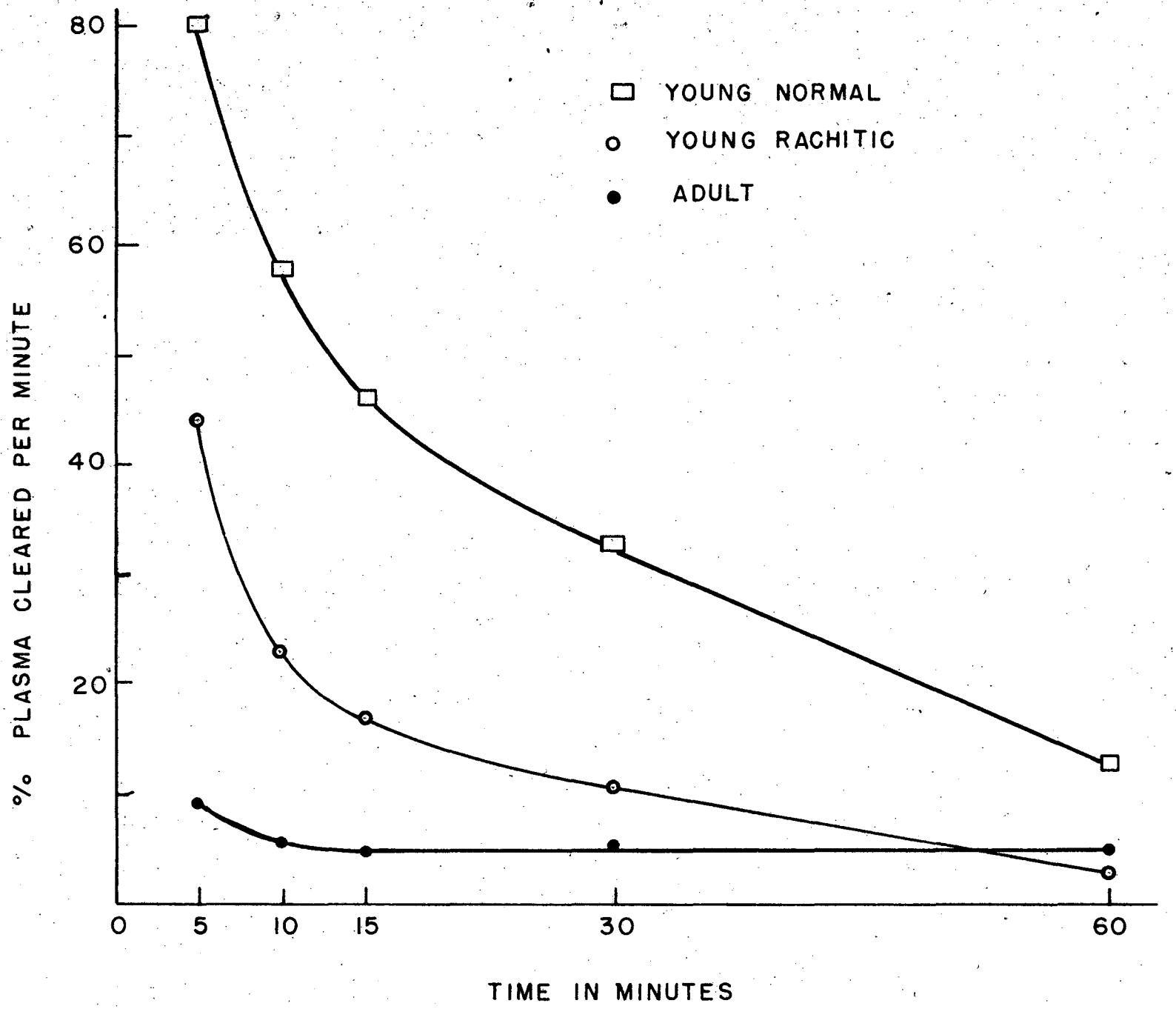
YOUNG NORMAL
YOUNG RACHITIC
ADULT
% PLASMA CLEARED PER MINUTE
80
60
40
20
0
5
10
15
30
60
TIME IN MINUTES

FIG. 2

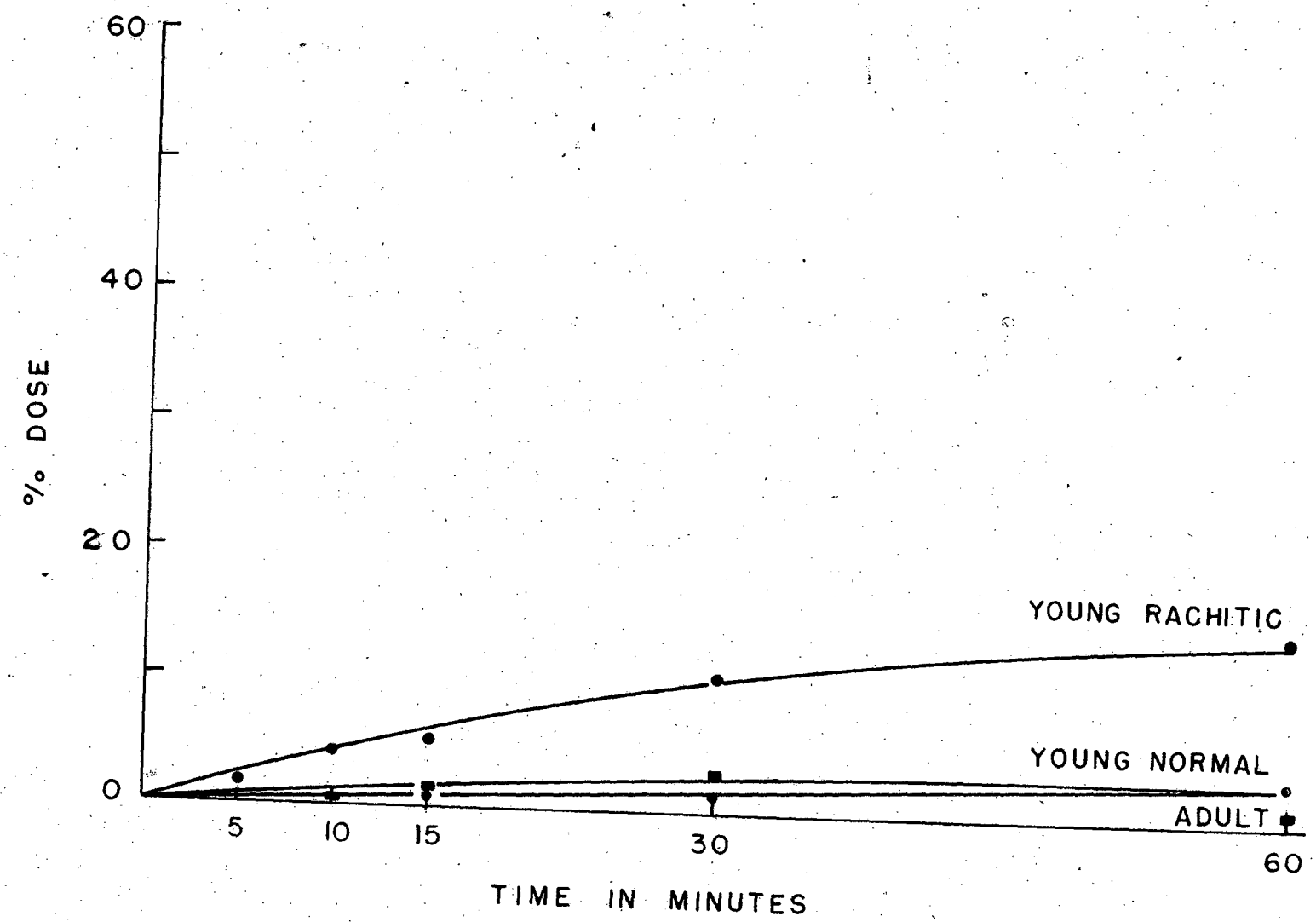
60
40
20
0
% DOSE
YOUNG RACHITIC
YOUNG NORMAL
ADULT
5
10
15
30
60
TIME IN MINUTES

FIG. 3

II. BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge

Project 48A - II

The Radiological Use of High Energy Deuteron Beams

by C. A. Tobias, Hal Anger, P. P. Weymouth and R. Lowry Dobson

Introduction. With the completion of the 184 inch cyclotron in Berkeley (1) and the successful construction of a deflector system, it was possible to bring the 190 Mev deuteron and the 380 Mev alpha beams out into the air,(2), and to begin a study of the effects of these beams by direct irradiation of biological specimens. The direct biological use of deuteron beams was attempted earlier in Berkeley by Marshak, MacLeish, and Walker (3) in 1940. These and other investigators have been aware for some time of the potential usefulness of high energy particle beams for radio-biological studies and their suitability for biological investigations. R. R. Wilson (4) advanced the idea of using fast proton beams to deliver radiation doses to selected deep-lying regions of the animal body without injuring the skin and intervening tissues. R. E. Zirkle (5) pointed out that such particle beams may be focused or screened until a cross-section of the beam is small enough to study effects of irradiation under the microscope on single cells or on parts of single cells.

Outline of Potential Uses of High Energy Particle Beams. It seems worthwhile to enumerate here some of the physical principles on which expectations are based concerning potential use of the cyclotron beams in biology and medicine. These are as follows:

1. Accelerated charged particles from the cyclotron may be focused so that their paths form a parallel ray through a considerable thickness of material. Since the number of such particles may be measured with ease, parallelism appears to be of advantage in the study of certain biological actions of radiation, especially when the target hypothesis is involved.

2. Each particle as it leaves the cyclotron has within close limits the same specific ionization and rate of energy loss in matter. The ionization may be measured in an ionization chamber quite accurately, and this property together with the one mentioned above enables one to deliver accurate doses of particles with uniform ionization. The precision afforded by these properties is of value when the dependence of biological effects on specific ionization is to be studied quantitatively. In contrast, when using X-ray beams, gamma rays, or beta rays to induce biological effects, one always deals with a number of ionizing electrons distributed in random directions and having great variations in their specific ionization. Thus the relationship between specific ionization, number of particles, and direction of particles is hard to derive in these cases.
If the various available beams (proton, deuteron, alpha, carbon*) leave the cyclotron with the same speed, their specific ionization will vary

* The use of carbon has not been attempted in the 184" cyclotron thus far. In the 60" cyclotron weak carbon beams are available. (11)

in proportion to the square of the charge on their component particles. Thus the ionization ratios of proton to alpha to carbon particles will be 1 to 4 to 36.
This affords tests for biological effectiveness at widely varying levels of specific ionization.

3. High energy particle beams produced in the cyclotron are very penetrating. For example, the 190 volt deuteron beam now available penetrates about 17 centimeters of soft tissue. Scattering is of much less importance than in the case of X-ray beams or electron beams, and the linear penetration of the beam thus allows one to hit targets lying deep under the skin quite accurately, and as will be seen below, somewhat selectively.

4. The rate of energy loss in matter increases as the particles lose energy, and reaches a peak just before they stop. This relationship is expressed usually with the well known Bragg curve - to be reproduced and studied later in this paper. Correspondingly the particles ionize more heavily near the end of their range and the dose delivered may be greater near the terminal end of the beam. This is the property that affords selective irradiation of deep-lying tissues. Thus highly selective irradiation of well defined internal regions of the animal body may be possible for the first time without the necessity of surgical procedures.

5. Single particles or a small bundle of particles may be directed to well defined regions of individual cells and the effects of irradiation of these regions may be directly observed.

The above properties show that high energy particle accelerators become very versatile tools in the study of the biological effects of radiations. In fact, it is hoped that their use might increase our knowledge concerning the fundamental nature of the radiation effects, in addition, they also may become valuable experimental therapeutic tools to produce regression of tumors and other localized therapeutic effects.

Experiments Concerning the Physical Properties of the Beam. Before the new 184 inch cyclotron was put to use for biological experimentation, it was necessary to perform a number of tests concerning the physical properties of the beam and to confirm the theoretical relations on which some of the previous paragraph was based. In order to do this, an apparatus was constructed to be used in the study of the ionization, scattering, and absorption of the particles. The beam was brought out into the air by a combination of magnetic and electro-static deflection (2). The particles emerged from the vacuum chamber through a 1/8" aluminum window well collimated so that their divergence was only a few minutes of arc. Figure 1 shows the arrangement used for the ionization and scattering measurements. Various instruments used in this connection were mounted on a set of parallel tracks which were aligned exactly in the direction of the beam. For alignment a special ionization chamber was used having four segments (Figure 2).
On the tracks the following instruments were mounted:

1. An ionization chamber to monitor beam intensity and ionization.

2. Absorbers of varying thickness and varying materials.

3. An analyzing ionization chamber placed immediately behind the absorbers.

The ionization current in this chamber was compared to that of the monitoring chamber and plotted in function of the absorber thickness.

4. A Faraday Cage was mounted behind all this equipment in an evacuated box. This collected the particles of the primary beam and measured their flux.

5. Photographic plates could be mounted to intercept the beam in various positions and angles.

After the necessary physical measurements were completed, the various instruments were removed except for the monitoring chamber and a set of absorbers behind it. A suitable holder was mounted behind these to hold the biological specimens, which then could be exposed to the beam. In the particular experiments described below mice were exposed. They were confined to a small plastic cylinder with thin walls and this cylinder was held in the beam by means of a "V" shaped holder. For schematic details see Figure 3.

Information was being sought regarding four types of interactions of the beam with matter:

1. Inelastic collisions. Some of the fast particles interact with the nuclei of atoms, producing transmutations. These particles are removed from the beam, thus decreasing the beam current. At the same time the transmutation products may add some other types of ionizating particles to the beam.

2. Range straggling. The range of the fast particles produced in the cyclotron shows fluctuation around the mean range: energy loss in matter by producing ionization and excitation is a statistical process. Measurement of the distribution of ranges is of importance in the determination of dosage.

3. Multiple elastic scattering. Collisions with atomic nuclei result in deviation of some of the fast particles from their original direction and it produces a widening of the beam near the end of the range.

4. Specific ionization, and specific energy loss in function of the particle energy and range.

Good theoretical formulas are available to predict most of the above properties, but they have not been checked experimentally thus far in the 200 Mev range.

Results. The data obtained are preliminary and incomplete. They allowed us however to start some biological experimentation and to verify some of our hopes as to the potential usefulness of the beam. The best data we have are in aluminum absorbers and in polystyrene.

Figure 4 shows one of the Bragg curves obtained in aluminum. The mean range $R_m = 17.8$ g cm^{-2} and the extrapolated range $R_o = 18.1$ g cm^{-2}. The mean range was used to evaluate the deuteron energy to be 190 Mev. Range energy tables prepared by Serber et al (6) and Smith (7) were used. The root mean square fluctuation of the

range is computed from the formula

$$\delta R^2 = \frac{2}{\pi} \left(R_o^{\ 2} - R_m^{\ 2}\right) = 0.107 \text{ cm}^2$$

This may be checked against an approximate formula for the straggling, derived by Wilson (8), from Bethe's accurate equations for energy loss (9), and valid in the particular energy region.

$$\delta R = 4.5\, R_m / E_o^{\frac{1}{2}} \left(E_o / NZz^2 R\right)^{0.055} \qquad (1)$$

where R_m is the mean range in cm.

E_o is the rest energy of the deuteron in Mev (1860 Mev).

N is the number of atoms per cm^3 of absorber.

Z is the atomic number of the absorber.

z is the atomic number of the fast particle.

For deuterons we get $R^2 = 0.10 \text{ cm}^2$ from the theoretical formula.

There is agreement between experimental and theoretical values for the straggling. Since equation (1) is known to be on sound theoretical basis, this result may be taken as an indication that the deuteron energy is homogenous.

The range energy relationship for aluminum was checked by measuring the beam current in function of the absorber thickness in the Faraday Cage. A typical result obtained is shown in Fig. 5. Here the charge collected on the Faraday cup per unit ionization current on the monitoring chamber was plotted in function of the aluminum absorber thickness. The observed curve has two components: a, the "background" effect, mostly due to electrical leakage and to a small extent to ionization of recoil protons from the neutron background; "a" should be subtracted. The component "b" resembles somewhat the expected curve. Its straight part is sloping slightly corresponding to inelastic collisions and wide angle elastic collisions which miss the Faraday cup. The R_m mean range and δR correspond well to the figures obtained using the Bragg Curve. The part of the curve that falls off rapidly represents the straggling of the range of the particles. With improved technique it is hoped that more exact curves will be obtained in the future.

From the slope of component b, as well as from the deviation of the Bragg curve from the theoretical one, the combined cross-section for inelastic scattering and wide angle elastic scattering may be estimated.

In 16 g/cm^2 aluminum about 25 percent of the beam was affected due to these causes. The overall cross section for the above range is

$$\sigma = 7 \times 10^{-25} \text{ cm}^2 \qquad \text{(Aluminum)}$$

The theoretical rate of energy loss was checked by comparing ionization measurements in the monitoring and detecting chamber to beam current measurements. If the beam is on for a time interval t and we have the number of deuteron particles "n" in the beam from Faraday cage readings,

$$n = \frac{Q_f}{ze} = \frac{C_f \Delta E_f}{ze} \qquad (2)$$

where Q_f = total charge collected.

C_f = capacity of cage leads to ground.

ΔE_f = change in potential slideback voltmeter.

ze = charge of particle

From ionization chamber measurements

$$n = \frac{Q_I}{\ell ze\rho} \frac{1}{\frac{dE}{dx}} = \frac{C_I \Delta E_I}{\ell ze\rho \frac{dE}{dx}} \qquad (3)$$

where Q_I = change collected in saturation current of ion chamber.

C_I = capacity of collecting electrode and leads.

E_I = potential change of slideback voltmeter during exposure.

ℓ = effective length of chamber, cm of air.

$\frac{dE}{dx}$ = rate of energy loss of particle per g air.

ρ = density of air gcm^{-3}

The agreement between ionization and component b of the beam intensity was excellent, confirming the theoretical values of $\frac{dE}{dx}$ within the experimental error.

Wilson also gave an approximate expression for the root mean square deviation of the particles of the beam from their original straight trajectory due to multiple scattering, based on Williams' calculation of scattering (10).

$$y_{rms} = 5.7\, R \left(\frac{Z}{E_o}\right)^{\frac{1}{2}} \left(\frac{E_o}{NZz^2 R}\right)^{0.055} \qquad (4)$$

The theoretical rate of energy loss was checked by comparing ionization measurements in the monitoring and detecting chamber to beam current measurements. If the beam is on for a time interval t and we have the number of deuteron particles "n" in the beam from Faraday cage readings,

$$n = \frac{Q_f}{ze} = \frac{C_f \Delta E_f}{ze} \qquad (2)$$

where Q_f = total charge collected.

C_f = capacity of cage leads to ground.

ΔE_f = change in potential slideback voltmeter.

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From ionization chamber measurements

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where Q_I = change collected in saturation current of ion chamber.

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This formula was checked by measuring y_{rms}. Photographic plates were exposed to the beam and placed behind various thicknesses of Al absorbers. The density of the plates was measured with a photoelectric cell.

Experimentally $y_{rms} = 0.8$ cm

Theoretically $y_{rms} = 0.4$ cm

The measurements will have to be further refined, and the validity of the deviation of the formula will have to be checked further.

The above measurements were repeated on polysterene. They yielded generally the expected results, but will be reported later when more complete data will be available. With the aid of the stopping power s (for tissue and polysterene, as compared to air s = 1.06) and with formulas (1) and (4) we have now enough data to determine the dose in any depth of animal tissue from ionization measurement in the monitoring ion chamber. The dose may be conveniently expressed in rep units (1 rep = 83 erg g^{-1} tissue). Along the center of the beam the dose rate is

$$\frac{dD}{dt} = \frac{(I - I_o)\,\epsilon\, S \left(\frac{dE}{dx}\right)_{x=\tau}}{\ell a z e \cdot f(\tau, a) \cdot \left(\frac{dE}{dx}\right)_{x=o}} \qquad (5)$$

where t = time.

I = ionization current.

I_o = background ionization current.

ϵ = energy per ion pair.

S = stopping power of tissue to air.

τ = tissue thickness (variable tissue thickness is denoted by x).

a = area of beam aperture

$f(\tau, a)$ = area correction due to scattering

ℓ = effective length of ion chamber

ze = charge of particle

ρ = density of air

$\left(\frac{dE}{dx}\right)_{x=o}$ = rate of energy loss in tissue of the high energy particles at x = o

$\left(\frac{dE}{dx}\right)_{x=\tau}$ = measured rate of energy loss (from Bragg curve) in tissue at $x = \tau$

while the density of the particles arriving at depth τ is given by:

$$\frac{dP}{dt} = \frac{(I - I_o)\epsilon}{\chi ze \left(\frac{dE}{dx}\right)_{o\ air}} \quad \frac{1}{af(\tau, a)} \quad (1 - \sigma_t N \tau), \qquad (6)$$

where σ_t = cross section for inelastic collisions in tissue.

N = number of atoms per cm^3 in tissue.

The above results show that even though deuteron beams are suitable to deliver a somewhat selective dose in a deep lying part of tissue, in the case of the 190 Mev deuterons, the ratio of specific ionization between peak value and its value at the skin is not as favorable as was predicted for protons by Wilson. 90 Mev protons or 380 Mev alpha particles seem to be more suitable. The dose delivered near the end of the particle range may be made relatively large compared to the dose received at the skin by special methods. One might be able to use a conically converging beam with the focus at the peak of the Bragg curve. This method would be expensive however. An alternate method would consist of cross firing, that is of irradiating the same spot in the tissue from various directions by successive exposures or by rocking the biological specimen around the point where the dose is to be delivered. The data given above only represent the first step in a planned series of measurements in which the properties of proton and alpha beams also will be investigated in a more precise manner and in much more detail.

Lethal Effect of the Deuteron Beam on Mice. A photographic plate was exposed to the beam in the spot where the mice were placed. (See Plate I) The circular blackening is due to the effect of the beam crossing the plate. The bakelite cylinder holding the mice was put on the "V" shaped holder, indicated in the photograph, in such a way that the deuteron particles crossed the body of the mice longitudinally and the density of deuteron particles was about constant throughout the whole cross section of the animals. A glance at the range energy curve or the Bragg curve tells us that almost all deuteron particles will cross the mice and come out still having a high energy. Thus they were exposed to uniformly high energy particles, their average energy being about 170 Mev and their average energy loss per gram tissue being about 7.2 Mev $g^{-1}cm^2$. Because of the high intensity of the deuteron beam, the individual exposure time lasted only a few seconds. One should keep in mind, however, that the cyclotron beam is an intermittent one. Under the conditions used, there were 90 pulses of particles per second, each pulse lasting for 10 micro seconds only. Six groups of 25 mice each were exposed to the deuteron beam, and four weeks following bombardment, the animals were examined for radiation effect. Figure 6 shows the percentage of mice surviving in function of the dose given in rep. The 50% LD appears to be 150 ± 30 rep and the mean time required for obtaining this dose was 15 seconds.* Since the LD 50 for the same strain of Bagg Albino mice was found to be 675 r for 180 kv X-rays when the exposure lasted 2 hours, one might be tempted

*The mean dose rate was 10 rep sec^{-1}, but the instantaneous dose rate during each pulse of beam amounted to about 11,000 rep sec^{-1}.

to say that the effectiveness of fast deuterons compared to X-rays is 4. In all probability this would be erroreous in view of the fact that data obtained with fast neutrons by Dobson (12) indicate that in addition to specific ionization effect there is a time factor involved too. The average energy of the recoil protons in the neutron experiment was 90 million volts even though a considerable number of the protons had different energies. 90 Mev protons have the same ionization as the 180 million volt deuterons. With the accurate dose measurement available one would expect to get the same lethal dose for protons as for deuterons. However, the lethal dose turned out to be about 675 rep when the bombardment was given in two hours and 1300 rep when it was given in 24 hours. If we are to believe these results, we have a definite indication that the extent of lethal effect depends on the length of time for bombardment, that is on the rate of dosage. Zirkle (5) has found that fast neutron doses obtained in the pile, using neutrons from uranium fission, were also more effective if the time of exposure was shorter. In the light of these results one should evaluate the lethal effects caused by deuterons in taking the dose rate into account. Figure 7 has the LD 50 plotted for Bagg Albino mice in function of the time of exposure. The results are plotted in a log-log chart and it is surprising to see that the three points obtained lie close to a straight line.

Evaluating the results, we discover that the dose given is approximately proportionate to the 4th root of the length of time of bombardment.

$$LD\ 50\ (t) = \text{constant} \times t^{\frac{1}{4}}$$

The weight loss of these groups of mice was also determined and the average weight loss is plotted in Fig. 8. The mean time of death appeared to be less (about six days) than that obtained with LD 50 of X-rays for a two hour bombardment (12 days). Blood counts were made on several mice and the data available up to now indicate that changes observed are very similar to those observed after exposure to X-rays or neutrons. Gross examination of the animals during the course of the experiment revealed that most of them had typical signs of radiation damage. Post mortem examinations revealed hemorrhage in some of the animals and this added to our belief that they died from radiation injury. The present facilities permit us to test the LD 50 with the beam up to about two hour exposure time. At this time the fast neutron background becomes large enough to interfere with the results. L. W. Alvarez suggested that one might obtain higher dose rates than the ones reported here by exposing the mice directly to the internal beam of the cyclotron. This would probably allow one to produce LD 50 dose in about 1/10 of a second.

Discussion The above described experiments signify only the beginning of a long range of work that is being taken up using the cyclotron as a biological research tool. One should say at this point that the newness of the instruments and techniques make the data presented somewhat uncertain and we expect to improve their accuracy in the future.

Summary: The suitability of the 190 Mev deuteron beam as a source of radiation for producing biological effects was investigated. There is a good indication that fast particle beams will become precision tools in the study of the biological effects of radiation and in experimental tumor therapy. The lethal effect of the high energy deuteron beam on Bagg Albino mice was measured. The LD 50 was 150 rep when the length

of exposure was 15 seconds. The LD 50 appeared to change approximately proportionately to the fourth root of the length of exposure time.

It is a pleasure to thank Doctors John and Ernest Lawrence, Dr. Robert Thornton and the cyclotron crew for their interest and collaboration, and Dr. Herbert Moffitt, Connie Tregillus, and Jean Luce for their assistance.

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SCHEMATIC DRAWING OF EXPERIMENTAL SETUP FOR IONIZATION MEASUREMENTS ON HIGH ENERGY DEUTERON BEAMS.

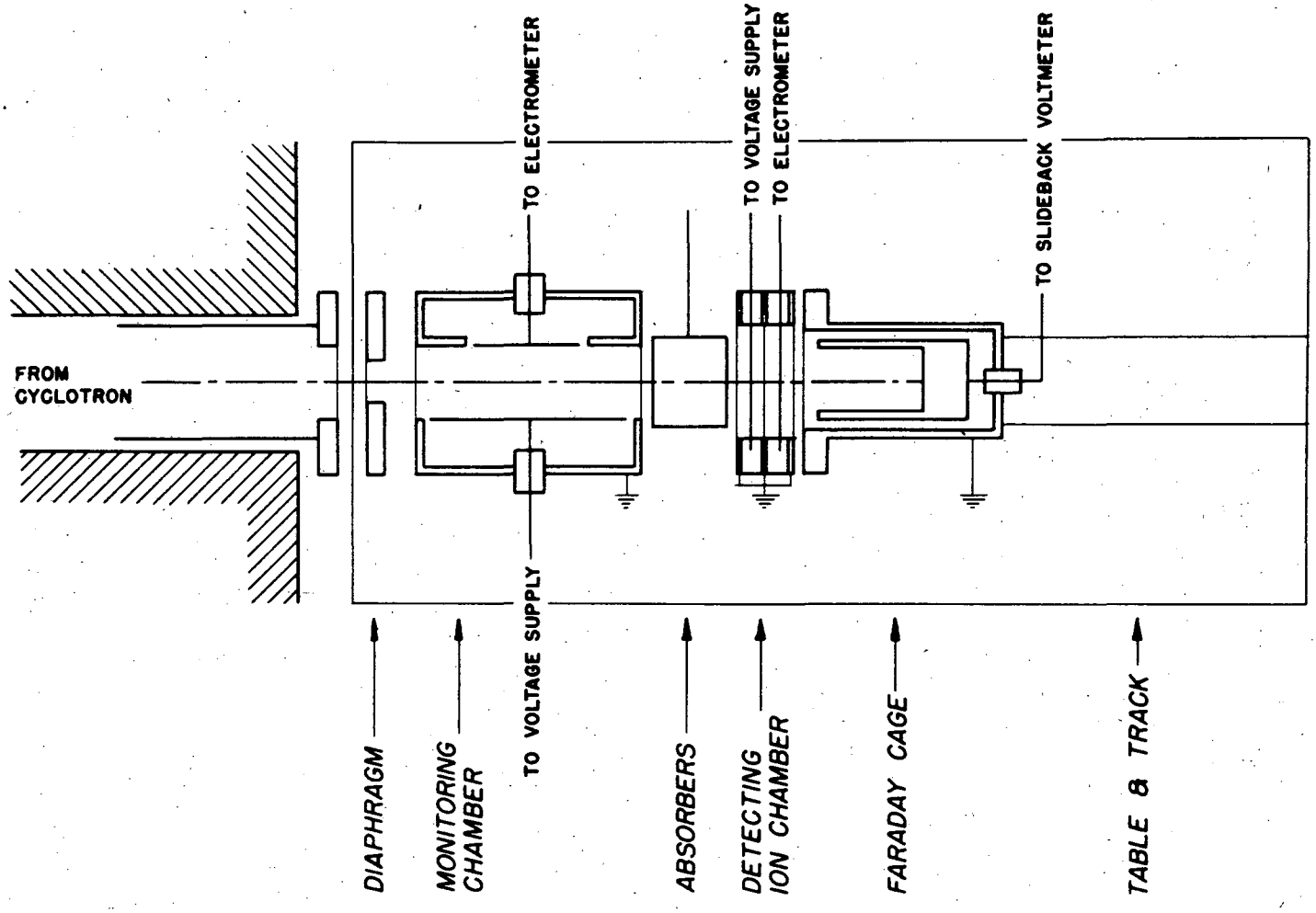

FIG. 1

CENTERING IONIZATION CHAMBER

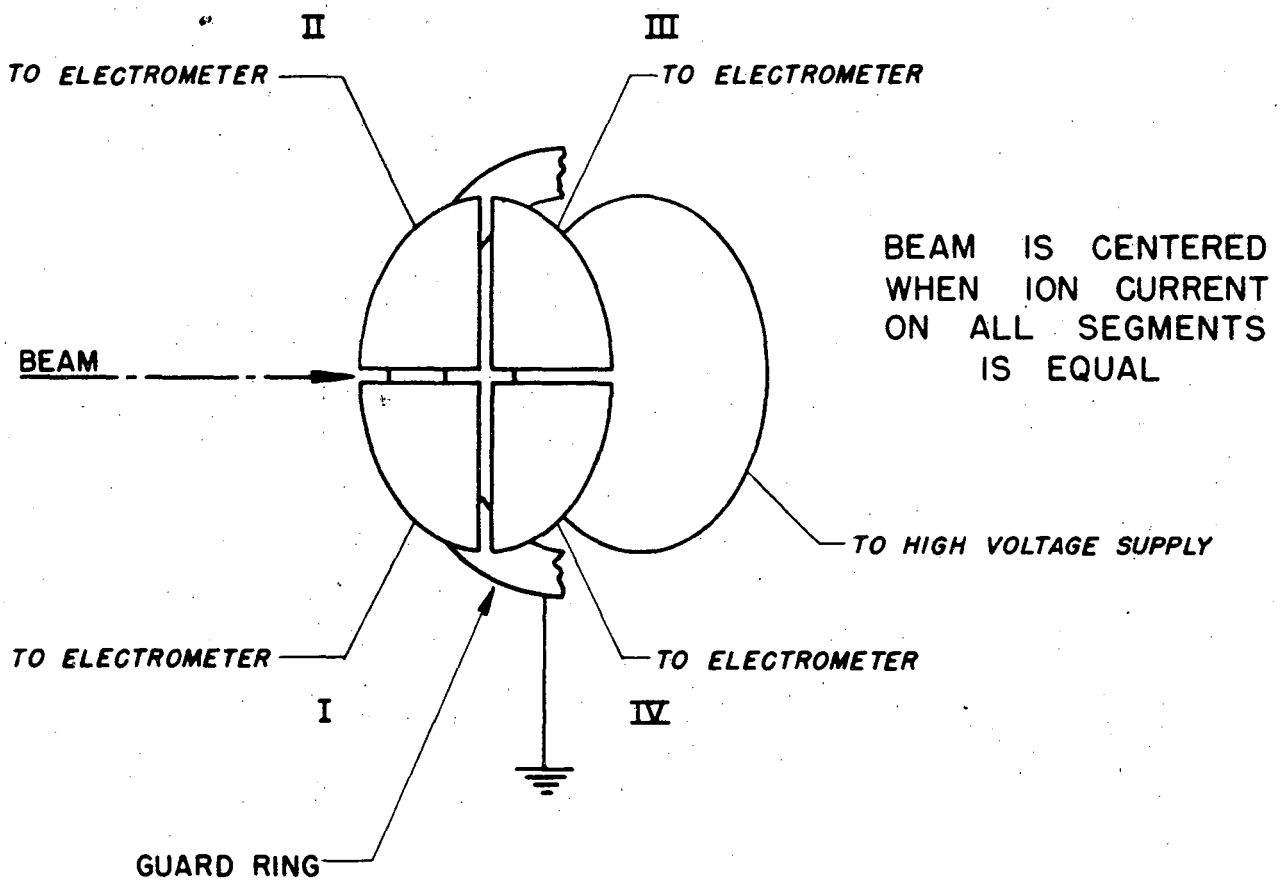

FIG. 2

SCHEMATIC SETUP FOR MOUSE EXPOSURES

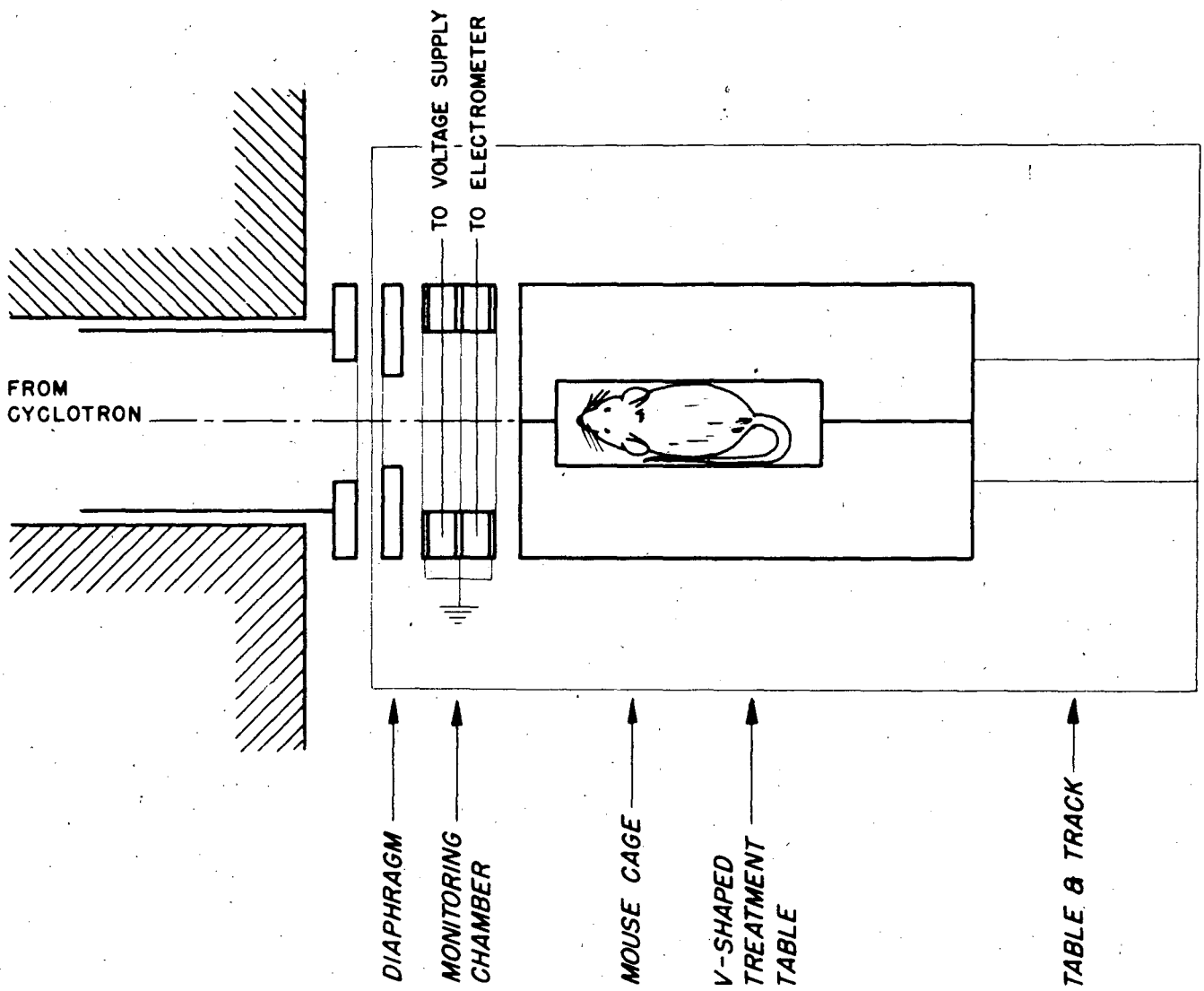

FIG. 3

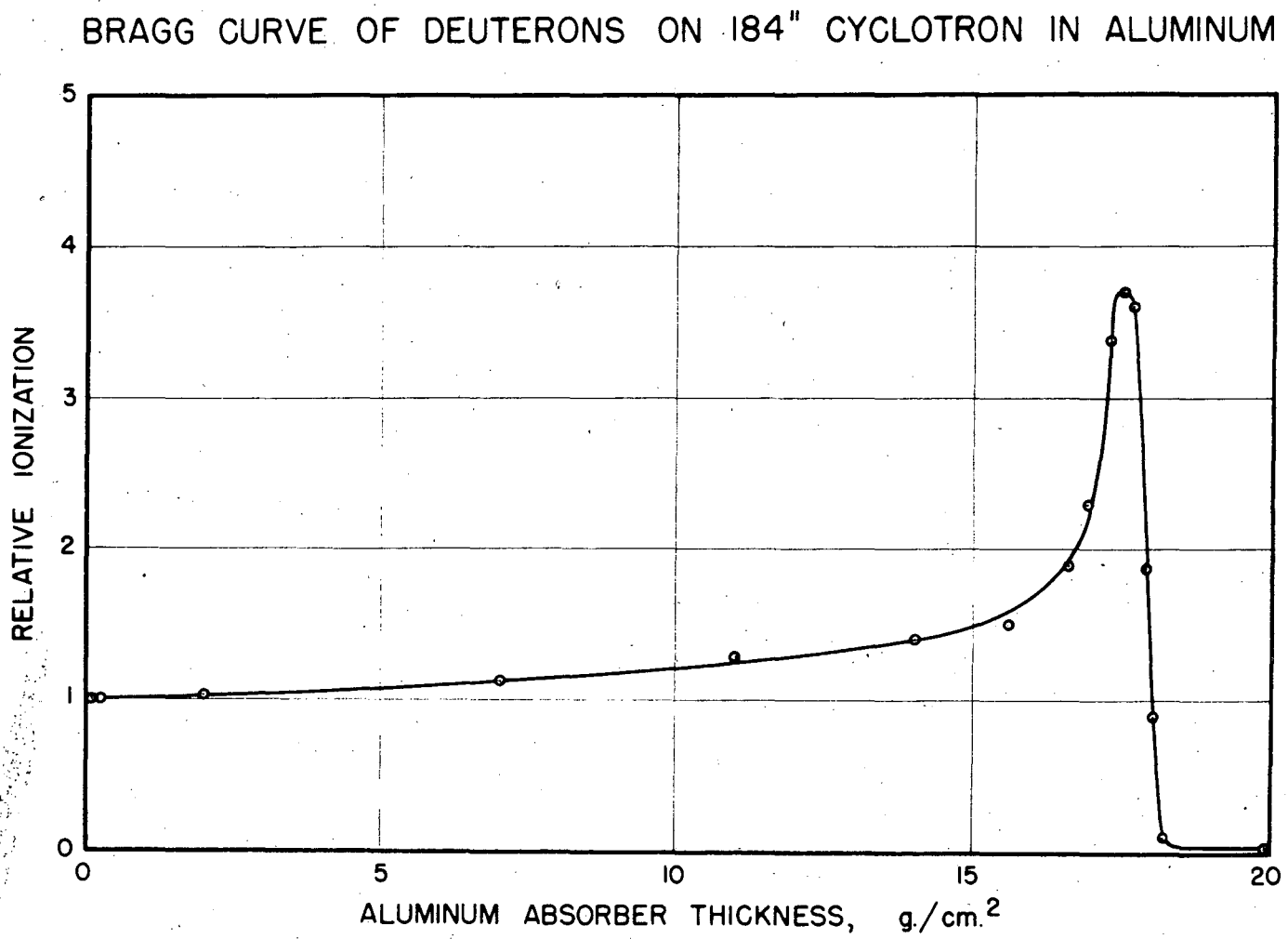
BRAGG CURVE OF DEUTERONS ON 184" CYCLOTRON IN ALUMINUM
RELATIVE IONIZATION
0
1
2
3
4
5
0
5
10
15
20
ALUMINUM ABSORBER THICKNESS, g./cm.2

FIG. 4

FARADAY CAGE READING FOR DEUTERON BEAM PASSING THROUGH AL ABSORBERS

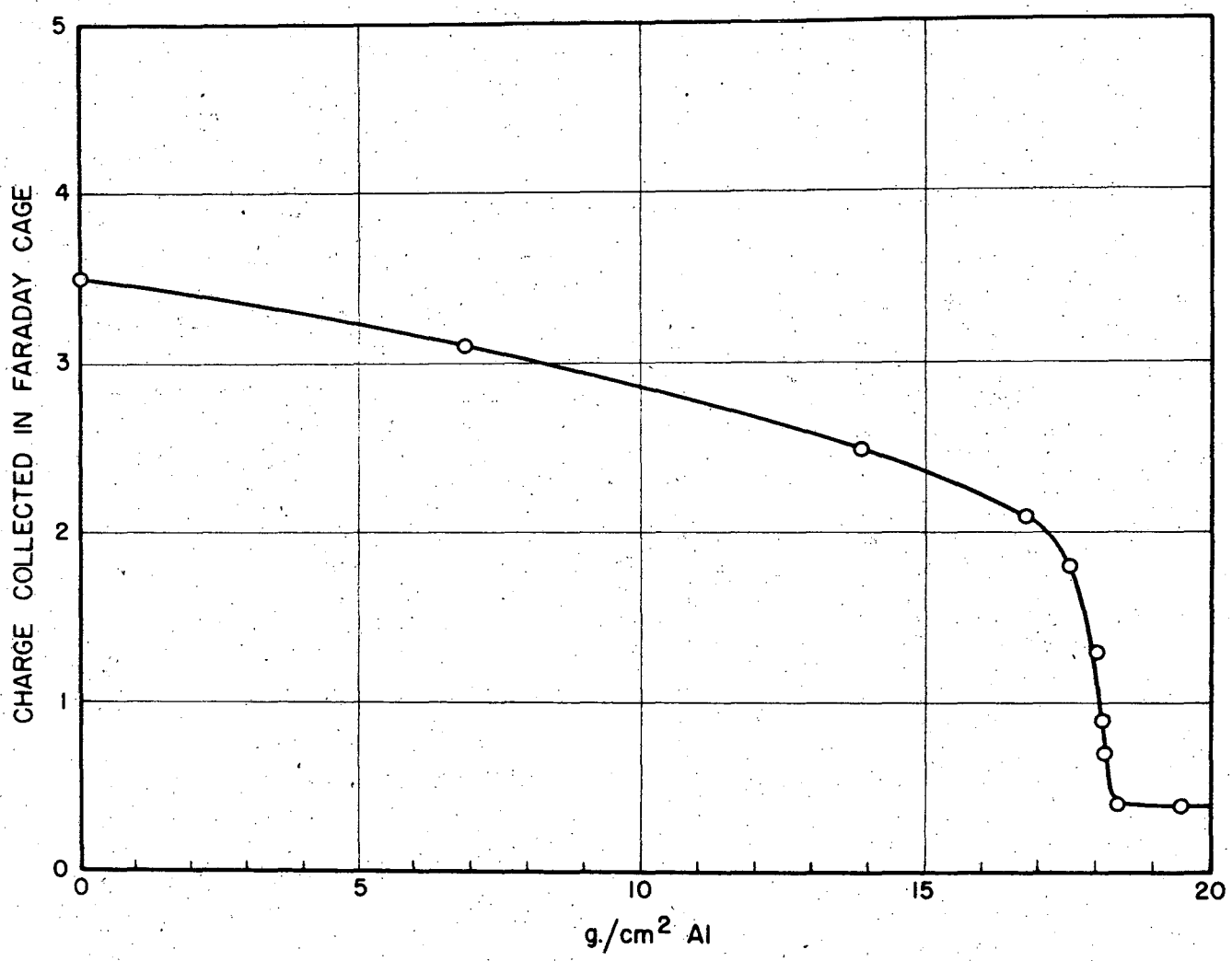

FIG. 5

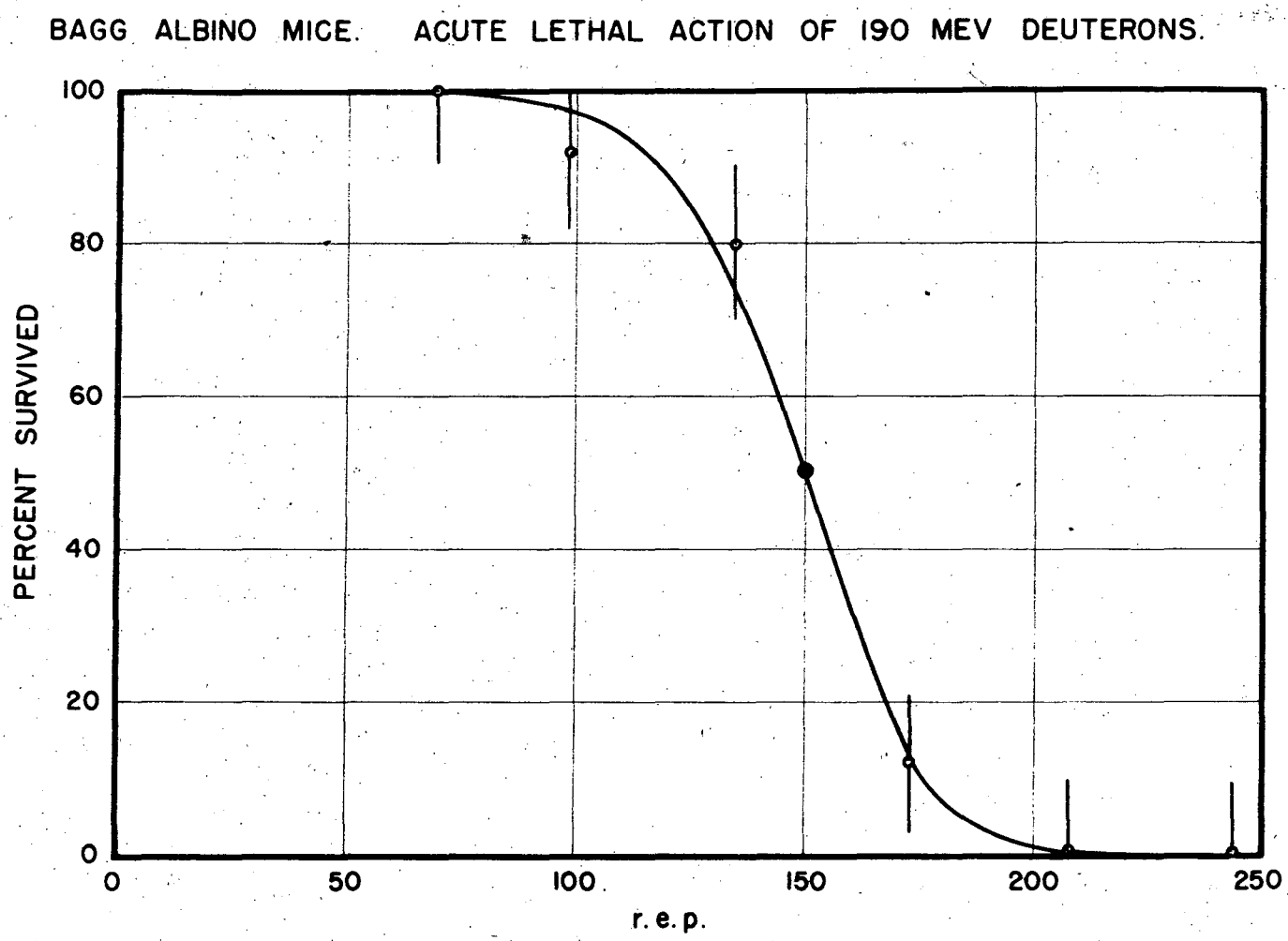
BAGG ALBINO MICE. ACUTE LETHAL ACTION OF 190 MEV DEUTERONS.
PERCENT SURVIVED
100
80
60
40
20
0
0
50
100
150
200
250
r. e. p.

FIG. 6

WEIGHT CHANGE OF BAGG ALBINO MICE AFTER EXPOSURE TO 190 MEV DEUTERONS

(AVERAGE OF 25 MICE IN EACH GROUP.)

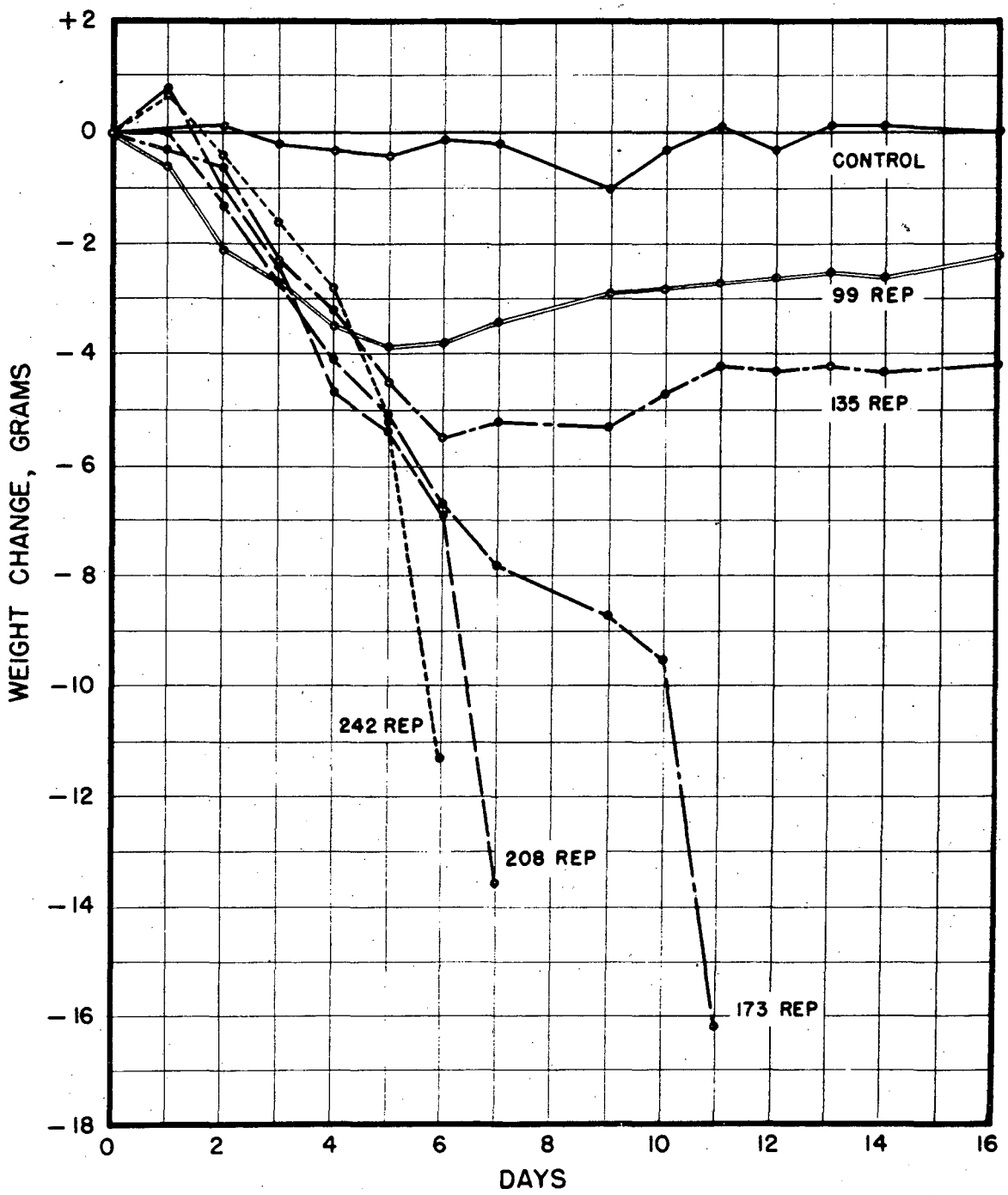

FIG. 7

RELATION OF LETHAL DOSE LD_{50} TO LENGTH OF EXPOSURE IN 184" BEAM $D = const. \times \sqrt[4]{t}$

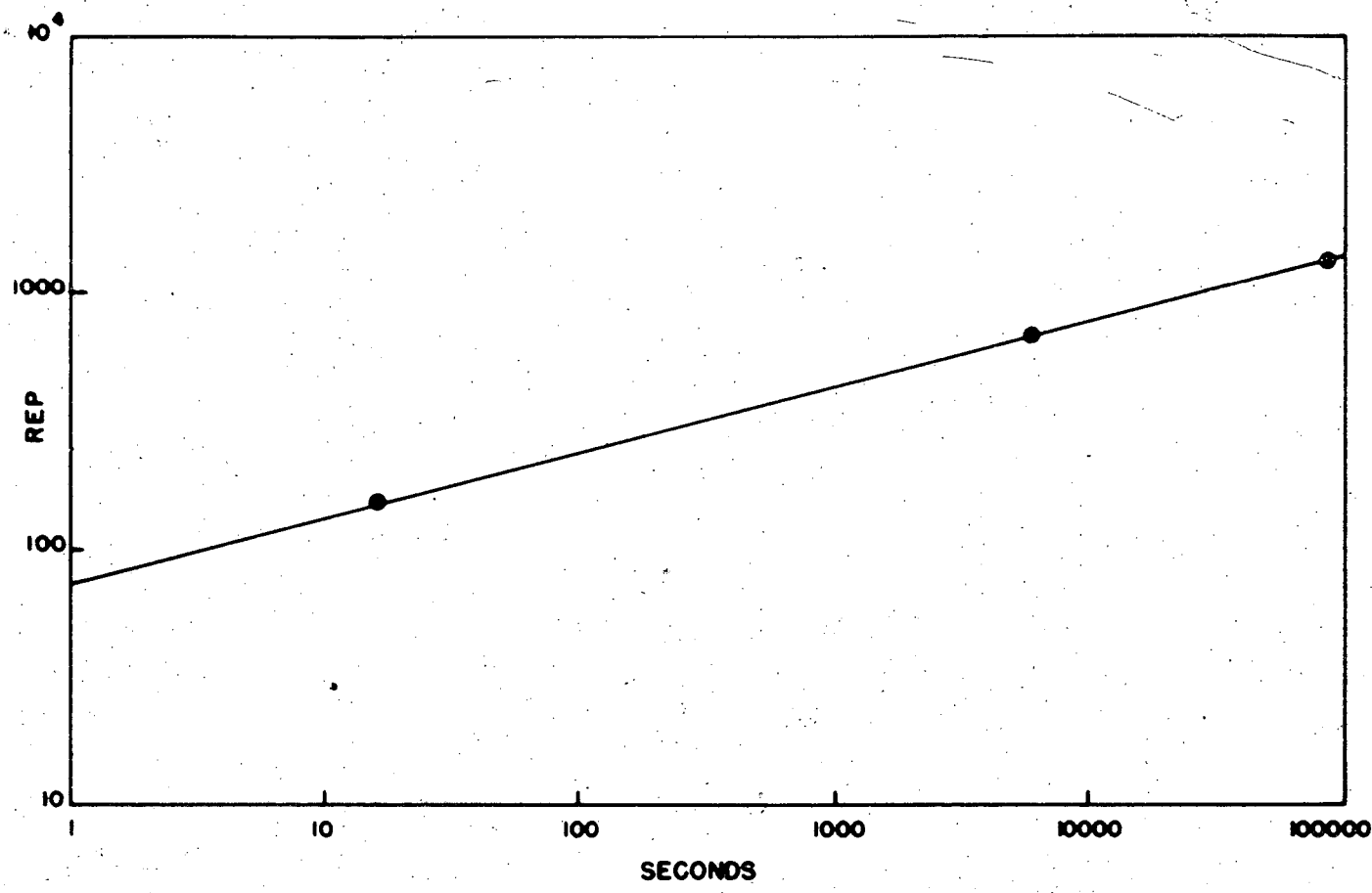

FIG: 8

PLATE I

Analysis of Micro-Composition of Biological Tissue by Means Of Induced Radioactivity

By Cornelius A. Tobias and Rayburn W. Dunn

The use of radioactive isotopes as tracers promises a wealth of information regarding the biochemical role of most elements and their compounds. Usually a radioactive sample of the element to be studied is administered to the plant or animal in a convenient form, and its distribution and rate of exchange are determined in later assays. This technique has, however, certain limitations, two of which will be discussed here.

1. Radioactive isotopes are not generally useful for measurements of the concentration of elements in the body or its parts. They can be used only to give a measure of the rate of exchange of the elements. There are exceptions to this rule; for example, the measurement of the total body water by the tracer dilution technique (1). Generally speaking, however, to the knowledge of the authors, no method has been described utilizing radioactivity for studying concentrations of elements in tissues. There are many important problems concerning trace* elements (2) which involve knowledge of their distribution. Some of these elements, such as Fe, Cu, Zn, and Mn, are known to be essential to life; others, like B, Al, Co, and Br, are known to be present, but so far very little is known about their function. Still others are poisonous in minute quantities; e.g., Hg, Se, and Cd. One limitation in the study of trace elements is the fact that microchemical or spectroscopic analysis is not quantitative for most elements below 10^{-7} g and there are great experimental difficulties in carrying out identification and assay of microquantities of such elements even in the higher range. It would be desirable to have methods of analysis which are accurate to well below 10^{-7} g, since it seems certain that much new information could then be derived concerning the biochemistry of trace elements in animals or plants, in health or disease.

2. The use of radioactive isotopes for tracer experiments requires that the radiation dose delivered to the tissue during the experiment should be small in order not to disturb normal biological functions. The safe limit for protection of health is considered to be 0.1 r e p per day, but it is not known whether or not such a dose might produce important biological changes. For this reason, it is advisable to keep the dose delivered by radioactive tracer isotopes below this safe limit. If certain tissues concentrate or selectively absorb the isotope, it is sometimes hard to avoid high dosage of such tissues during a radioactive "tracer" experiment. Another difficulty is frequently encountered with short-lived radioactive isotopes; if they are to be used in a "tracer" experiment involving a considerable time interval, the initial dose has to be relatively high in order that at the end of the experiment sufficient radioactivity will be present for measurement.

The above two difficulties encountered in the study of trace elements may be removed by using a very simple technique, i.e., the activation technique. It was employed first for the purpose of microchemical analysis of traces of gallium in iron by Seaborg and Livingood (3) in 1938. The chemical aspects of the subject were reviewed by Clark and Overman (4). The use of this technique for biological studies

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*"Trace" elements are stable chemical elements, the presence of which in small quantities is essential for the lives of plants and animals. "Tracers" are radioactive or stable isotopes of elements suitable for study of the biochemical and physiological role of each element or its compounds.

was begun by us early in 1947 (5).* For biological experimentation the activation technique may be used in more than one way. In some instances, where determination of the amount or concentration of various types of trace elements is desired, one might take a sample of the tissue or tissue extract, process it in a convenient way, for instance, by ashing, then expose the sample to a source of nuclear particles (for example, a pile or a cyclotron). Several of the elements present in the sample will become radioactive. After exposure, the amount of each radioactive isotope formed may be measured by standard radiochemical techniques. If one is interested in the radioactive isotope A, produced from a trace element B which was present in the original sample, one may first isolate the isotope A by adding carrier amounts of A, together with smaller amounts of each of the other elements which were originally present in trace quantities, and then separate A chemically. A pure product or compound of A may then be obtained, which can be used to measure and identify its radioactivity, and to determine its absolute disintegration rate. If the proper procedure is used, these data should conform with the established data for pure radioisotope A. If the cross-section for the nuclear process which produces isotope A from stable isotope B is known, and furthermore, if the particle flux F, the time of exposure t, and the time lapsed since the exposure are also measured, then the mass of the element B originally present in the sample may be calculated from the formula

$$X = \frac{c\,A\,\epsilon^{\lambda\tau}}{\sigma F \varphi R\,(1-\epsilon^{-\lambda t})},$$

where:

- X = unknown mass
- A = atomic weight
- R = Avogadro's number
- F = particle flux
- λ = decay constant of induced radioactivity
- σ = cross-section of "B" to form A
- t = length of time of exposure to neutrons
- τ = length of time elapsed between neutron exposure and time of measurement of rate of disintegrations of the chemically separated sample "A"
- c = rate of disintegrations of sample "A" measured at time
- φ = isotope abundance of the isotope responsible for the nuclear transmutation in B

An alternative procedure involves the simultaneous irradiation of a sample containing an unknown amount of B and a reference standard containing a known amount of B. If the constants of irradiation are the same for the two samples, the ratio of their induced radioactivities will be the same as the ratio of the masses of the known and unknown samples. The above concentration relationships hold only if the total mass of the sample is so small that the fraction of particles absorbed by the sample is small compared to the original number of particles in the beam. At the present time, the most convenient source for such activation experiments is the slow neutron pile, and the most prominent nuclear reaction is radiative capture of thermal neutrons.

A slightly different situation arises if one desires to study the distribution of a particular element or a compound to which the element is firmly

*Independently Bruce and Robertson have also used this method (11).

attached in the plant or animal body. In some cases it is practicable to administer to the animal a small or "trace" amount of the substance under study, in its stable form. After waiting a suitable length of time, one may carry out an activation experiment, as described above. The measurement of the induced radioactivity will be indicative of the distribution of the element. With the help of the above formula, one may then determine the amount of an element C present in each sample. However, since there is usually a small amount of element C present in each part of the tissue, even prior to its addition, one should separately determine the original amount and subtract it. Thus one may obtain the fraction of the trace dose which was present in the sample. This second aspect of the activation experiments raises a question which is sometimes overlooked in the study of metabolism by means of radioactive tracers; namely, the fact that the distribution of a radioactive tracer depends a great deal on its dilution by the inactive form of the same element originally and either normally or abnormally present in the body. In the study of the rate of biochemical reactions of an element A, radioactive tracers of A are of value only if the amounts of A present in each of its several chemical compounds are also known. This is expanded in a general theorem by Sheppard (6) and certain special cases have been treated theoretically by one of us (7). Thus the method of activation analysis has an important role in the dynamic aspects of tracer biochemistry.

One of the most attractive features of the method described in this paper is its extreme sensitivity. The formula indicates the factors influencing this sensitivity and one may say that the most important of these is the flux of neutrons. It has been stated that the flux of slow neutrons in one of the Clinton piles amounts to 5×10^{11} neutrons cm^{-2} sec^{-1}. Assuming this figure, the sensitivity of this method appears remarkable, indeed, since for some elements it is about 1,000 times greater than that of any other known method. Unfortunately, a number of important elements produce radioactive isotopes with too short a half-life to be useful. Still, there are some 50 whose half-lives, as well as cross-sections, are suitably large. Some of these elements are listed in Table 1, together with the minimum amounts may be measured with 10 per cent accuracy. One should emphasize that the method will not require special techniques for each element, except those of radiochemistry. Furthermore it is possible to study the concentration of several elements simultaneously.

Experimental. In order to test the ideas outlined above, one normal female mouse, age six months, was injected in the tail vein with 100 μg of stable gold in the form of the sodium gold thiosulfate salt. On the 30th day after injection, the animal was sacrificed. Upon autopsy and dissection, the various organs of the mouse were found by visual inspection to be normal. A group of 19 representative samples was selected.

In addition, 20 ml of blood from a leukemic patient were fractionated into plasma, white cells, and red cells, making a total of 22 biological samples. All samples were wet ashed using aqua regia and hydrogen peroxide. Precautions were taken to prevent contamination of the samples with foreign elements.

Each sample was then irradiated by slow neutrons in the Hanford pile. After irradiation and a suitable cooling period, the ash was dissolved again in aqua regia. A small portion was used to prepare samples for counting. Typical decay curves from the counting of the latter are to be found in Figure 1. The effective half-life of several of the tissue ash samples was found to be between 14 and 15 days, which would indicate that the principal activity is due to P^{32}. By using the value of the counting rates obtained on the fourth day after removal from the pile, the

relative activities of several of the samples were determined. These data for the tissues of the mouse are shown in Table 2, where the samples are listed according to decreasing radioactivity per mg of wet tissue. Also listed are the activities per mg of estimated dry ash. The radioactivity per unit wet weight is roughly proportional to the phosphorus content of each organ, while the relative activity per mg dry ash weight is almost constant for most organs, indicating that the ash has a constant percentage of phosphorus present. At the end of 60 days the radioactivity of phosphorus decreased sufficiently to make some of the longer life components appear. The radioactivity of the blood fractions from a human leukemic patient, shown in Table 3, indicates an interesting conclusion, namely, that the relative radioactivity induced in the white cells per mg dry ash weight is about 10 times as high as that induced in red cells, or 50 times as high as the radioactivity induced in the plasma. Our attention is now focused on isolating the different radioactive isotopes which are responsible for the white cell radioactivity. One additional sample contained 10 μg of pure gold, as the chloride, and another was blank. The gold sample was used to monitor the neutron flux of the pile and to furnish a standar for the gold distribution studies, while the other sample was used to determine whether the impurities which might be dissolved from the walls of the tubes holding the samples could influence the results. The disintegration rate obtained in this latter sample was negligible compared to the ones obtained in the tissue ash samples. Besides determining the gross radioactivity of the samples, it was planned to study the distribution of gold and the distribution of a number of other radio-isotopes which it was suspected would be formed after such irradiation. A guide for this work was given by the results of Curtis and Teresi (8), who had previously studied neutron activated tissue ash with the idea of determining what the importance of induced radioactivities might be in the biological effects due to slow neutrons in the animal body. The first part of this work, namely, the study of the distribution of gold, is now complete. Other isotopes with longer half-lives are still being studied. One reason for choosing gold was the considerable experience the authors gained in the use of these isotopes in studying rheumatoid arthritis (9). One of us (R.D.) devised a simple technique for quantitative separation and assay of radioactive gold from tissue ash by means of electroplating (10).

Prior to any chemical manipulation, a solution containing 25 μg of each of the following elements was added to each of the activated samples: Au, Sr, Ba, Zn, Cd, Hg, Co, Se, As, Bi, Fe, and Cu. These were to act as carriers for the radioactive isotopes present in trace amounts. To begin the separation, silver was precipitated as AgCl. After the removal of Ag, gold was precipitated by adding hydroxylamine hydrochloride solution and heating. Following repeated precipitation, the gold was electroplated on platinum planchets. Separation of mercury and other elements was subsequently carried out. These data will be reported later.

Table 4 gives the results of the distribution of radioactive gold. These parallel somewhat the data obtained previously, studying the distribution of Au 198, which was injected intravenously in mice. 2.3 per cent of the Au injected was recovered, which indicates that the rest of it was excreted in the one month period. An interesting point which should be noted, and one that clearly illustrates the very powerful possibilities which this technique offers, is shown in Table 5, which lists the Au found in the blood of a leukemic patient. The computations give 14 μg of gold for the total white cell volume of the body. To determine this small amount, one needed only about 10 cc of blood. All of the above data were obtained in duplicate samples. 70 per cent of the determination checked within 10 per cent. The rest of them checked within 20 per cent. Each of the samples obtained also showed some Hg 124 and some Ag 107 radioactivity. It will be necessary to check on the half-lives of these samples

before the actual values will be reported. A second group of elements consisting of iron, zinc, and cobalt is being processed from the same irradiated tissue samples at the present time. All of the above data have been taken from the tissue of a single mouse and one person, and it should be clear that the data should not be taken as final. Analysis of a statistically valid set of samples will be necessary.

Discussion. The above considerations and experimental data indicate that microanalysis of tissue constituents by induced radioactivity is a very suitable technique for the determination of ultramicro amounts of a number of elements. It is expected that the technique will play an important role not only in tracer biochemistry but in plant nutrition, pharmacology, and toxicology as well.

Summary. A technique for the analysis of inorganic microcomponents of biological tissue by means of induced radioactivity is described. Theoretical implications of this technique and its connections with radioactive tracer methods are discussed. Preliminary data on the radioactivities found in a set of neutron-irradiated tissue ash sample are reported.

Acknowledgements. The authors acknowledge with pleasure the interest and collaboration of John H. Lawrence and the assistance of Constance Tregillus and Robert Oswalt.

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TABLE I

RADIOACTIVE TRACE ANALYSIS BY MEANS OF THE (n, γ) REACTION
ASSUMED NEUTRON FLUX $5 \times 10^{11} cm^{-2} sec^{-1}$

Element	Starting Isotope	Abundance of Starting Isotope %	Final Isotope	Decay Constant sec^{-1}	$\times 10^{24}$ Capture cross Section cm^2	Minimum Amount measured g (10% accuracy)
11 Na	23	100	24	1.3×10^{-5}	0.4	1×10^{-9}
12 Mg	26	11.1	27	1.1×10^{-3}	0.048	4×10^{-7}
13 Al	27	100	28	4.7×10^{-3}	0.23	1×10^{-8}
14 Si	30	4.2	31	6.8×10^{-5}	0.11	2×10^{-8}
15 P	31	100	32	5.7×10^{-7}	0.23	1×10^{-9}
16 S	34	4.2	35	9.5×10^{-8}	0.26	6×10^{-9}
17 Cl	37	24.6	38	3.1×10^{-4}	0.61	1×10^{-8}
19 K	41	6.6	42	1.6×10^{-5}	1.0	1×10^{-9}
20 Ca	44	2.06	45	4.6×10^{-8}	0.6	1×10^{-7}
21 Sc	45	100	46	9.7×10^{-9}	2.8	4×10^{-10}
25 Mn	55	100	56	7.4×10^{-5}	12.8	1×10^{-10}
26 Fe	58	0.28	59	1.7×10^{-7}	0.32	4×10^{-8}
27 Co	59	100	60	4.1×10^{-9}	0.73	4×10^{-9}
29 Cu	63	70.1	64	1.5×10^{-5}	3.1	6×10^{-11}
30 Zn	64	50.9	65	3.3×10^{-8}	0.51	2×10^{-9}
33 As	75	100	76	7.2×10^{-6}	4.6	4×10^{-10}
35 Br	81	49.4	82	5.6×10^{-6}	2.25	1×10^{-9}
47 Ag	107	51.9	108	3.6×10^{-8}	48.3	1×10^{-10}
48 Cd	114	28.0	115	3.5×10^{-6}	11.0	1×10^{-10}
53 I	127	100	128	4.6×10^{-4}	6.8	2×10^{-9}
79 Au	197	100	198	3×10^{-6}	24.5	4×10^{-11}

TABLE II

RELATIVE RADIOACTIVITY OF IRRADIATED ASH
ONE WEEK FOLLOWING EXPOSURE TO THERMAL NEUTRONS

Tissue	Wet Weight, mg.	Estimated Ash Wt., mg.	Relative Activity* per mg. wet wt.	Relative Activity* per mg. ash wt.
Bone	29.8	7.9	480	1,800
Pancreas	179.6	3.9	60	2,700
Kidneys	305.6	3.9	40	3,100
Thymus	61.8	0.8	39	3,000
Spleen	141.4	2.7	37	2,000
Liver	1,458.8	57	35	900
Brain	426.1	6.8	35	2,200
Heart	107.2	1.1	32	3,200
Lung	175.2	2.1	32	2,700
Ovaries	21.8	0.3	27	2,000
Adrenals	11.6	0.2	25	1,500
Lymph Nodes	30.8	0.2	25	3,000
Muscle	70.4	0.9	24	1,900
Red Cells	0.15 ml.	3	7	350
Gall Bladder	14.6	0.1	14	1,500
Skin	101.6	5.1	13	260
Tendon	5.4	0.4	10	140
Gut	3,832.7	64	7	440
Plasma	0.15 ml.	3	0.4	20
Control Sample Tube (empty)	very small	very small	very small	very small

*Mean of measurements on two samples.

TABLE III

RELATIVE RADIOACTIVITY OF IRRADIATED BLOOD ASH
FROM A PATIENT WITH LYMPHOID LEUKEMIA
(one week after exposure to neutrons)

Tissue	Estimated Ash Wt., mg. used in determination	Relative Activity* Per mg. ash wt.
Red Cells	114	1
White Cells**	8	11
Plasma	280	0.2

* Mean of measurements on two samples
** The white cells were prepared by centrifuging with beef albumen.

TABLE IV
DISTRIBUTION OF GOLD IN A MOUSE*

	Mass of Organ in g	Amount of Au 197 per g Wet Tissue	Total Amount of Au 197 per Organ in g
Monitor Gold Sample			10×10^{-6} g
Liver	1.458	4.4×10^{-10} g	640×10^{-9} g
Ovary	0.022	4.3×10^{-10} g	9.5×10^{-9} g
Thymus	0.062	3.2×10^{-10} g	19×10^{-9}
Adrenals	0.012	3.1×10^{-10} g	[illegible]
Lung	0.175	2.6×10^{-10} g	46×10^{-9} g
Lymph Nodes	0.031	2.2×10^{-10} g	6.8×10^{-9} g
Spleen	0.141	1.7×10^{-10} g	24×10^{-9} g
Kidney	0.306	1.6×10^{-10} g	49×10^{-9} g
Heart	0.107	1.5×10^{-10} g	16×10^{-9} g
Bone	2.600	1.1×10^{-10} g	290×10^{-9} g
Pancreas	0.015	1.1×10^{-10} g	1.6×10^{-9} g
Skin	3.100	1.0×10^{-10} g	310×10^{-9} g
Gall Bladder	0.015	1.0×10^{-10} g	1.5×10^{-9} g
Tendon	0.050	0.7×10^{-10} g	3.5×10^{-9} g
Muscle	11.20	0.65×10^{-10} g	730×10^{-9} g
Red & White Cells	1.05	0.65×10^{-10} g	69×10^{-9} g
Brain	0.502	0.2×10^{-10} g	10×10^{-9} g
Gut	3.6	0.09×10^{-10} g	32×10^{-9} g
Plasma	1.0	0.05×10^{-10} g	5×10^{-9} g
Total	25.446		2276.5×10^{-9} g or ~2.3% of total injected.

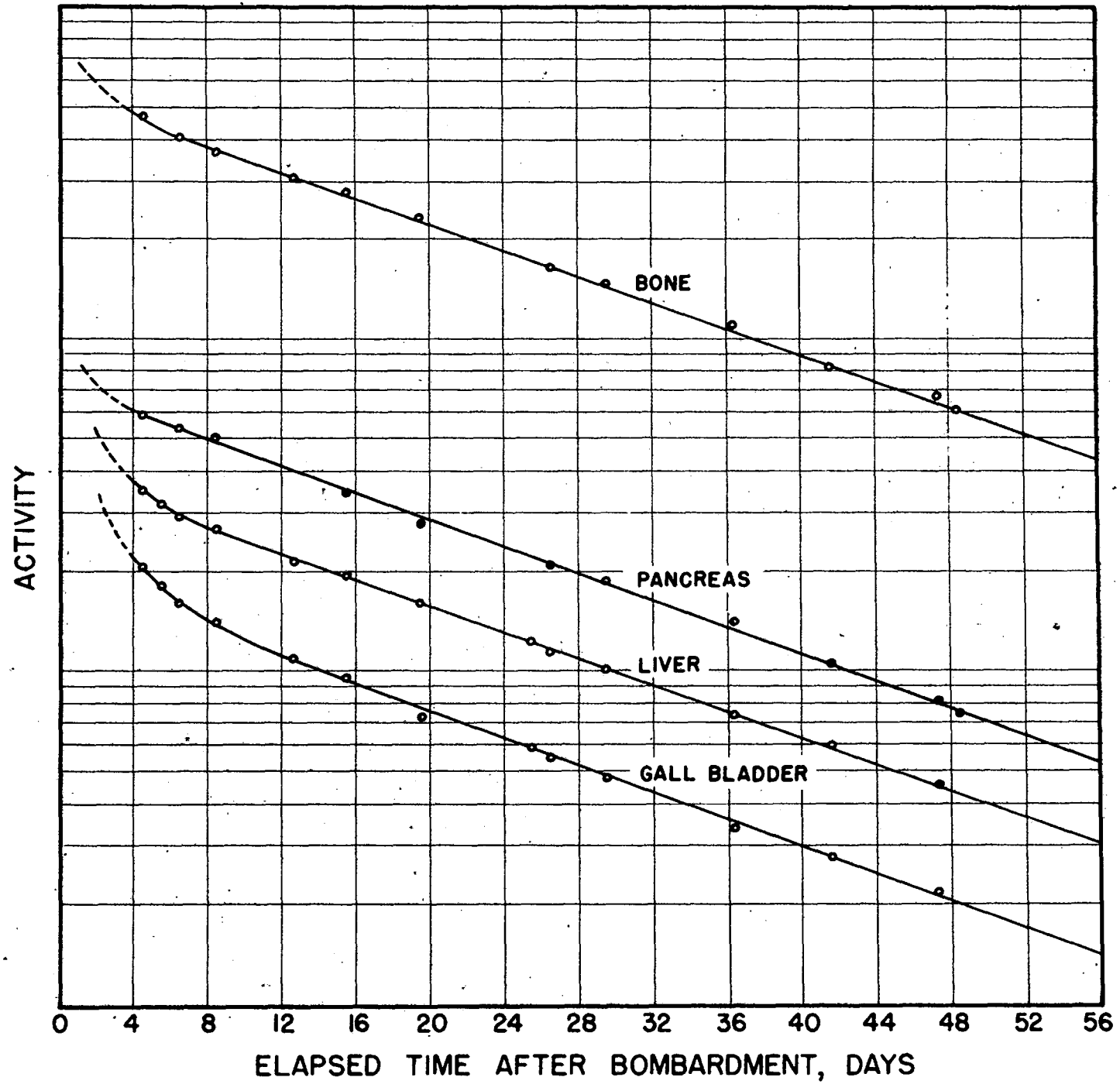
*100 micrograms of stable gold administered intravenously to a mouse in the form of gold sodium thiosulphate. Mouse sacrificed 30 days after administration, tissues wet ashed and irradiated in the Hanford Pile. Subsequently the gold was removed by radiochemical methods, its half-life and β- ray energy verified and counted in duplicate samples

TABLE V.

DISTRIBUTION OF GOLD IN HUMAN BLOOD
FROM A LEUKEMIC PATIENT

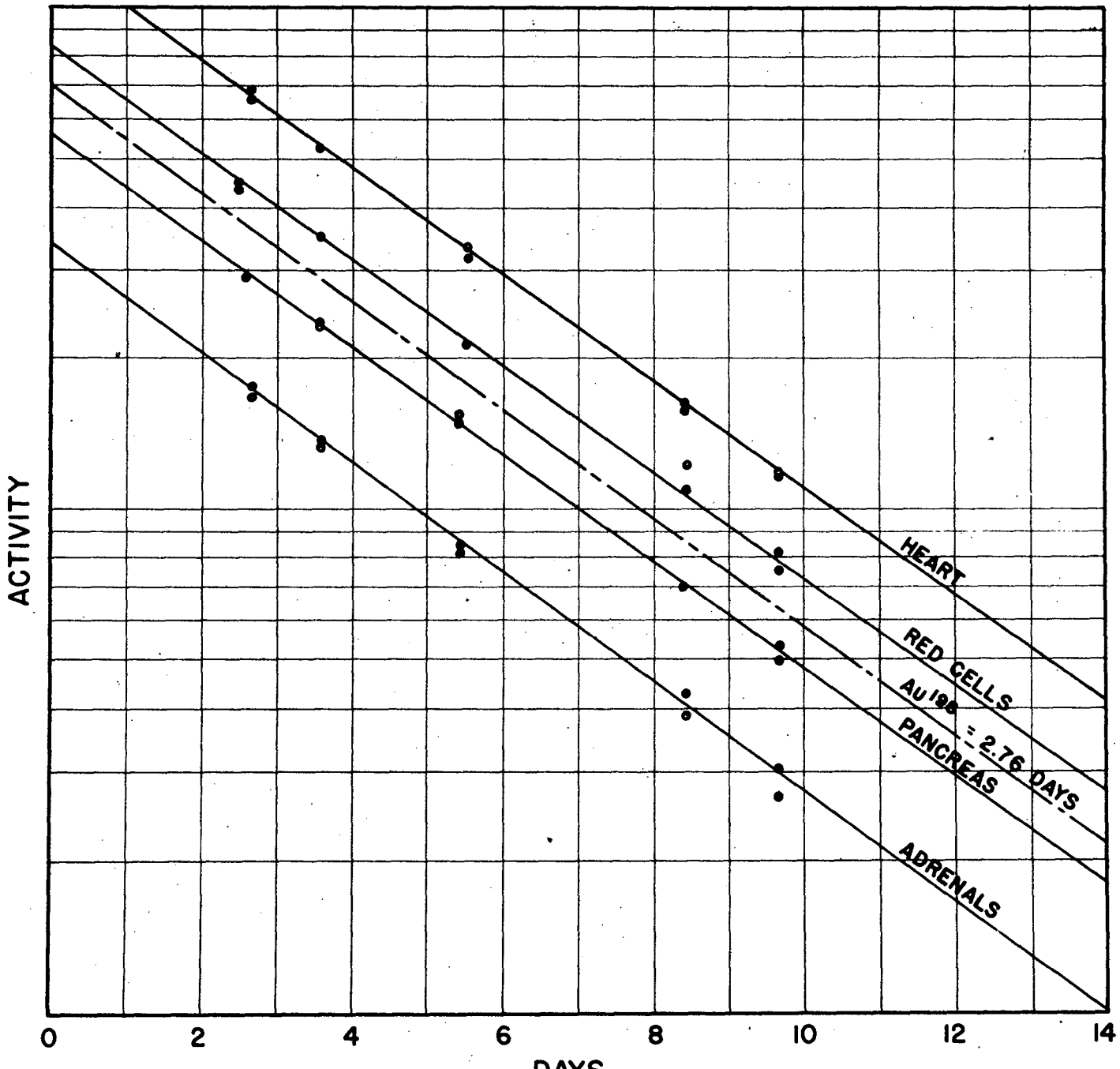
	Wet Mass g (estimated)	g of Au^{197} per g wet mass	Total Au^{197} in Circulation of Person
Red Cells	130	11×10^{-8}	14.3×10^{-6} g
White Cells	2,585	0.4×10^{-8}	10.3×10^{-6} g
Plasma	2,650	0.07×10^{-8}	18.5×10^{-6} g

REPRESENTATIVE DECAY CURVES OF ASHED TISSUE MATERIAL AFTER NEUTRON BOMBARDMENT



~~FIG. 2~~ Fig. 1.

REPRESENTATIVE DECAY CURVES OF Au^{198} RECOVERED FROM TISSUE SAMPLES WHICH WERE WET ASHED, FOLLOWED BY NEUTRON BOMBARDMENT



~~FIG 1~~ Fig. 2

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 From External and Internal Sources

B. V. A. Low-Beer

The objectives of this program were discussed in the previous Quarterly Report (UCRL 41).

The present report deals with the hematological changes observed in patients treated for arthritis with radioactive phosphorus administered intravenously.

The radioactive phosphorus used was prepared in the Oak Ridge chain reacting pile and standardized at the Radiation Laboratory in Berkeley. Carrier free P^{32} was used in these studies, and was made isotonic for intravenous administration by the addition of stable sodium chloride. Specific activities varied from 250 microcuries/cc to 550 microcuries/cc. The lower values for specific activity reported in this study are due to lapse of time between preparation and use of material. Each preparation was checked for toxicity by means of intravenous administration to rats.

Total doses used on patients varied from 3500 microcuries to 8000 microcuries. Individual doses varied from 500 to 2000 microcuries, administered at weekly intervals, except in three patients whose treatment course had to be prolonged for clinical reasons, up to 39, 40, and 41 days respectively.

Radioactive phosphorus present in the body was calculated as a function of the amount introduced plotted against excretion and decay. The values obtained by these calculations are called the "radiation level" which has been described in detail by Doctors B. V. A. Low-Beer, John H. Lawrence, and Robert S. Stone in Radiology, November 1942. Some discrepancy may exist between radiation levels reported in this study and those which have been described in the literature, since the latter have been obtained from excretion studies with carrier free P^{32}. Excretion studies are now in progress with carrier free P^{32} on some patients included in the present study, so that the question of the effect of carriers on rate of excretion can be determined. From this information the true radiation level for carrier free P^{32} can be calculated. The term "radiation level" expresses the amount of radioactive material present in the body at any particular time.

Techniques used in these hematological studies are the same as described in the P. P. R. report except that blood counts were not made daily

on these patients. Counts were made each week, just prior to each treatment. After the treatment period counts were made once a week for four weeks, then every two weeks for two months, then once every four weeks unless some marked change was observed, in which case counts were made approximately once a week.

Of the 21 patients treated, 4 were men and 17 were women. The age range was 16 to 67 years. Twelve of the patients were between the ages of 50 and 67 years. Twelve patients have been under observation for a sufficiently long time to permit analysis of hematological changes. Only 10 of these will be discussed here, however, as charts have been prepared for these patients. (Table No. 1). The remaining 11 patients in this group will be discussed in a later report.

Patients Receiving 6000 - 7000 Microcuries of P^{32} - (Graphs 1 - 4)

Total White Count

Four of the 10 patients considered in this report received from 6000 - 7000 microcuries of P^{32}. Two of these patients showed an "abortive rise" of the total leucocytes and neutrophiles after the first dose of P^{32}. All 4 of the patients showed beginning decrease in total leucocytes, neutrophiles, lymphocytes and monocytes after the second dose. These decreases became marked and reached the lowest value at about the 40th day following beginning of treatment.

Recovery from the leucopenia began between the 50th and 70th days after beginning of treatment. Original values were restored around the 120th - 140th day after beginning of treatment. Two of these patients showed a second decrease in total leuocyte count, neutrophiles, lymphocytes, and monocytes around the 200th day after beginning of treatment. In 2 of these patients count rose around the 300th day after beginning of treatment to a value slightly in excess of the original count. Both the neutrophile and lymphocyte counts showed this rise. In all of these 4 patients neutrophiles and lymphocytes showed the same quantitative effects. The effect on the monocytes was irregular in the 4 patients.

Lobe Index

Three of the patients showed marked decrease of the lobe index beginning around the 50th day after beginning of treatment and continuing throughout the observation period, which in these patients was from 350 to 400 days. One of the patients showed a less marked but noticeable decrease in lobe index.

Erythrocytes and Hemoglobin

All of the patients showed moderate fluctuation of red cell and hemoglobin values during and immediately following the treatment period.

No significant changes were observed in the packed cell volume in any of the 4 patients.

Sedimentation Rate

No significant changes were observed in any of the 4 patients.

Platelets

All 4 of the patients showed very marked decrease in platelets at around the 60th day after beginning of treatment, followed by recovery in all cases.

Prothombin Concentration

No significant changes in prothrombin concentration were observed in any of the 4 patients.

Cholesterol

No changes in cholesterol values were noted for any of the 4 patients.

Patients Receiving 8000 Microcuries P^{32} - (Graphs 5 - 10)

Total White Count

Six patients received total doses of 8000 microcuries of P^{32} and were observed for periods from 230 - 400 days. One of the patients showed a slight abortive rise in total leucocyte count after the first dose. All 6 of the patients showed a marked decrease in total leucocyte count which reaches its lowest point at about the 60th day after beginning of treatment. The neutrophile count followed the total leucocyte count in all of the patients while the lymphocyte count in 4 patients was much more sharply decreased than the neutrophiles. Monocyte counts showed fluctuations in all patients. Recovery of the total leucocyte count, the neutrophiles and the lymphocytes began about the 70th day and was complete about the 160th to 200th day after beginning of treatment. In 3 patients the leucocyte count after recovery exceeded the original count. At about the 280th to 300th day after beginning of treatment a second decrease in total leucocytes, neutrophiles and lymphocytes was observed in 3 of the patients. These patients have not been under observation long enough to determine the full extent of this decrease or the time of recovery.

Lobe Index

Three of the patients showed marked decrease in lobe index, beginning during the treatment period and continuing throughout the period of observation.

Erythrocytes and Hemoglobin

All 6 patients showed moderate fluctuations in erythrocyte count and hemoglobin concentration throughout the observation period. No significant changes in packed cell volume were observed.

Sedimentation Rate

No significant changes were observed in any of the patients.

Platelets

In 4 patients marked decrease in platelet count was observed, starting during the treatment period and followed by recovery which began around the 60th day after beginning of treatment. Recovery was complete around the 240th - 280th day.

Prothrombin Concentration

No significant changes were observed in any of the patients.

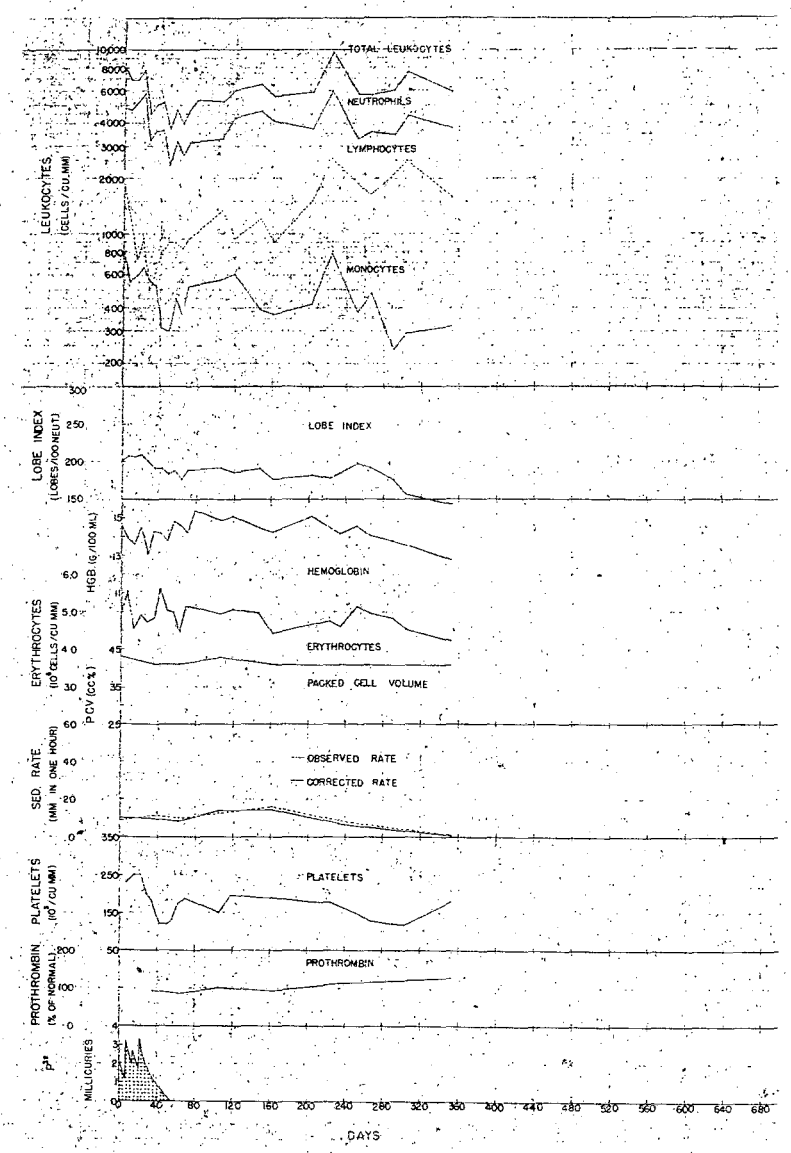
Patients Treated with Total Body X-Ray Irradiation - (Graphs 11 - 13)

During the period covered by this progress report, observation of 6 patients previously treated with total body x-ray irradiation was continued. The only noteworthy feature in these patients' hematological reaction was the fact that in 3 of these patients the lobe indices continued to decrease till the last observation on the 500th, 1180th, and 1220th day, respectively.

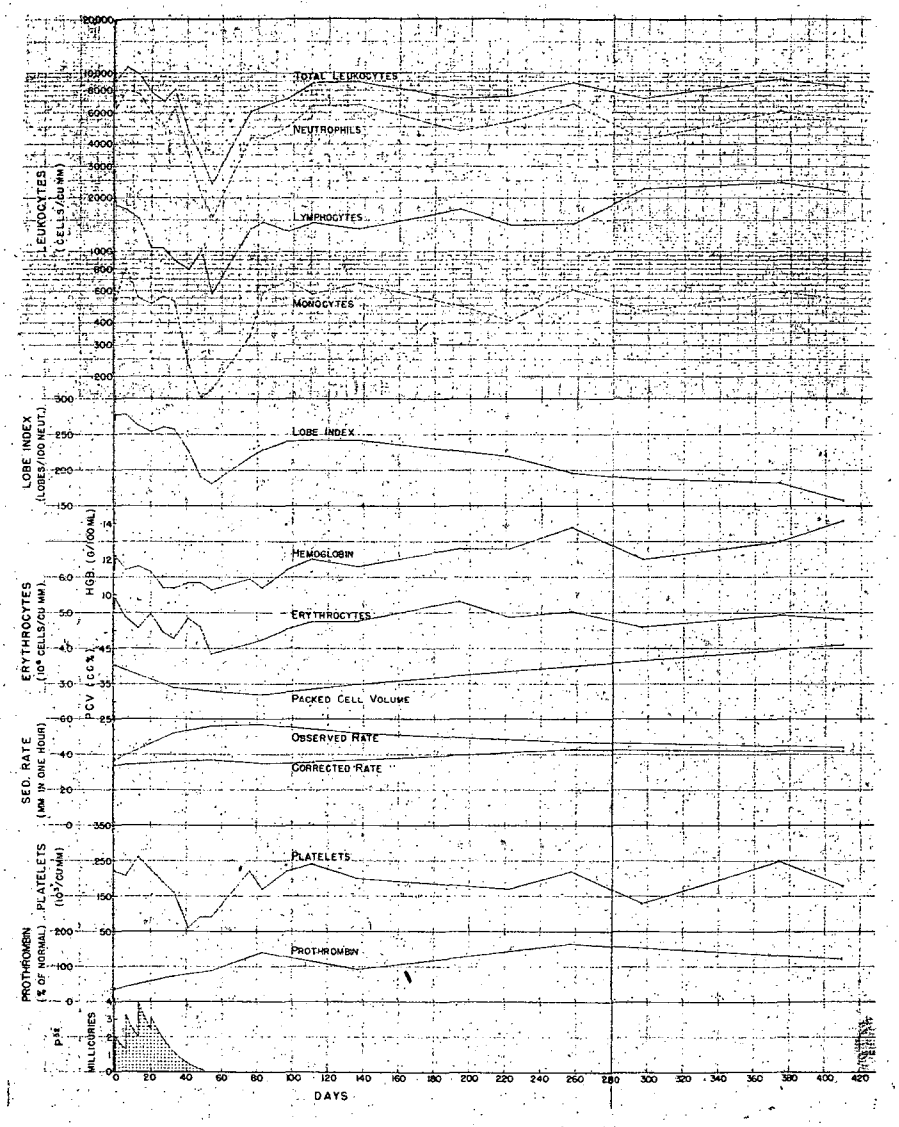
In this report period 5 new patients have been started on P^{32} treatment. Excretion studies are being made on each of these patients.

TABLE I

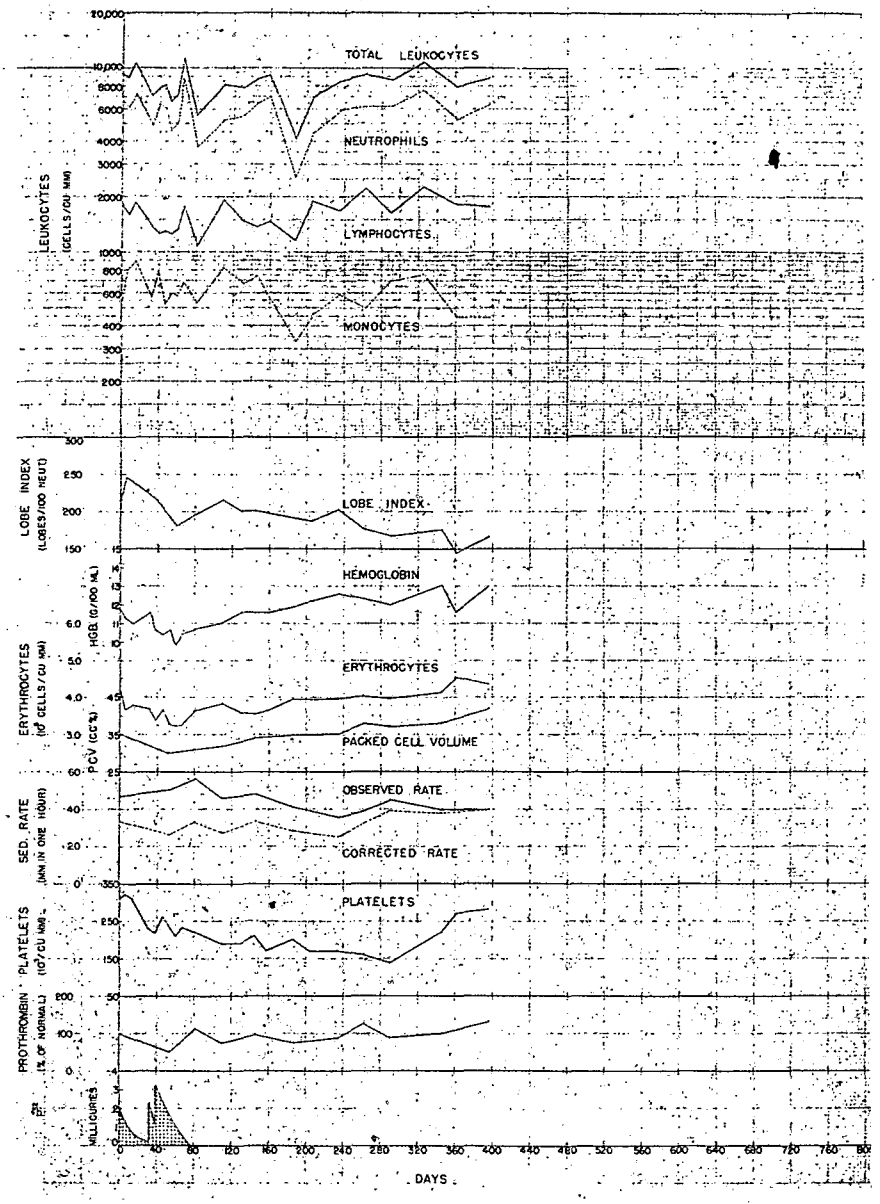
Patient Number	P^{32} Dose in µc	Interval Days	P^{32} Dose in µc	Interval Days	P^{32} Dose in µc	Interval Days	P^{32} Dose in µc	Interval Days	P^{32} Dose in µc	Total Dose	Total Time
34	2000	7	2000	7	760	7	1620			6380	21 days
36	2000	6	2000	7	2000	7	700			6700	20 days
41	2000	32	2000	7	2000					6000	39 days
42	2000	26	2000	7	2000	7				6819	40 days
33	2000	7	2000	7	2000	7	1000	7	1000	8000	28 days
35	2000	7	2000	7	2000	7	2000			8000	21 days
39	2000	7	2000	7	2000	27	2000			8000	41 days
45	2000	7	2000	7	2000	6	2000			8000	20 days
46	2000	7	2000	6	2000	7	2000			8000	20 days
47	2000	8	2000	7	2000	7	2000			8000	22 days



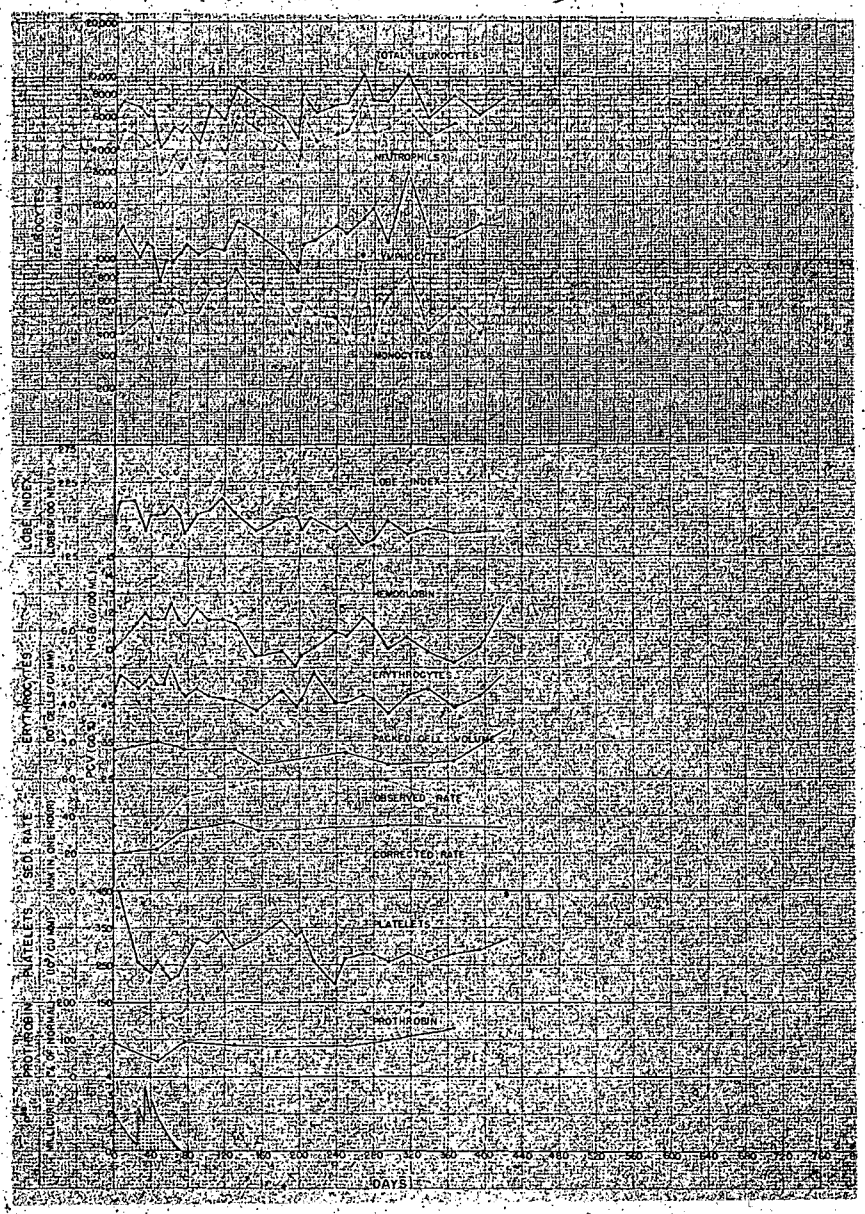
Graph I —— Patient # 34



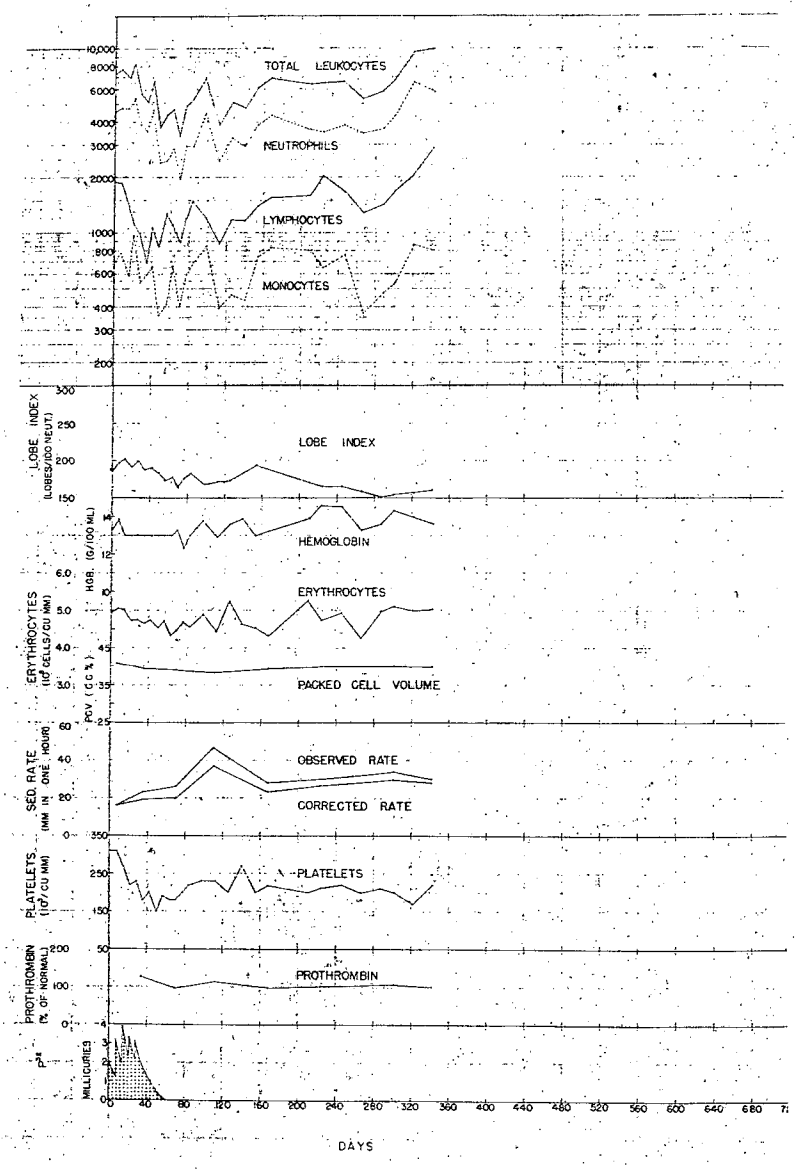
Graph II —— Patient #36



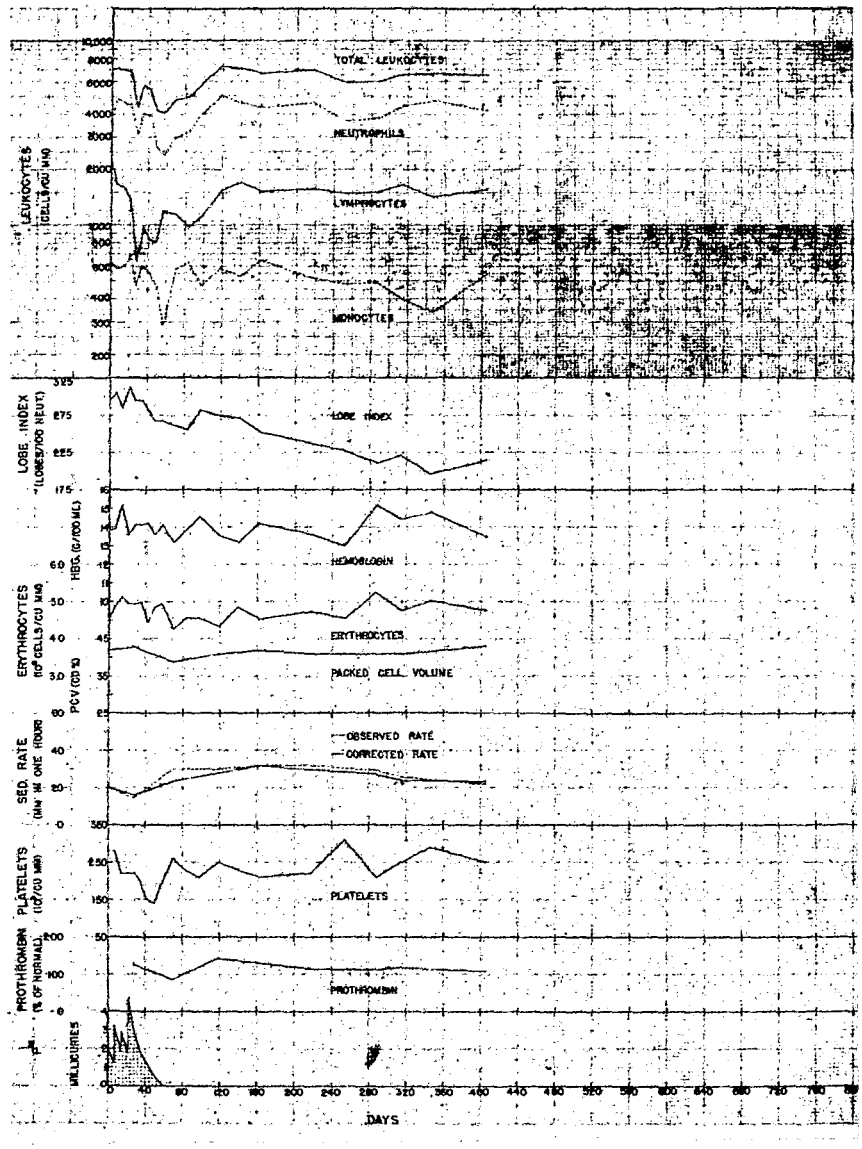
Graph III —— Patient # 41



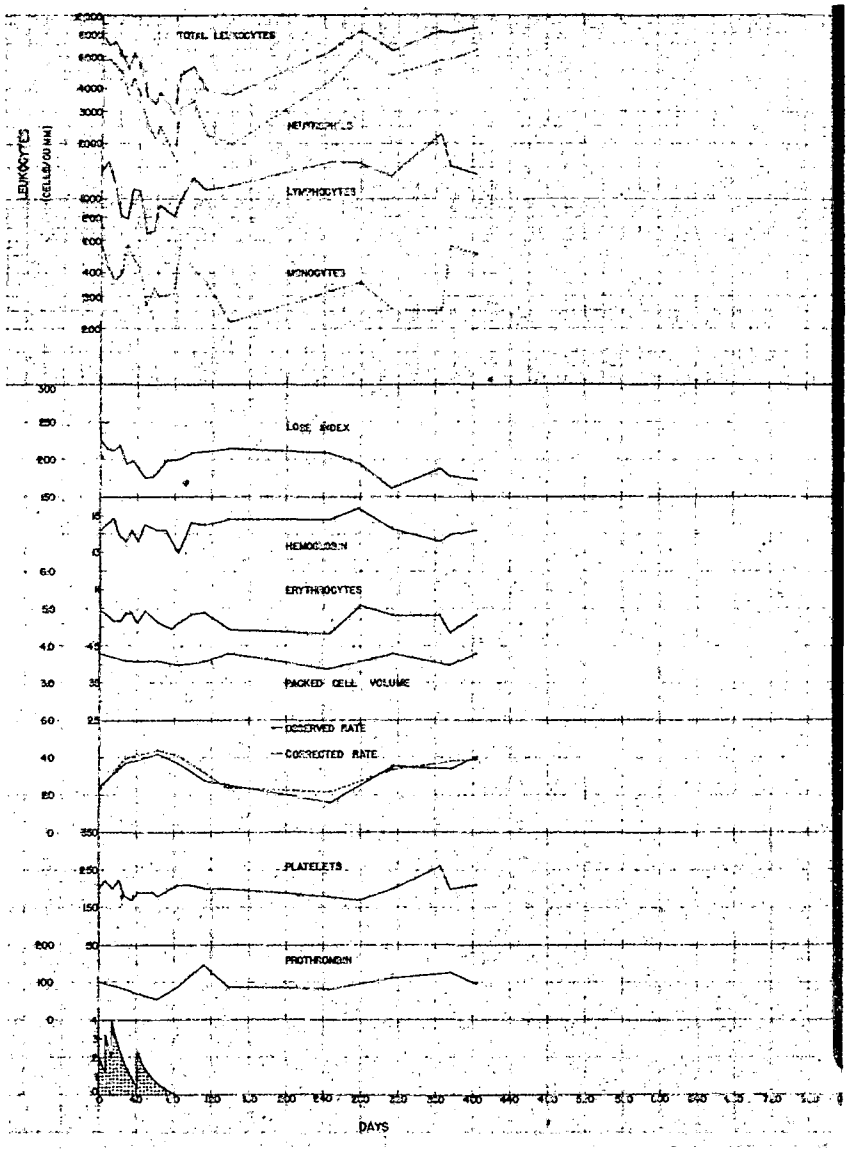
Graph IV —— Patient # 42



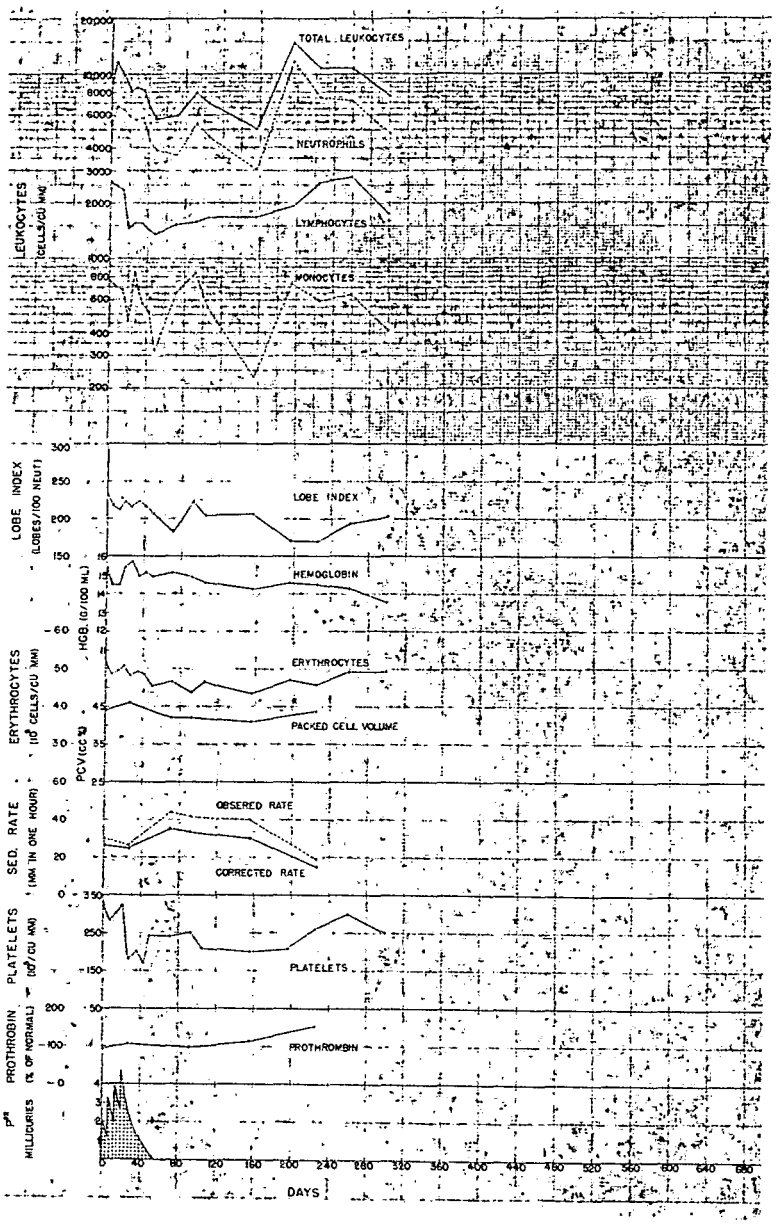
GRAPH V — PATIENT # 33



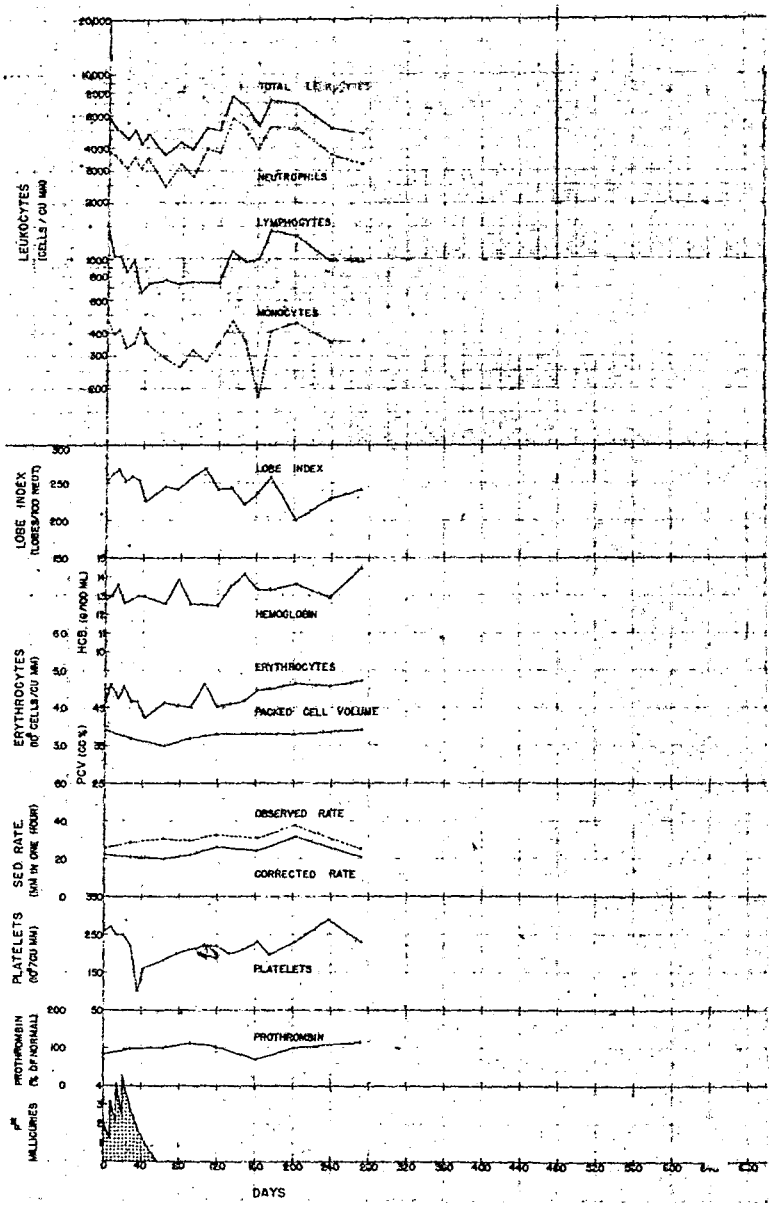
Graph VI —— Patient # 35



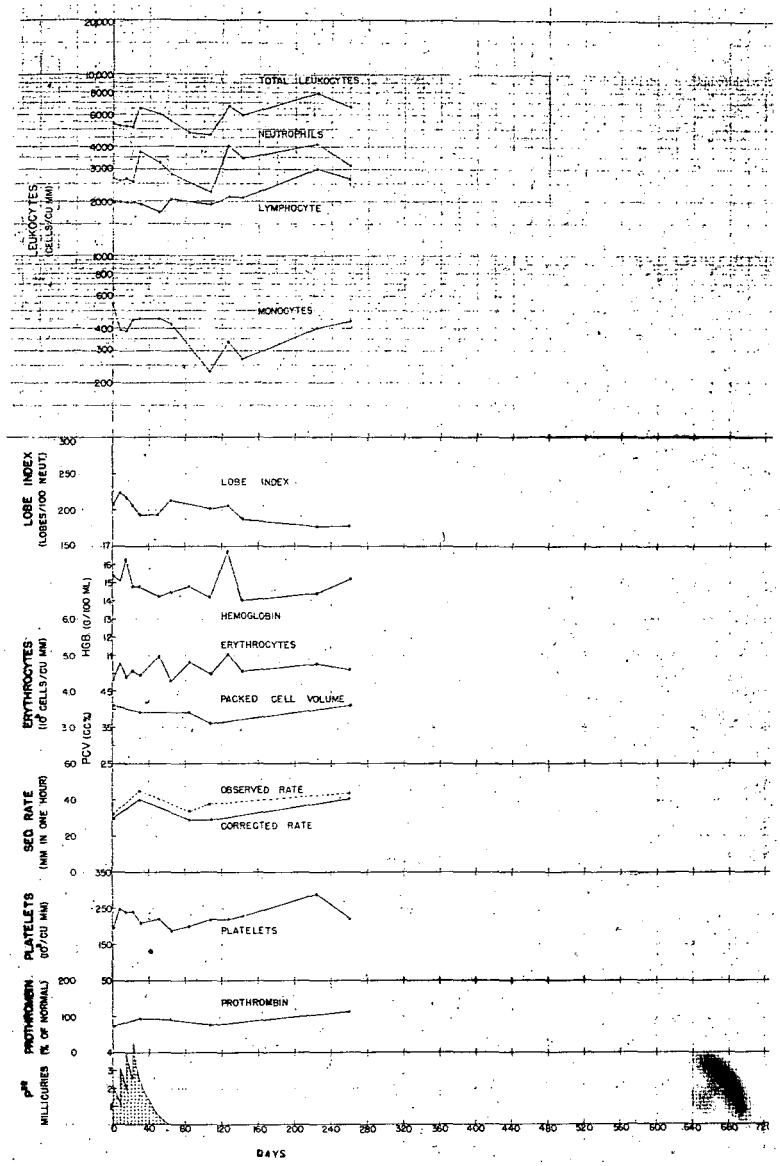
Graph VII — Patient # 39



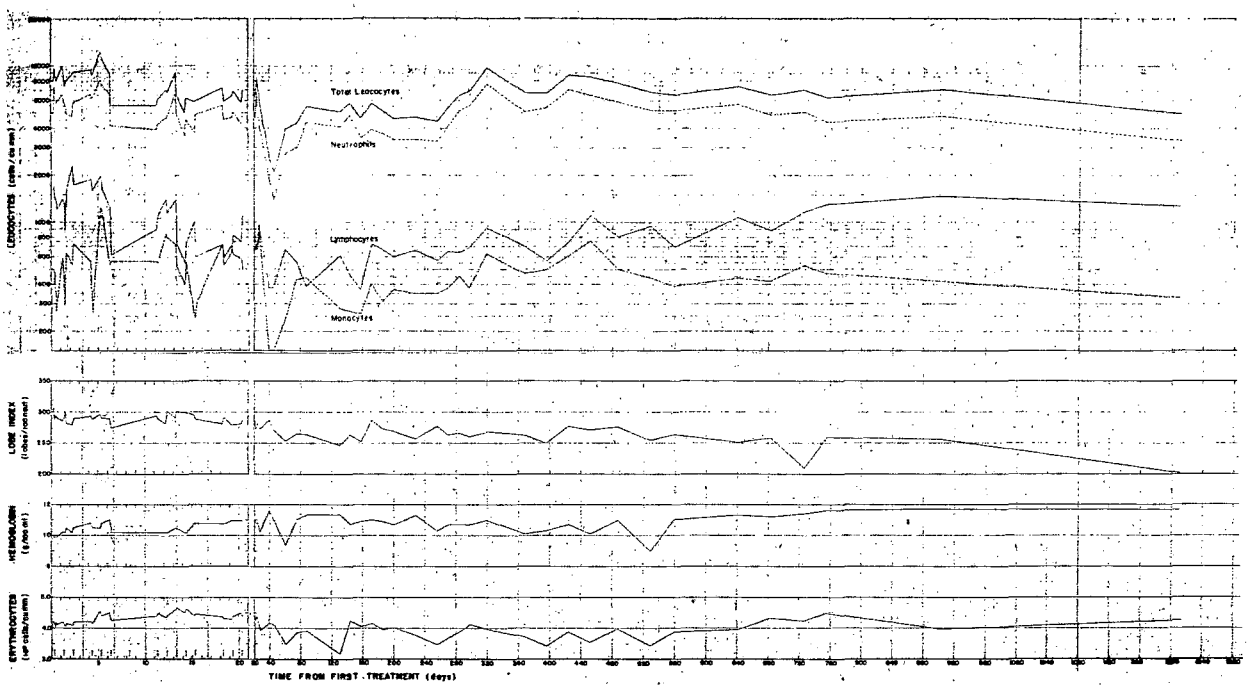
Graph VIII — Patient #45



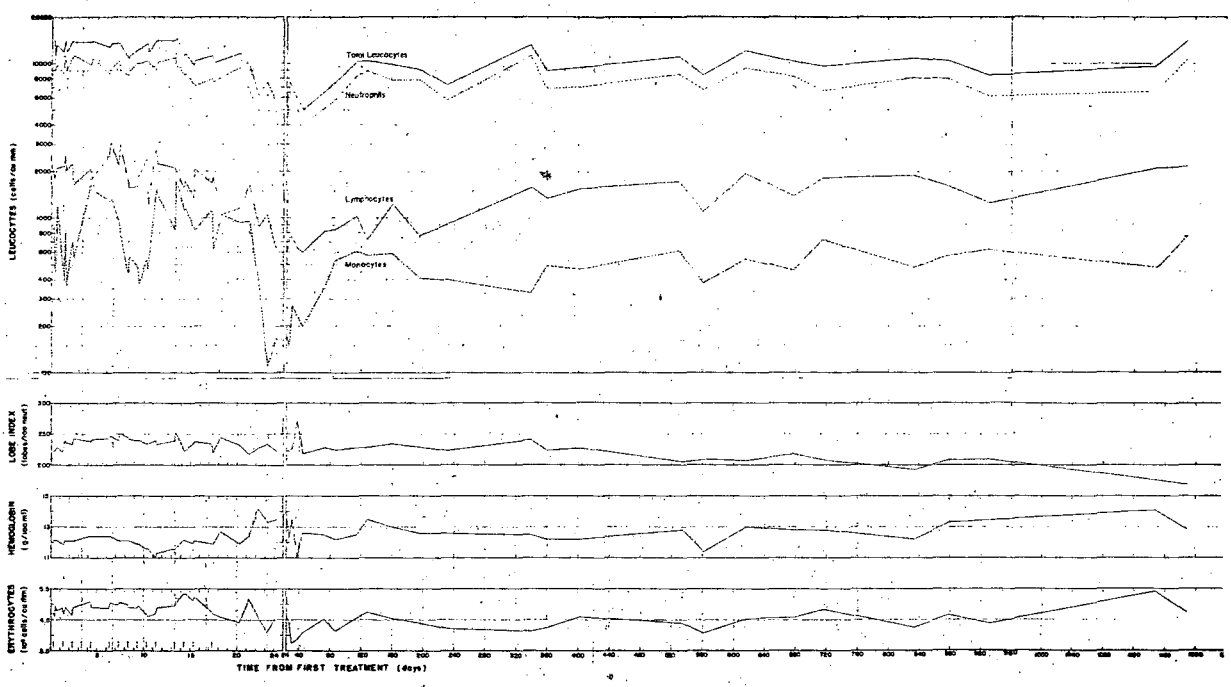
Graph IX — Patient #46



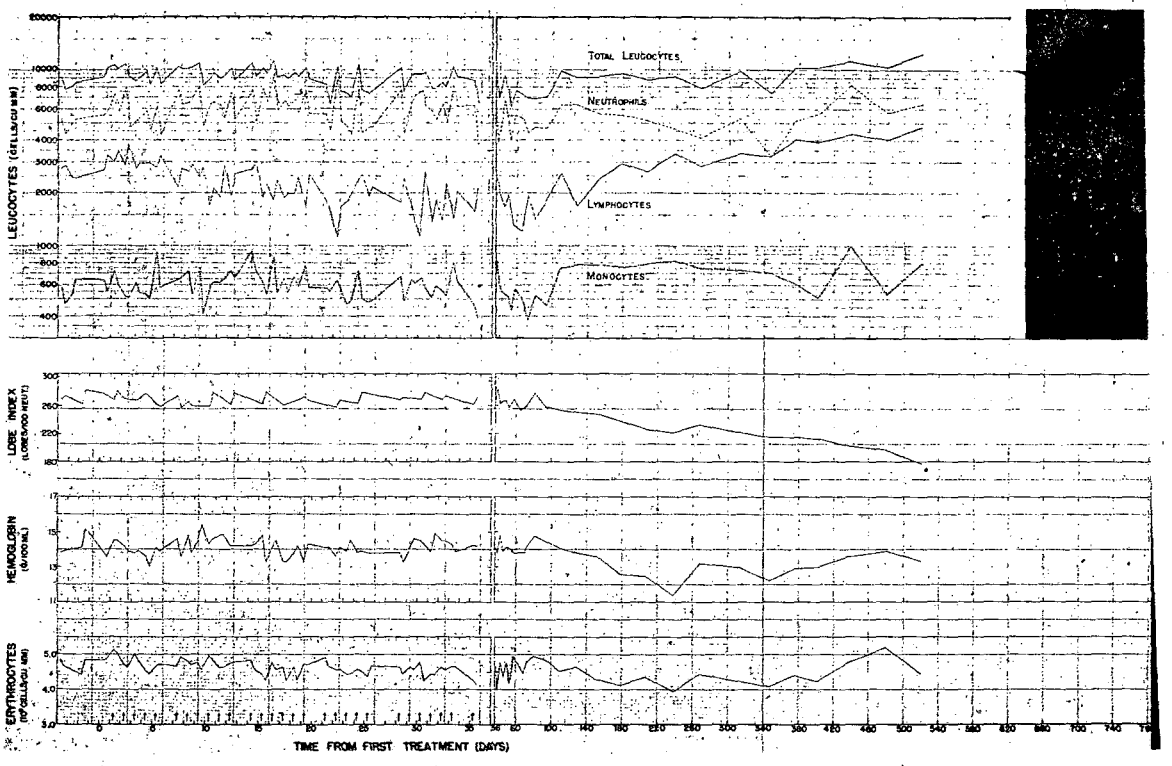
GRAPH X — PATIENT # 47



GRAPH XI — PATIENT # 21



GRAPH XII — PATIENT # 22



GRAPH XIII — PATIENT # 30

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

Earl R. Miller

From January 1 to March 31, 1948, 140 millicuries of I^{131} was received each month and was administered to 34 patients as follows:

Tracer doses only (250 microcuries or less)	16
Test doses (up to 2000 microcuries per dose)	5
Tracer and therapeutic doses	12
Therapeutic doses alone	1
TOTAL	34

On certain of these patients the following studies were made:

1. In vivo measurement of uptake of I^{131} by the thyroid gland as a function of time following administration of the dose. Measurements were made several times daily over a period of 48 hours.

2. Excretion of Iodine^{131} in the urine over the same period of time.

In addition to the above routine studies, special measurements and procedures were done in selected cases as follows:

1. Autoradiographic studies were made on the thyroid glands of ten patients who had received tracer doses of iodine at least 24-hours prior to surgery.

2. Routine blood counts and urinalyses were done on the two patients with carcinoma of the thyroid who had received 25 to 50 millicuries of radioactive iodine several months previously.

3. The amount of radioiodine in the thyroid gland was measured just before surgery in six patients who underwent subtotal thyroidectomy for non-toxic nodular goiter. Immediately after operation, the removed tissue was weighed and its content of I^{131} was measured. In all but one instance, the surgeon was able to estimate the amount of thyroid left in the neck at operation. One of the six patients had no measurable uptake of radioiodine in the neck preoperatively, and the specimen removed likewise showed no activity. In another instance the data were inconclusive since only a tiny nodule of tissue was removed from the neck, and the major portion of the gland was left intact. In only four of the six cases was a satisfactory comparison possible between the amount measured in vivo, and that contained in the surgical specimen.

Assuming a homogeneous distribution of I^{131} in the thyroid, the following relationships will obtain:

$$\frac{\text{Wt. of removed spec.}}{\text{Total wt. of gland}} = \frac{\text{Microcuries } I^{131} \text{ removed in spec.}}{\text{Microcuries } I^{131} \text{ in total gland}}$$

The total weight of the gland is determined by adding the weight of the removed specimen to the estimated weight of the tissue remaining in the neck.

	1.	2.	3.	4.
1. Weight of removed specimen...grams.....	22	5.5	20.5	23*
2. Estimated wt. of tissue left in situ.....	2	2	10.5	?
3. Estimated total wt. of thyroid.....	24	7.5	31	
4. Total microcuries measured in neck pre-operatively.....	10	55	52	63
5. Total microcuries measured in removed specimen.....	8	42	35	24
6. Predicted microcuries in total gland based upon (1), (3), & (5).....	8.7	57	53	--*
7. % error between observed and predicted totals, (4) & (6).....	13	3.7	1.9	14.3

*The patient's neck was not measured until the second post-operative day, and the measurement was corrected for decay to correspond with the measurement of the specimen 48 hours previously. No studies of urinary excretion were done on this patient post-operatively and it seems reasonable that part of the apparent error may have been due to loss of iodine through excretion.

The percentage error in the above data, represents in part the error inherent in our methods of measuring I^{131} in the thyroid gland in vivo, and in part that due to errors in estimating the weight of tissue left in situ at operation. When the amount of tissue remaining in the neck is small, errors in estimating the weight of tissue left in situ at operation. When the amount of tissue remaining in the neck is small, errors in estimation of tissue weight are small. On the other hand, when the amounts of iodine contained in the total specimen are relatively small, a greater percentage error occurs in counting.

Since the patients used in this study had nodular goiters, it is probable that there is an inhomogeneous distribution of radioiodine throughout the glands and this fact was demonstrated autoradiographically in two cases. However, the heterogenicity of the iodine distribution in the

removed specimen and in that which remained in the thyroid are probably not greatly dissimilar.

It is impossible to draw wide conclusions from so small a series of cases, however, it is intended that the problem be fully appraised after many more such observations have been gathered.

Physical Studies.

In the past three months, the counting equipment has been checked daily before work is begun. The threshold voltage and plateau characteristics of the GM tube are determined, as are its responses to known amounts of Radium and I^{131}. In addition, the following special studies have been carried out:

1. The effect of variations in the discriminator setting of the scaler upon the number of counts per minute obtained from various fixed amounts of I^{131} and upon plateau characteristics of GM tube. (The latter observations which at first appeared to be of significance, were later found to be caused by defects within the tube itself.)

2. Alterations of the resistance within the pre-amplifier circuit and resultant effects upon number of counts and upon oscilloscopic tracings from known sources of radiation.

3. Studies of the relationship between various volumes of sample containing constant amounts of I^{131} and their distances from the GM tube.

Bottles of four sizes were used, 13, 23, 33, and 60 cc. Three bottles of each size were employed and contained approximately 1, 2, and 3 millicuries respectively. Measurements of each of the twelve bottles were taken at distances of 20, 40, 60, and 80 cm. From the data obtained it may be stated, briefly, that when the various samples are measured at distances of from 20 to 80 cm, it is not possible to distinguish the differences in size of the sources. However, preliminary studies done more recently suggest that there is a significant difference in the number of counts obtained from the same quantity of radioiodine contained in 13 cc and 60 cc bottles when measured at a distance of less than 10 cm. It may ultimately be possible to estimate the size of the source by measuring the same sample at a short (under 10 cm) and a relatively long (20 to 80 cm) distance. Again, further study is required and is now in progress.

4. Absorption curves were prepared under varied circumstances, with small and large samples, measured at short and long distances. The filtration effects of several materials were studied as follows: lead, copper, paper, prestwood. The amount of radiation absorbed by each filter material is a function of mass in grams per square cm, but this function is different for different materials, i. e., materials of lower atomic number absorb less per unit mass per square centimeter than do materials of high atomic number.

5. Study of changes in the number of counts per minute obtained from a known amount of I^{131} when a suspended sample is measured in air and measured with various amounts of water acting as a backscattering medium and filter.

6. Determinations of the number of counts per minute lost through

coincidence, at various levels of activity.

7. An attempt was made to determine the effects, if any of reversing positions of two filters, one lead, the other aluminum. No demonstrable effects were observed in this instance. Since others have observed such effects, this will be studied further.

8. Preliminary studies were begun on the exposure of film to gross sources of I^{131} in an effort to determine time necessary to produce detectable blackening for variable amounts of iodine. This method is to be studied further in an attempt to calibrate it for possible use in dosimetry.

IV. HEALTH PHYSICS AND CHEMISTRY

Project 48.

Health Chemistry

N.B. Garden

Further progress on the development of equipment and techniques, whose purpose is to accomplish the goal of absolute control and trapping of radioactive substances, has taken place during this quarter. Emphasis has been on simplicity in design of the equipment with the object in mind of its decontaminatability, reproducibility, and universal use. An attempt is being made to eliminate the creation of equipment for specific, isolated performances but to make parts and accessories which are interchangeable. This attempt is illustrated in certain aspects of the new lead-shielded gloved hood now under construction.

Further progress can be seen in the elimination of contamination in the laboratories due not only to the increased use of gloved boxes but to the improvement in the less spectacular, routine techniques, such as in more detailed planning in the handling of targets and the accessories involved therein, the making readily available of small containers, trays, tongs, and other handling equipment which all help to eliminate not only the occurrence of contamination but also the receiving of radiation by the personnel involved. With the advent of less and less need for routine monitoring and surveying, more time has become available for anticipating the needs of the chemist in the line of small details, which, by necessity, because of lack of time and personnel, had to be more or less by-passed in former days.

Development during this quarter in addition to the gloved hoods and their accessories has been the accession and readying of a velometer for air-flow measurement further spinner column developments, a new target assembly for the 60-inch cyclotron, and a high temperature furnace for spectrum analysis of radioactive isotopes.

The collection and disposal of radioactive waste continued to be adequate for the present needs. The contaminated material in the Army 2001 Warehouse, Oakland, numbering approximately one hundred forty items and weighing individually from one to around ten thousand pounds, has been packaged and is being disposed of at sea, four trips being required.

A central stock of currently-unused isotopes is being collected in Bldg. 5, which isotopes are available for use by anyone desiring them. In addition to this stock, records are on hand and being gathered regarding the presence of other isotopes on the Project, many of which are available on request.

The chart of Figure 1 illustrates the set-up of the Health Chemistry Organization. It illustrates the personnel assigned to each of the three divisions of activity, showing special responsibilities within the group; an equally important fact illustrated is the overlapping of duties among the three groups.

This is of necessity because of the smallness of the group and because of the relation of activities and necessity of cooperation amoung the groups. This chart is in no way official or permanent but merely serves to show what set-up has taken shape and been in practice with good success for some months and will so remain for the present time.

Health Physics

B.J. Moyer

Aside from routine matters of monitoring areas and personnel, there has been a problem of variation of sensitivity among various lots of film used in personnel film badges. It has been found necessary to provide with each lot of film (all ostensibly the same) a separate calibration curve for the photometer to convert densities into readings of dosage.

Data are being accumulated on the radiation fields of the linear accelerator, and of the cyclotron as its shielding is being augmented. A discussion of this may be incorporated in a following quarterly report.

HEALTH CHEMISTRY ORGANIZATIONAL SETUP

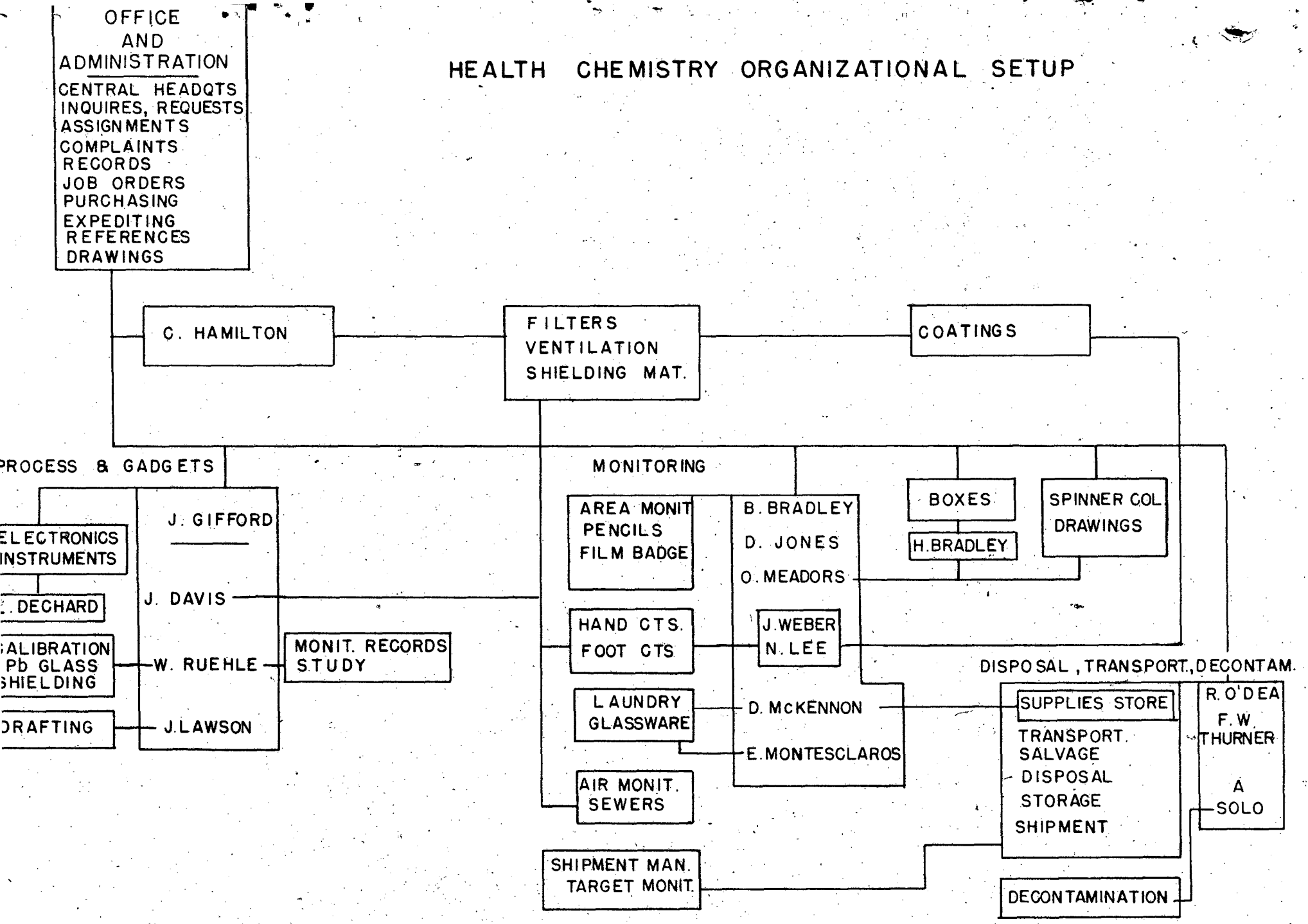


FIG. I

RECEIVED
LAWRENCE RADIATION LABORATORY

SEP 16 1964

TECHNICAL INFORMATION DIVISION
LIVERMORE