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I THE METABOLIC PROPERTIES OF PLUTONIUM AND ALLIED MATERIALS

J. G. Hamilton

Project 48 A-I

Radioautography and Histology

C. W. Asling

Rats which had been subjected to a smoke chamber containing plutonium were sacrificed 64 days after exposure and hisotlogic sections of their lungs prepared. Radioautographs were made on NTA emulsion.

Multiple discrete autographs of the tracer element were obtained. By far the greatest majority were clusters of tracks converging on single cells. Most of these cells were either free in the alveoli or lay against the alveolar walls. The cells were large, rounded or polygonal, with eosinophilic cytoplasm; their nuclei were usually rounded and vesicular, although occasionally small and pyknotic. They appeared to be alveolar macrophages ("dust cells"). The tracks emanated from foci in these cells; rarely were there multiple foci, and commonly the area was single, restricted, and lay to one side of the nucleus but near it. The foci were very small, a micron or possibly less in them (Fig. 1). A few binucleate cells were seen; the focus of the cluster lay between the nuclei. It may be suggested that the foci were in the vacuoles or "segregation apparatus" of these cells. It cannot be said whether or not they emanated from carbon particles of dimensions below the limit of resolution.

A few of the macrophages contained carbon or dust particles. In such cases the tracks were not sharply focused, but appeared to arise diffusely in the cytoplasm (Fig. 2).

Some of the cells from which clusters of tracks emanted were incorporated in alveolar walls, and probably represented fixed macrophages.

A small but appreciable number of foci was found which bore no relation to cells. However, in the immediate neighborhood of their centers there could be found in several instances pyknotic nuclear remnants and amorphous eosinophilic material. This suggested that these cells had died and disintegrated, leaving the vacuolar contents lying free. Some few foci were found which had no obvious relationship to any formed elements.

Stray tracks were sometimes found, most often in the alveolar spaces, for which no structural basis could be observed. It is most unlikely that these represent any un-phagocytosed original inhaled particulate matter in submicroscopic dimension, considering the long recovery interval (over two months) which had elapsed. They may represent a further stage in cell destruction and disintegration with liberation of contents.

Photomicrographs of radioautographs of rat lung, 64 days after inhalation of plutonium "smoke". Alveolar macrophages, X800, double exposure (at plane of section and in plane of NT-A emulsion).

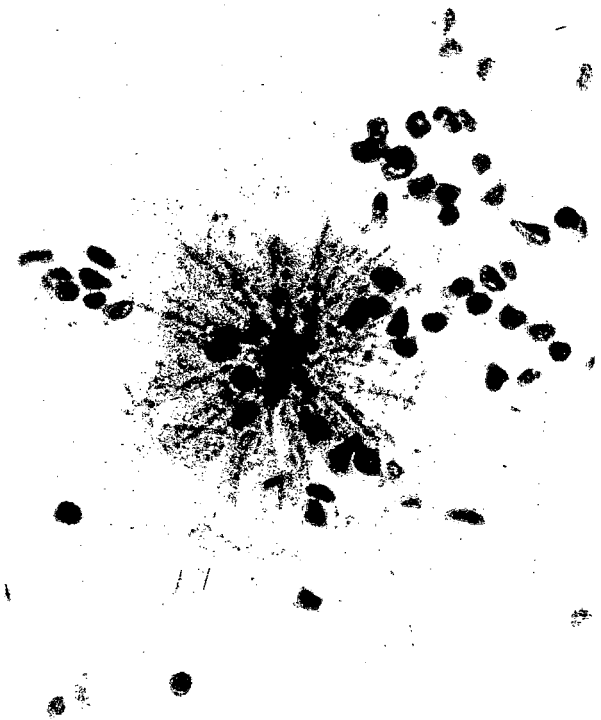

Figure 1. Tracks convergent on a single focus in cytoplasm just beside the nucleus.

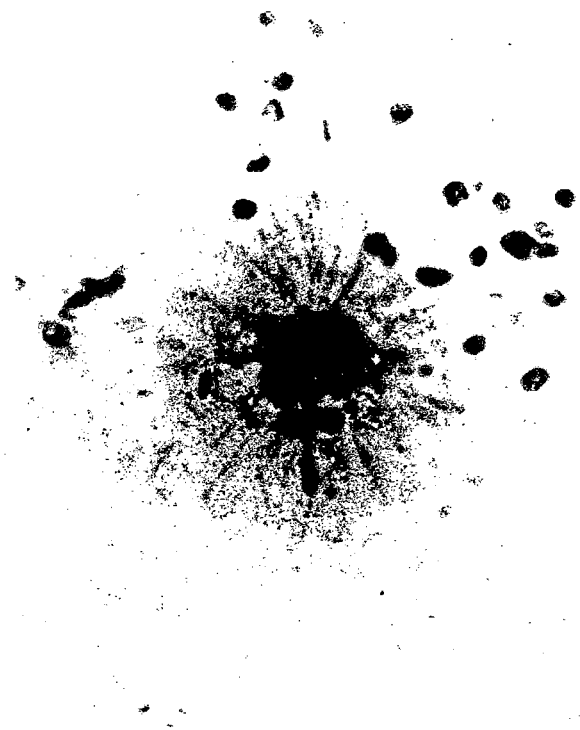

Figure 2. Tracks originating diffusely. Note presence of many carbon particles in cytoplasm surrounding nucleus.

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The pattern of dispersal was of interest. Areas of concentration were seen, showing three or four foci per high power field; few truly solitary foci were found. On the other hand, large regions were seen in which no foci were found in a low-power field; even single tracks were lacking in these regions. No obvious anatomical landmark separated areas of concentration from negative areas, although the possibility remains that they represent regions served by different bronchioles.

Metabolism of Fission Products

K. G. Scott

Terbium (Tb^{160}). The fate of terbium, using pile produced Tb^{160} as a tracer, has been studied in rats. This material was injected intramuscularly without complexing agents. There was 0.6 microgram of stable terbium administered to each animal which contained 6 microcuries of Tb^{160}. Sixty percent remained at the injection site the first day, 52 percent after the fourth day, and 30 percent after 32 days. Of the material absorbed, it may be seen from examining Table I that the deposition of Tb, when given to rats in microgram amounts, is similar to that of the other lanthanide rare earths. For example, there was observed initially high skeletal and liver deposition with slightly lesser amounts in kidney, lung, and spleen. Twenty percent of the absorbed material was excreted in the urine 1 day after its administration. Four days after the administration of Tb, a slight retention was observed in the soft tissue content. This was reflected in an increase in fecal elimination, as a part of the Tb eliminated by the body is apparently accomplished by excretion by the liver into the gastro-intestinal tract. This is later found in the feces. The excretion of Tb in the liver as compared to the 1 day group was only 23 percent, or 3 percent more than that observed in the 1 day group.

Thirty-two days after the intramuscular injection of Tb, all but 29.7 percent was absorbed from the injection site. With the exception of liver, kidney, and spleen, the soft tissue concentration is low, averaging less than 0.2 percent of the dose per gram of wet weight tissue. As can be seen from examination of Table I, the major organ in which Tb is deposited for this time period is the skeleton, this group of animals having 56 percent of the dose in the skeletal system.

Tb was not lost from the skeleton in any large amounts in these time periods, and for this reason appears to remain in the body for relatively long periods of time after parenteral uptake.

When Tb, complexed with sodium citrate and using Tb^{160} as a tracer, is administered to rats by intramuscular injection, greater uptake from the injection site was observed than that which is shown for the uncomplexed material in Table I. Thus, at 1, 4, and 32 days after injection of the complexed Tb, 10 percent, 8 percent and 4 percent respectively of the injected dose was absorbed. However, once this material is absorbed, the tissue deposition of the originally complexed Tb is not dissimilar from the uncomplexed material. These data are summarized in Table II.

The deposition of uncomplexed Tb in rats after intravenous administration, using 30 microcuries of Tb^{160} as a tracer, at 1, 6, and 32 days after injection is summarized in Table III. It can be seen from these data that this route of administration of Tb does not result in an organ deposition which is different from that observed after intramuscular injection as shown in Table I. Furthermore, complexing of Tb with sodium citrate, as shown in Table IV, does not alter the tissue deposition or excretion to any great extent when compared to the uncomplexed intravenous studies or the intramuscular studies.

TABLE I

DEPOSITION OF TERBIUM IN THE RAT USING Tb^{160} AS A TRACER 1, 4, and 32 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. SIX-TENTHS MICROGRAM TERBIUM WAS ADMINISTERED TO EACH RAT.

Organ	1 day		4 days		32 days	
	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.14	.17	.10	.17	.10	.10
Lung	.63	.23	.36	.21	.30	.13
Spleen	.26	.23	.23	.25	.55	.36
Blood	1.92	.12	.31	.02	.05	<.02
Liver	18.7	1.89	12.8	1.11	4.79	.51
Kidney	3.72	1.78	2.75	1.55	2.21	.78
Adrenal	<.03	-	<.02	-	<.02	-
Thyroid	<.03	-	<.02	-	<.02	-
Lymph Gl.	-	.23	-	.17	-	.08
Pancreas	.09	.09	.02	.04	.07	.05
Brain	<.03	<.03	<.02	<.02	<.02	<.02
Fat	-	-	-	-	-	<.02
Stomach	.57	.17	.42	.08	.20	.05
Sm. Int.	1.60	.17	.90	.06	.35	.02
Lg. Int.	1.58	.23	1.55	.17	.18	.02
Skeleton	37.8	1.72	38.6	2.37	56.1	2.75
Muscle	4.67	.04	3.74	.03	3.18	.02
Skin	6.30	.14	4.16	.13	3.00	.08
Eyes	<.03	.06	<.02	.08	<.02	.03
Pituitary	<.03	-	<.02	-	<.02	-
Gonads	.20	.09	.13	.06	.18	.07
Urine	20.4	-	23.3	-	10.4	-
Feces	1.37	-	10.6	-	18.2	-

TABLE II

DEPOSITION OF TERBIUM COMPLEXED WITH SODIUM CITRATE IN THE RAT USING Tb^{160} AS A TRACER 1, 4, and 32 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED IN PERCENT OF DOSE. SIX-TENTHS MICROGRAM OF TERBIUM AND 12 MILLIGRAMS OF SODIUM CITRATE WERE ADMINISTERED TO EACH RAT.

	1 day		4 days		32 days	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.11	.13	.11	.16	.05	.05
Lung	.54	.23	.31	.20	.08	.06
Spleen	.25	.21	.30	.04	.13	.11
Blood	.66	.05	.11	.01	<.19	.01
Liver	14.3	1.82	8.25	1.18	.67	.06
Kidney	3.92	2.24	2.80	1.78	.64	.27
Adrenal	<.01	-	<.01	-	<.01	-
Thyroid	.01	-	<.01	-	<.01	-
Lymph Gl.	-	.20	-	.23	.02	.07
Pancreas	.05	.08	.03	.05	.01	.01
Brain	.01	<.01	.03	.03	<.01	<.01
Fat	-	-	-	-	-	<.01
Stomach	.61	.29	.42	.36	.16	.03
Sm. Int.	1.29	.19	.87	.19	.22	.02
Lg. Int.	1.30	.27	.67	.20	.13	.01
Skeleton	44.6	2.47	52.7	3.14	50.2	2.62
Muscle	3.61	.04	3.29	.04	1.99	.02
Skin	5.20	.16	4.99	.20	2.08	.05
Eyes	.01	.05	.03	.08	<.01	.03
Pituitary	<.01	-	<.01	-	<.01	-
Gonads	.15	.07	.20	.08	.06	.02
Urine	20.8	-	20.6	-	30.6	-
Feces	2.50	-	4.20	-	12.9	-

TABLE III

DEPOSITION OF TERBIUM IN THE RAT USING Tb^{160} AS A TRACER 1, 6, and 32 DAYS AFTER INTRAVENOUS ADMINISTRATION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. SIX-TENTHS MICROGRAM OF TERBIUM WAS ADMINISTERED TO EACH RAT.

	1 day		6 days		(one animal only) 32 days	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.18	.22	.12	.17	.04	.04
Lung	.41	.28	.27	.18	.12	.07
Spleen	.28	.30	.23	.27	.10	.06
Blood	.25	.02	.03	<.01	.01	<.01
Liver	10.6	1.47	4.30	.60	.92	.08
Kidney	3.08	2.08	1.36	.92	.71	.35
Adrenal	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-
Lymph Gl.	.02	.38	.05	.21	.02	.04
Pancreas	.09	.10	.03	.06	.01	.01
Brain	.02	.01	.01	.01	.01	<.01
Fat	-	.02	-	.02	-	.01
Stomach	.82	.49	.34	.20	.13	.06
Sm. Int.	1.64	.23	1.04	.15	.28	.02
Lg. Int.	1.33	.36	.46	.10	.09	.01
Skeleton	55.8	4.34	59.9	4.72	63.5	4.74
Muscle	3.48	.04	3.77	.04	3.08	.03
Skin	5.96	.16	3.78	.12	1.83	.04
Eyes	.01	.04	.01	.05	<.01	-
Pituitary	<.01	-	<.01	-	<.01	-
Gonads	.12	.07	.11	.05	.05	.02
Urine	14.0	-	19.6	-	20.8	-
Feces	2.02	-	4.60	-	10.7	-

TABLE IV

DEPOSITION OF TERBIUM COMPLEXED WITH SODIUM CITRATE IN THE RAT USING Tb^{160} AS A TRACER, 1, 6, and 32 DAYS AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. SIX-TENTHS MICROGRAM TERBIUM AND 6 MILLIGRAMS SODIUM CITRATE WERE ADMINISTERED TO EACH RAT.

	1 day		6 days		32 days	
Organ	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.13	.14	.09	.12	.07	.10
Lung	.38	.22	.37	.19	.33	.16
Spleen	.19	.19	.20	.19	.14	.15
Blood	.23	.02	.03	<.01	.02	<.01
Liver	9.79	1.22	4.05	.46	.76	.07
Kidney	1.60	1.10	1.59	.99	.91	.49
Adrenal	<.01	-	<.01	-	<.01	-
Thyroid	<.01	-	<.01	-	<.01	-
Lymph Gl.	.02	.33	.04	.18	.03	.11
Pancreas	.07	.07	.03	.05	.02	.02
Brain	.02	.01	.01	<.01	.03	.01
Fat	-	-	-	.02	-	<.01
Stomach	.69	.28	.35	.15	.16	.04
Sm. Int.	1.41	.19	.64	.07	.27	.02
Lg. Int.	1.96	.38	.39	.06	.11	.01
Skeleton	55.5	4.30	58.0	4.29	47.0	3.25
Muscle	2.32	.02	2.80	.03	3.50	.03
Skin	5.21	.16	3.50	.10	2.05	.05
Eyes	.02	.05	.01	.04	.01	.04
Pituitary	<.01	-	<.01	-	<.01	-
Gonads	.11	.05	.10	.05	.08	.04
Urine	19.0	-	21.7	-	33.9	-
Feces	1.26	-	6.14	-	10.5	-

Scandium (Sc^{45}). Two studies involving carrier-free Sc^{45} have been conducted in rats in which both groups of animals were sacrificed 1 day after (1) intramuscular injection of 0.7 microcuries of Sc^{45}, and (2) intravenous injection of 1.5 microcuries of Sc^{45}. In general, the metabolism of this element is reminiscent of that of yttrium. For example, the uncomplexed material is absorbed with great difficulty from the injection site, there being but 8 percent absorbed in the first day. After absorption, the major areas of deposition are skeleton, liver, and kidney, although the skeleton values observed were lower than those observed for yttrium. The excretion is primarily fecal and probably represents material which has been eliminated by the liver by excretion in the bile. These data are summarized in Table V.

When Sc^{45} is given intravenously, 60 percent of the material injected was found in the liver 1 day after injection. The percent retention per gram of liver and spleen are approximately the same, being the neighborhood of 6 percent of the dose per gram per organ and these tissues show the greatest predilection for this material when they are compared to the other soft tissues and skeleton in the body. This retention was probably related to the reticulo-endothelial activity of these organs. These data are summarized in Table VI.

Tantalum (Ta^{182}). Carrier-free Ta^{182} has been given to rats, each animal receiving 11 microcuries by intramuscular injection. They were sacrificed at 16 and 32 days. This material is absorbed from the injection site with ease and is practically complete. In this sense it is rather different from the fate of Ta when large amounts of carrier are present. Sixteen days after administration, approximately 1 percent of the injected material remained in the animals which demonstrates the ability of the animal to readily excrete Ta in minute amounts as opposed to the low rate of excretion and lengthy organ retention of this same material when given to rats in microgram amounts. Similar data from animals sacrificed at 32 days also demonstrated the lack of retention of Ta in their tissues. All but approximately 1 percent of the material was eliminated in this time period. The excretion of this material occurs approximately in a ratio of 4 in the urine to 1 in the feces.

Manganese (Mn^{52}). Carrier-free Mn^{52} has been studied in the rat, each animal receiving 4 microcuries by intravenous injection. Animals sacrificed 2 hours after administration of this material demonstrate that it is rapidly removed from the blood since this fluid contained but 0.3 percent of the dose originally administered. Mn was readily picked up by soft tissues, the highest concentration beginning with liver, and then being followed by kidney, heart, small intestine and stomach. Large amounts of material were found in the contents of the small intestine. However, at this time period, less than one-tenth of 1 percent of the Mn so administered was excreted. The animals sacrificed at 1 day after intravenous administration showed that this material is rapidly excreted from the body since 44 percent was found in urine and feces. Liver and kidney continued to retain large amounts of this material as well as there being large amounts associated with the gastro-intestinal tract, this being the apparent route of excretion after the Mn is eliminated into the G. I. tract via the liver and the bile. These data are summarized in Table VII.

TABLE V

DEPOSITION OF CARRIER-FREE Sc^{45} IN THE RAT 1 DAY AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE.

Organ	% per organ	% per gram
Heart	.23	.23
Lung	.85	.38
Spleen	.77	.85
Blood	12.4	.92
Liver	8.69	.85
Kidney	1.62	1.00
Adrenal	.08	-
Thyroid	<.08	-
Lymph Gl.	.08	.38
Pancreas	.54	.23
Brain	.15	.08
Stomach	.46	.15
Sm. Int.	4.38	.46
Lg. Int.	3.31	.31
Skeleton	14.1	.85
Muscle	4.15	.05
Skin	5.46	.23
Eyes	<.08	-
Pituitary	<.08	-
Gonads	.08	.31
Urine	7.62	-
Feces	34.9	-

TABLE VI

DEPOSITION OF CARRIER-FREE Sc^{45} IN THE RAT 1 DAY AFTER INTRAVENOUS INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE.

Organ	% per organ	% per gram
Heart	.14	.15
Lung	.66	.32
Spleen	5.33	5.71
Blood	3.75	.26
Liver	60.1	6.68
Kidney	.86	.48
Adrenal	.02	-
Thyroid	.01	-
Lymph Gland	.03	.40
Pancreas	.12	.18
Brain	.03	.02
Fat	-	.08
Stomach	.44	.25
Small Intestine	4.46	.50
Large Intestine	1.68	.24
Skeleton	6.30	.38
Muscle	4.38	.04
Skin	4.98	.15
Eyes	.04	.10
Pituitary	<.01	-
Gonads	.53	.21
Urine	1.01	-
Feces	5.09	-

TABLE VII

DEPOSITION OF CARRIER-FREE Mn^{52} IN THE RAT 2 and 24 HOURS AFTER INTRAVENOUS INJECTION AS $MnCl_4$. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE. SMALL TISSUES WERE LUMPED FOR EACH GROUP OF 3 RATS.

	2 hour		24 hour	
Organ	% per organ	% per gram	% per organ	% per gram
Heart	1.24	1.67	.39	.43
Lung	1.29	.62	.76	.36
Spleen	1.22	.92	.63	.63
Blood	.30	.02	.12	<.02
Liver	20.8	2.21	11.6	1.21
Kidney	8.16	5.20	4.91	2.77
Adrenal	.15	-	.12	-
Thyroid	.02	-	<.02	-
Lymph Gl.	-	-	-	.12
Pancreas	-	-	3.23	1.79
Brain	.12	.07	.12	.08
Fat	-	.14	-	.21
Stomach	1.82	1.56	1.34	1.17
Stom. Cont.	.10	.03	.22	.12
Sm. Int.	6.58	1.84	2.27	.44
Sm. Int. Cont.	20.4	5.75	1.94	.48
Lg. Int.	4.28	1.05	2.82	.79
Lg. Int. Cont.	4.37	1.58	2.68	.90
Skeleton	6.16	.37	5.25	.29
Muscle	14.2	.14	9.45	.08
Skin	7.74	.21	7.06	.20
Gonads	1.02	.45	.84	.43
Urin	.02	-	3.04	-
Feces	.07	-	41.3	-

Chromium (Cr^{51}). Preliminary studies involving the deposition of carrier-free Cr^{51} in rats following intramuscular injection are in process. The rats were sacrificed at 1 and 16 days after administration of 2 microcuries per animal of Cr^{51}. These data are summarized in Table VIII. At the early time period, large amounts of Cr^{51} were excreted in the urine. The residue remaining in the body was found rather uniformly mixed with all of the tissues of the rat. However, because of the low concentration seen in the red cells as compared to the relatively high concentration in the plasma, it must be presumed that Cr does not exist in the blood stream as an ion or a small molecule since the space in the in the red cell for materials of this type is relatively half of that of the plasma. Sixteen days after the administration of Cr^{51}, over 78 percent of the material absorbed was excreted. At this time period, kidney, skeleton, spleen, and liver contained the highest tissue concentrations per gram. Cr^{51} is not absorbed from the injection site readily, 47 percent and 33 percent were found at the injection site 1 and 4 days after its administration.

Astatine (At^{211}). Studies upon the metabolism of At have been continued in the rat. It has been shown that At follows the pathway of iodine in the body to some extent. For example, it is possible to astatine-block the thyroid by the addition of 1 milligram of iodine carrier per dose of At to each rat studied. In this case, where the control animals averaged an astatine uptake of 1.74 percent, those receiving 1 milligram of carrier iodine, the At uptake by the thyroid was 0.45 percent. Similar results were obtained by placing animals in iodine-block by daily injections of 1 milligram of potassium iodide for 6 days previous to the administration of At. In this study, the control animals had an average thyroid uptake of 0.84 percent. The animals which were given iodine previous to the administration of the At had an average thyroid uptake of but 0.1 percent. On the other hand, the reduction of iodine in the diets of rats resulted in an increase and greater than normal At uptake. For example, when rats were placed on an iodine-free diet for 2 weeks prior to the injection of At, these animals had an average thyroid uptake of At of 2.34 percent, whereas the control animals on an iodine normal diet demonstrated an At thyroid uptake of 0.97 percent. Owing to the fact that At might be complexed with iodine in the body, it seems logical to postulate that the existence of this complex is the explanation as to why At "mimics" the metabolism of iodine in the thyroid.

TABLE VIII

DEPOSITION OF CARRIER-FREE Cr^{51} IN THE RAT 1 and 16 DAYS AFTER INTRAMUSCULAR INJECTION. VALUES ARE CORRECTED FOR RECOVERY AND EXPRESSED AS PERCENT OF DOSE.

Organ	1 day % per organ	1 day % per gram	16 days % per organ	16 days % per gram
Heart	.20	.22	<.06	<.06
Lung	.68	.44	.17	.11
Spleen	.48	.48	.30	.30
Plasma	5.92	.72	<.06	<.06
Cells	.70	.09	<.06	<.06
Liver	3.31	.39	2.20	.21
Kidney	1.39	.81	1.27	.68
Adrenal	<.04	-	<.06	-
Thyroid	<.04	-	<.06	-
Lymph Gland	-	.68	-	.30
Pancreas	.46	.24	.17	.08
Brain	.04	<.04	<.06	<.06
Fat	-	.15	-	<.06
Stomach	.22	.17	<.06	<.06
Stom. Cont.	.06	.33	<.06	<.06
Sm. Int.	.68	.15	.23	.06
Sm. Int. Cont.	.61	.26	<.06	<.06
Lg. Int.	.89	.30	.25	.08
Lg. Int. Cont.	2.29	.96	<.06	<.06
Skeleton	10.6	.68	8.64	.55
Muscle	7.36	.06	4.53	.04
Skin	6.01	.15	3.71	.08
Eyes	<.04	-	<.06	-
Pituitary	<.04	-	<.06	-
Gonads	.54	.33	.30	.13
Urine	56.2	-	63.6	-
Feces	1.46	-	14.7	-

Effect of Whole Body Radiation on Extra and Intracellular Electrolytes

John Z. Bowers

Previous studies have indicated that there are variations in the concentration of radioactive sodium in feces and urine following exposure of rats to total body irradiation at the LD_{50} level and above. These are in essence an increase in the concentration of the isotope in the feces with diarrhea, and a corresponding fall in the urinary concentration. These studies have been continued by determinations of total sodium and potassium in urine and feces using the Beckman flame photometer.

Fig. 1 follows the total amount of sodium and potassium excreted in the urine and feces following 710 r total body irradiation. It is evident that despite the striking rise in concentration of sodium in diarrheal feces, there is no increase in the total amount of sodium excreted which agrees with previous reports emphasizing the ability of the kidney to defend sodium when loss through other channels is excessive or intake depressed. Depression of potassium excretion also occurs but is neither as prompt nor as marked as with sodium. This finding supports the reports that the kidney is less able to defend potassium than sodium when intake is depressed or losses through other channels increase. In animals receiving larger doses of total body irradiation (1370 r), the dissociation of the normal relationships between sodium and potassium was even more striking.

The changes are particularly evident when one compares the urinary and fecal ratio of sodium to potassium (Na/K), for in the animals receiving 710 r the urinary ratio was depressed on days 2, 3, 4, 5 and 6 post-irradiation and on days 5 and 6 in the feces.

Investigations on the alterations of electrolytes in irradiated animals led us to study the variations in sodium and potassium content of the various organs and tissues of irradiated rats. Several aspects of acute radiation injury suggest that there should be significant losses of intracellular potassium. We were interested to determine the extent and chronology of such loss and associated movements of sodium. We assumed that a significant expansion of sodium space which could not be accounted for by an increase in the weight of the organ, in the water content of the organ, or by a rise in plasma sodium of similar magnitude would of necessity imply the movement of sodium into cells and that this would be associated with or follow a movement of potassium out of cells.

Method. Slonaker rats weighing approximately 250 grams each were placed on a synthetic diet complete for the rat. Each animal received 2.0 microcuries of Na^{22} subcutaneously and 24 hours later 880 r of total body x-irradiation: rate 130 r per min., 15 m.a., 0.5 m.m. Cu and 1.2 m.m. Al. The dose was verified with a paraffin phantom using a Victoreen r meter. The animals were then serially sacrificed at 0 time (9 rats), 24 hours (8 rats), 48 hours (9 rats), 72 hours (8 rats), 96 hours (5 rats), 120 hours (5 rats) and 9 days (6 rats). Three rats were retained as controls and sacrificed on the fifteenth day. At the time of sacrifice the animals were anesthetized with chloroform, 2.0 cc of

heart blood was withdrawn into a heparinized syringe and the animal was then sacrificed with additional chloroform. The various organs and tissues were removed cleanly, the gastro-intestinal tract was opened with scissors, the contents carefully removed and the tissues washed gently with Tyrode's solution and blotted with filter paper. After wet weighing, all organs and tissues were dried at 104°C and re-weighed. They were then ashed in the muffle at 500-600°C and counted using conventional procedures. The sodium space for an organ was calculated by the following equation:

$$\frac{\text{Percent of dose per gram tissue}}{\text{Percent of dose per ml plasma}} \times \frac{0.93}{0.95} \times 100 = \text{sodium space}$$

Subsequently, the ash was redissolved in N/10 HCl and sodium and potassium determined on the flame photometer.

Results. The data listed in the following tables and figure are in a measure self-explanatory. There is a pronounced expansion of sodium space in several of the radiosensitive organs--namely, lymph nodes, gastro-intestinal tract and spleen. The gonads which are considered to be highly radiosensitive do not follow the other organs. The lungs and kidney show a slight expansion of sodium space at a time interval much greater than that for the "sensitive" tissues. We assume that the lack of alteration in the sodium space of the liver implies a lack of cellular damage which coincides with the reports on failure to demonstrate significant histo-pathological changes in this organ at similar dosage levels. Skeletal sodium space expands within 24 hours.

Water Content. Table I gives the percentage water content of various tissues on the days following irradiation. Our initial figures are in good agreement with those of other investigators. We were impressed by the lack of any significant alteration in these figures save for the ninth day after irradiation when the gastro-intestinal tract, gonads and lungs all showed an increase of water content.

Body and Tissue Weights. The animals showed a progressive weight loss which was continuing on the ninth day post-irradiation. As has been emphasized by many investigators, the most striking weight loss appeared in the spleen and was next most evident in the liver. See Table II.

Comments. When one considers individual tissues, our data are in general, consonant with existing ideas as to the histo-pathological alterations with radiation injury.

The data reported suggest that there is a rapid and pronounced loss of potassium from a number of radiosensitive tissues. This could be explained as the result of depression of intracellular metabolic processes. The potassium loss is accompanied by a depletion of sodium which we cannot explain at this time.

As cellular injury advances, there is a movement of sodium into sensitive tissues which may represent an effort at the restoration of osmotic equilibrium or a loss of competancy by the cellular membrane.

Other investigators have demonstrated that potassium and sodium may exchange in muscle and liver. Our studies indicate that this may happen in a number of other organs and tissues when cells are injured.

A complete report on these studies will be submitted in the near future.

TABLE I

PERCENTAGE WATER CONTENT OF VARIOUS ORGANS AND TISSUES OF RATS FOLLOWING ACUTE WHOLE BODY IRRADIATION.

Organ	0 days	1 day	2 days	3 days	4 days	9 days
Spleen	76.5	70.5	73.7	71.7	70.2	77.5
Lymph Nodes	59.1	53.5	62.7	59.5	-	-
Sm. Intest.	78.6	76.7	83.1	77.4	79.6	84.1
Lg. Intest.	71.7	75.0	79.0	77.9	77.6	84.8
Stomach	73.9	75.4	79.5	80.6	80.4	81.6
Gonads	83.1	85.1	84.8	84.7	82.3	90.3
Liver	70.0	72.9	73.4	71.0	69.9	76.1
Kidney	77.5	75.0	77.3	75.0	71.8	80.3
Brain	77.2	77.1	78.4	77.3	77.7	80.8
Heart	73.7	69.4	79.8	76.9	73.8	80.1
Lungs	71.5	76.2	75.7	73.1	72.7	84.6

TABLE II

VARIATIONS IN THE WHOLE ORGAN WEIGHT OF THE RAT AT VARIOUS TIME PERIODS FOLLOWING WHOLE BODY X-RAY IRRADIATION

Organ	0 days	1 day	2 days	3 days	4 days	5 days	9 days
Aver. Init. Wt.	214.1	210.0	222.75	216.7	204.1	209.5	213.6
Aver. Final Wt.	214.1	210.0	211.5	188.2	172.0	172.0	150.1
Aver. Wt. Loss	-	-	11.25	28.5	32.1	37.5	63.5
Spleen	.522	.466	.422	.331	.344	.177	.304
Sm. Intest.	4.74	4.53	4.06	3.08	3.42	3.49	4.18
Lg. Intest.	2.39	2.69	2.46	2.05	1.62	1.73	2.08
Stomach	1.34	1.475	1.33	1.36	1.45	1.24	1.09
Gonad	2.17	2.28	2.25	2.01	1.92	1.99	1.80
Liver	8.12	8.68	8.59	7.59	5.64	5.32	7.33
Lungs	1.64	1.84	1.78	1.475	1.282		1.27
Kidney	2.01	1.875	1.95	1.67	1.58	1.53	1.58

TABLE III

DISTRIBUTION OF RADIO-SODIUM IN THE ORGANS OF THE RAT AT VARIOUS TIME PERIODS FOLLOWING X-RAY IRRADIATION. THE DATA ARE EXPRESSED IN PERCENT OF DOSE PER GRAM WET WEIGHT OF TISSUE.

Organ	0 days	1 day	2 days	3 days	4 days	5 days	9 days
Heart	.55	.65	.46	.48	.48	.60	.73
Lung	.64	.46	.68	.82	.67	.81	1.00
Spleen	.45	.46	.58	.51	.79	.68	.26
Blood(plasma)	1.19	1.31	1.22	1.34	1.26	1.24	1.45
Liver	.48	.50	.55	.48	.50	.50	.53
Kidney	.63	.84	.77	.76	.77	.57	1.00
Lymph Node	.51	.78	.16	.96	1.29	4.10	2.61
Pancreas	.29	.42	.36	.42	.25	.54	.68
Brain	.51	.66	.53	.56	.83	.80	.81
Stomach	.60	.37	.32	.45	1.01	.98	.53
Sm. Intest.	.43	.44	.27	.85	.98	.85	.40
Lg. Intest.	.61	.38	.30	.79	.98	.63	.36
Skeleton	1.17	1.65	1.42	1.28	1.56	1.43	1.41
Balance	.25	.38	.36	.35	.38	.34	.46
Muscle	.30	.32	.34	.34	.29	.29	.40
Skin	.67	.44	.52	.63	.57	.59	.53
Eyes	.240	1.15	1.07	.98	.97	1.15	1.33
Gonads	.62	.64	.48	.29	.64	.46	.63

TABLE IV

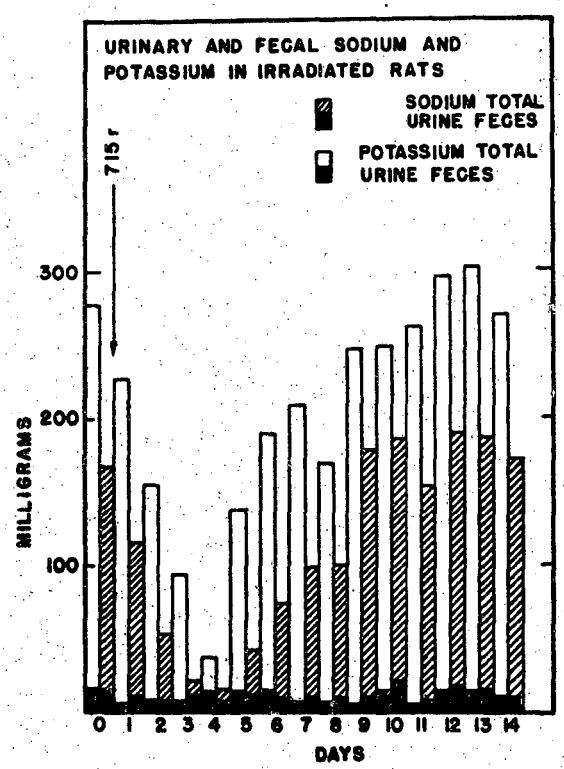
VARIATIONS IN SODIUM SPACE OF THE ORGANS AND TISSUES
OF THE RAT FOLLOWING X-RAY IRRADIATION

Organ	0 days	1 day	2 days	3 days	4 days	5 days	9 days	Controls 15 days
Lymph Node	39.8	66.5	12.2	66.6	95.2	300.7	166.5	41.2
Sm.Intest.	33.4	37.4	20.6	59.0	72.4	63.5	25.7	43.6
Lg.Intest.	50.3	32.2	20.8	58.9	72.3	47.4	23.2	
Stomach	49.6	31.7	24.0	31.2	74.5	73.5	33.9	53.5
Spleen	35.0	39.4	44.2	35.2	58.0	58.3	16.7	26.5
Gonads	48.4	54.6	36.5	20.1	47.2	24.5	40.4	45.2
Kidney	49.2	71.6	58.7	52.8	56.8	42.8	64.1	61.7
Heart	43.0	55.5	35.0	33.4	35.4	45.0	46.8	39.5
Lung	50.0	39.2	51.6	56.7	49.5	60.8	64.1	58.5
Liver	36.7	42.5	41.8	33.2	36.8	37.4	33.9	34.6
Brain	39.8	39.2	40.4	38.9	61.2	60.0	52.0	43.8
Skin	51.5	37.5	39.6	43.6	42.0	44.2	34.0	51.8
Skeleton	90.6	141.0	121.0	88.8	108.0	107.0	90.0	104.0
Plasma	1.19	1.09	1.22	1.34	1.26	1.24	1.45	1.19

TABLE V

ALTERATIONS IN POTASSIUM CONTENT OF VARIOUS ORGANS OF THE RAT FOLLOWING ACUTE TOTAL BODY RADIATION. (POTASSIUM CONTENT WAS DETERMINED WITH THE FLAME PHOTOMETER AND IS EXPRESSED IN MILLIGRAMS PER GRAM WET WEIGHT OF TISSUE.)

Organ	0 days	1 day	2 days	3 days	4 days	5 days	9 days
Spleen	4.50	2.25	3.37	4.00	3.56	3.29	-
Lymph Nodes	4.42	2.68	1.79	2.16	4.25	5.37	3.36
Sm. Intest.	3.13	2.24	1.01	1.58	1.54	2.58	1.73
Lg. Intest.	2.42	1.74	1.44	1.62	1.62	2.30	1.52
Stomach	2.33	1.65	1.47	1.37	1.15	1.72	1.70
Gonads	3.40	3.45	2.88	2.76	2.58	2.04	3.74
Liver	3.29	2.86	2.34	3.15	3.81	3.36	3.25
Skin	1.78	1.72	1.40	1.37	1.67	1.33	1.50
Plasma	0.22	0.19	0.24	0.19	0.21	0.21	0.15


URINARY AND FECAL SODIUM AND
POTASSIUM IN IRRADIATED RATS
SODIUM TOTAL
URINE FECES
POTASSIUM TOTAL
URINE FECES
715 r
300
200
100
MILLIGRAMS
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
DAYS

MU-962

Fig. 1

Chelating Experiments

Harry Foreman

Plutonium and Cerium. The in vivo experiments described in Progress Report UCRL-683 have been completed. The full details of the technique of the experiment have been presented in that report. In brief, the experiment was carried out as follows: Two groups of 6 rats each were injected with Pu^{239} and Ce^{144}. One group was kept as a control group and was given no further treatment. The second group was administered chelating agents in varying dosages at different periods of time. The dosages and time periods are indicated in the key to Table I.

Results. The results are presented in Table I and Figs. 1 and 2.

As can be seen from the Tables and Graphs, the administration of Ca EDTA (calcium chelate of ethylenediamine tetracetic acid) at time periods of 1 day and 15-20 days resulted in enhanced urinary excretion of the injected plutonium at levels approximately 10 times greater than the control animals. The effect lasted for several days after the cessation of the treatment. At 50-55 days Fe-3[1] increased the urinary excretion by a factor of 6 to 7 each day of administration and for 3 days after cessation of the drug. The administration of calcium citrate under the same circumstances as the other chelating agents did not affect the urinary excretion of the radio-elements whatsoever. The fecal excretion of plutonium was not affected by the chelating agents except when the Ca EDTA was administered during the first 24 hours and at this time there was a very marked effect.

The administration of Ca EDTA did not affect the urinary excretion of the cerium except when administered in the first 24 hours, when an effect of approximately 3 times as great as the control levels was obtained. The fecal excretion of cerium was also not affected by the chelating agents except when administered during the first 24 hours, and here again, as in the plutonium, a very pronounced effect was noted.

Discussion. It is of interest that the repeated day-to-day administration, at least for the length of time involved in this experiment, i.e., 4 to 5 days, continued to bring forth high levels of urinary radio-element excretion. In the rat at time periods when the plutonium is well fixed in the body the urinary-fecal excretion ratio is approximately 1:15. This means that an increase in urinary excretion of 10:1 does not affect the overall excretion very markedly. However, in human beings the urinary-fecal excretion ratio for plutonium is approximately 1:1, and here a ten fold increase in the urinary excretion of the radio-element will result in approximately a ten fold increase in the overall excretion of the plutonium. With increase in the excretion rate constant of a factor of ten, one could surmise that the biological half-life of the plutonium in the body could be decreased to one-tenth. In this experiment the dosage levels chosen were entirely arbitrary. It may be that the greater effects could be obtained with higher dosage levels. The lack of response of cerium urinary levels to the chelating agent administered

TABLE I

EFFECT OF CHELATING AGENTS ON EXCRETION OF PLUTONIUM AND CERIUM IN RATS

(Key to Tables on Page 29)

Time	Pu^{239} Control		Pu^{239} Experimental		Ce^{144} Control		Ce^{144} Experimental	
Days	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces
0-1-a	.057	0.09	3.26-b	8.52-b	3.68	0.62	10.8-b	12.2-b
1-2	.610	3.21	3.46	2.93	0.83	2.59	.95	2.38
2-3	.228	1.71	0.421	1.89	0.61	1.55	.22	1.93
3-4	.126	2.90	0.249	2.29	0.12	3.73	.19	5.58
4-5	.066	1.59	0.145	2.54	0.05	2.54	.11	2.66
5-7	.156	1.48	0.278	1.53	0.22	3.72	.35	7.44
7-8	.069	1.47	0.176	1.08	0.18	3.02	.08	2.46
8-10	-	-	-	-	-	-	-	-
10-11	.102	1.20	0.181	0.78	0.07	2.40	.13	2.35
11-12	.054	1.20	0.138	0.96	0.07	-	.06	1.85
12-14	.093	0.95	0.219	1.93	<0.01	4.58	.18	4.46
14-15	.032	0.53	0.340-c	0.54-c	0.05	1.03	.09-c	1.21-c
15-16	.036	-	0.352-c	-	0.04	1.40	.08-c	1.26-c
16-17	.039	0.63	0.370-c	0.24-c	0.04	1.87	.10-c	1.37-c
17-18	.033	0.71	0.255-c	0.62-c	0.03	1.81	.07-c	1.08-c
18-19	.027	0.37	0.228-c	0.57-c	0.02	0.86	.05-c	0.88-c
19-21	.054	0.24	0.228	0.24	0.04	3.51	.10	2.62
21-22	.032	0.61	0.103	0.55	0.05	1.57	.07	1.42
22-23	.028	0.34	0.046	0.46	0.02	1.37	.06	1.25
23-24	.031	0.35	0.017	0.33	0.05	-	.04	0.76
24-25	.030	0.41	0.030	0.35	0.03	1.23	.03	0.80
25-26	.020	0.40	0.017	0.28	0.03	1.36	.04	0.97
26-28	.038	0.15	0.068	0.44	0.06	1.83	.04	1.49
28-29	.026	0.34	0.030	0.21	0.03	0.68	.05	0.59
29-30	.028	0.24	-.049	0.22	0.03	0.82	.05	0.70
30-31	.020	0.24	0.30	0.10	0.03	0.62	.02	-
31-32	.017	0.19	0.033	0.19	0.03	0.49	.05	0.41
32-33	.022	0.18	0.026	0.13	0.02	0.50	.06	0.39
33-35	.050	0.20	0.086	0.22	0.06	0.69	.01	0.61
35-36	.014	0.14	0.021-d	0.22-d	0.02	0.36	.02-d	0.21-d
36-37	.024	0.19	0.022-d	0.09-d	0.02	0.30	.02-d	0.24-d
37-38	.012	0.14	0.023-d	0.14-d	0.04	0.31	.02-d	0.24-d
38-39	.017	0.19	0.013-d	0.15-d	0.01	0.34	.03-d	0.14-d
39-40	.010	0.15	0.014	0.10	0.01	0.24	.02	0.16
40-42	.015	0.13	0.034	0.13	0.05	0.50	.09	0.43
42-43	.012	0.12	0.015	0.15	0.02	0.26	.04	0.23
43-44	.016	0.14	0.015	0.14	0.03	0.19	.09	0.21
44-45	.018	0.09	0.015	0.11	0.02	0.13	.04	0.18
45-46	.010	0.10	0.011	0.10	0.01	0.22	.05	0.24
46-47	.020	-	0.005	0.11	0.02	0.15	.12	0.20
47-49	.027	0.10	0.003	0.14	0.01	0.26	.07	0.21
49-50	.009	0.10	0.067-e	0.19-e	0.02	0.15	.09-e	0.21-e
50-51	.012	0.11	0.070-e	0.11-e	0.03	0.16	-	0.17-e
51-52	.014	0.13	0.60-e	0.13-e	0.02	0.15	.06-e	0.14-e
52-53	.010	0.09	0.066-e	0.22-e	0.01	0.12	.27-e	0.03-e
53-54	.009	0.09	0.073-e	0.15-e	0.02	0.15	.39-e	0.02-e
54-56	.015	0.11	0.047	0.16	0.03	0.21	.08	0.26
56-57	.014	0.10	0.028	0.10	0.01	0.15	.01	0.10
57-58	.010	-.09	0.017	0.06	0.02	0.02	.04	0.06
58-59	.011	0.09	0.014	0.06	0.02	-	.06	0.05
59-60	.017	0.10	0.013	0.10	0.01	0.12	.04	0.11
60-61	.015	0.19	0.005	0.65	0.03	0.30	.06	0.59
61-63	.023	0.11	0.015	0.05	0.04	0.19	.04	0.04

(Key to Tables)

a) Figures represent percent of dose originally administered.

b) 25 mgm of calcium chelate of ethylenediamine tetracetic acid, (Ca EDTA) at 18 hours intraperitoneally.

c) 50 mgm of Ca EDTA intraperitoneally, twice daily.

d) 100 mgm calcium citrate intraperitoneally.

e) 100 mgm Fe-3 intraperitoneally. (Fe-3 is a commercial chelating agent. The structure has not been revealed.)

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at the later time periods than the first day could be explained by the relatively small difference in equilibrium constants of cerium and calcium. Estimates from the data of Plumb and Martell[2] would place the relative affinity of cerium for EDTA as compared to calcium for EDTA at approximately 40:20. This does not appear to be a large enough spread to cause displacement of the calcium by the cerium when very low blood levels of the cerium are present. It is worthy of note that the chelating agents had an effect on the fecal excretion of the radioelements only on the first day. If this observation holds true on repeat experiments, then it is of interest to speculate as to the reason for this curious phenomenon. It is possible that it may be related to the high liver levels or perhaps to the relatively high blood levels of the radio-elements at the initial time periods.

Beryllium Chelating Experiments. *In vitro* studies of chelating agents of beryllium have been continued. The method used was described in the last Quarterly Report. The results obtained are present in Table II. *In vivo* studies will be carried out on the most promising of the chelating agents. Mandelic acid appears to be the most likely of the chelating agents since it can be used in high dosage levels because of its low toxicity and because it is not metabolized in the body, but is excreted in the urine.

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[1] Commercial chelating agent sold by the Bersworth Chemical Company, Framingham, Massachusetts. The structure is not revealed.

[2] Unpublished results.

TABLE II

FORMATION OF SOLUBLE BERYLLIUM CHELATES AT pH 7

Positive	
Saccharic acid	
Mandelic acid	
Dicyandiamidine sulfate	
Negative	
Procaine	Mellitic acid
Creatine	Uric acid
Dimethylglyoxime	Sodium dihydroxy-tartaric acid
Succinic acid	Potassium thiocyanide
Aurintricarboxylic acid	Phthallic acid
Quinalizarin	Serime
Inositol	Urea
Cholic acid	Biuret
	Gallic acid

THE EFFECTS OF CHELATING AGENTS ON
URINARY EXCRETION OF PU-239

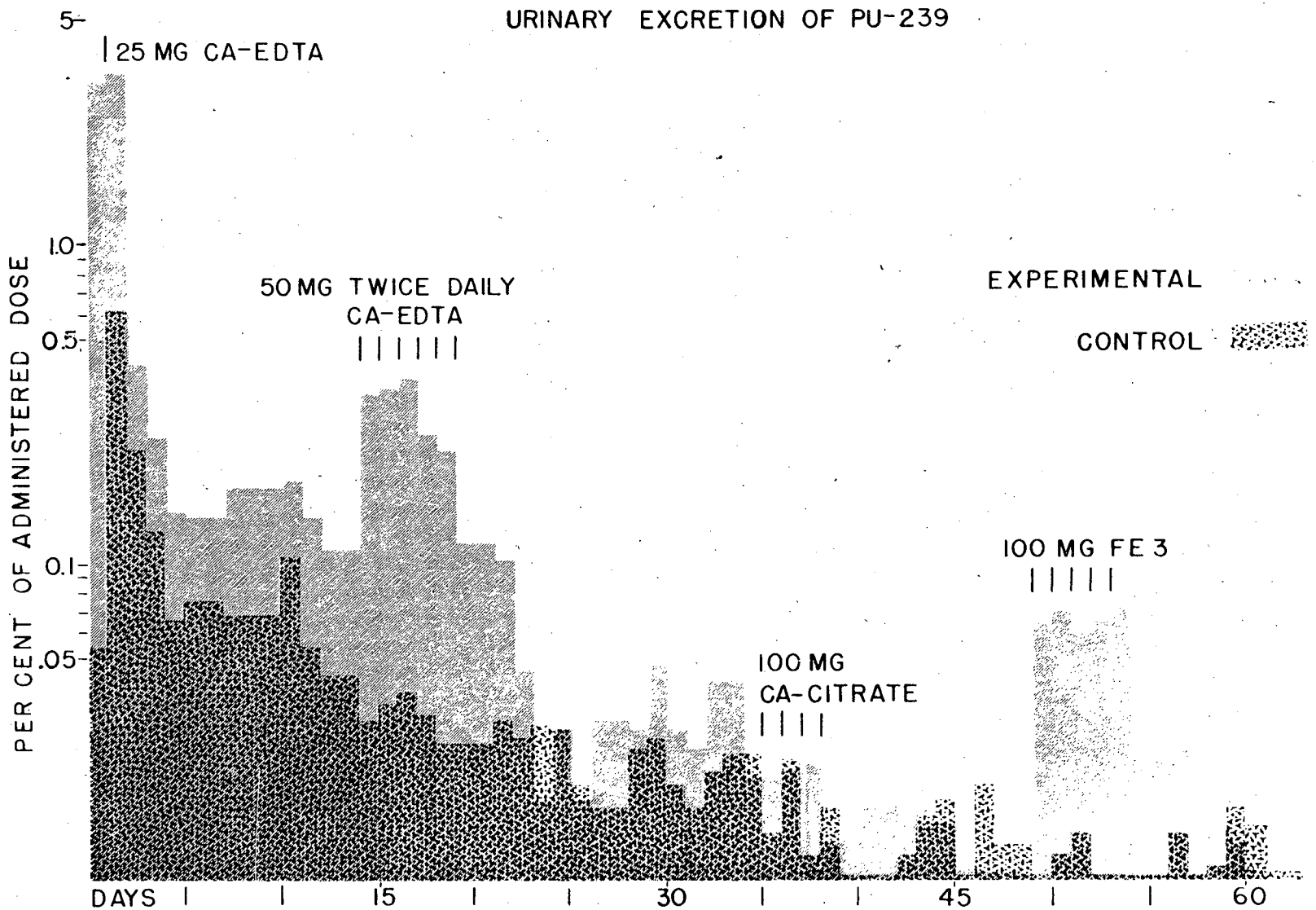

FIG. 1

07 9 69

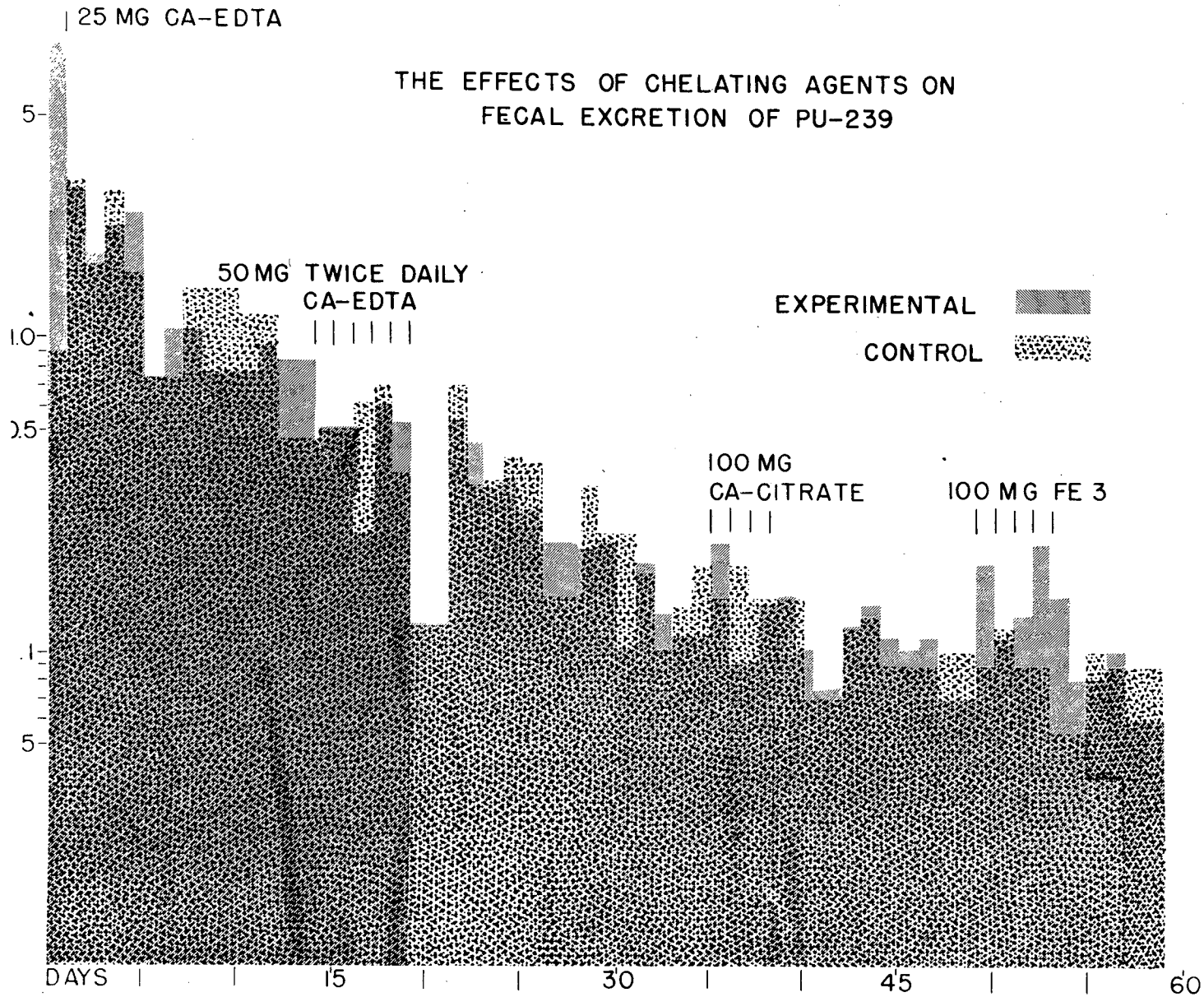
THE EFFECTS OF CHELATING AGENTS ON
FECAL EXCRETION OF PU-239
25 MG CA-EDTA
50 MG TWICE DAILY
CA-EDTA
EXPERIMENTAL
CONTROL
100 MG
CA-CITRATE
100 MG FE 3
5
1.0
0.5
.1
5
DAYS
15
30
45
60

FIG. 2

A Study of the Metabolism of Radioactive Calcium (Ca^{45}) in Young, Adult and Rachitic Rats

D. M. Thomson and D. Harold Copp

It has been shown by Jones and Copp[1] that there are profound differences in the metabolism of radioactive strontium in young, adult and rachitic rats (low phosphorus diet). This is particularly true of the kinetics of uptake of radio-strontium by the skeleton, and its excretion in urine. Both normal and rachitic young rats show a rapid initial uptake in bone, but while the depositied radioactive isotope remains firmly bound in the normal animal, it is rapidly lost from the rachitic skeleton. The uptake in the adult skeleton is much slower. Excretion of radio-strontium in urine is much higher in the rachitic animals, and the renal clearance is over ten times as great.

Although the biological behavior of strontium is very similar to that of calcium, it was felt that this work should be repeated using radioactive calcium, so that a more accurate picture would be obtained of the actual effect on calcium metabolism. In the following experiments, radioactive calcium (Ca^{45}) was injected intravenously, and the uptake in the skeleton, level in serum and excretion in urine and feces was determined at various time intervals up to 16 days following administration. In addition, the effects of a number of other factors on the bone uptake and excretion of radioactive calcium were also investigated.

Methods. The dose of radioactive calcium injected into each animal contained 5 μc of Ca^{45} with 1.25 mg Ca as calcium chloride in 0.25 cc of solution, approximately pH 4. This was administered by intravenous injection. The amount of carrier calcium present was found to be sufficient to raise the level of serum calcium as much as 25 percent, but later experiments with high specific activity calcium (0.01 mg Ca per μc) indicated that this amount of carrier had no significant effect on the distribution and excretion of the isotope.

Tissues and excreta were dry ashed, dissolved in acid, and a suitable aliquot was evaporated and weighed. A thin mica window counter tube was used for measuring the soft radiations from Ca^{45}, and a suitable correction was made for self-absorption in each case.

Animals. The adult animals were mature female rats of the Long-Evans strain, from 6 to 12 months old. Skeletal growth was at a minimum in these animals.

The rats with low phosphorus rickets were prepared according to the method described by Coleman et al[2]. They were weaned at 21 days, and fed a diet high in calcium (0.5 percent) and very low in phosphorus (0.03 percent) for 6 weeks. They were 9 weeks old and weighed approximately 100 grams at the time of the injection of radio-calcium.

The young normal animals were fed a complete diet from weaning until they were 9 weeks old, at which time they weighed approximately 200 grams. They were

then injected with the radio-calcium.

Procedures. After injection of the radioactive isotope, the animals were placed in metabolism cages, and urine and feces were collected separately. The rats were sacrificed at various time intervals from a few minutes to 16 days after the injection. In all, 64 young normal rats, 38 adults, and 69 animals with low phosphorus rickets were used.

At autopsy, the femur was removed and analyzed for Ca^{45}; the total Ca^{45} in the skeleton was estimated according to the method described by Jones and Copp[1]. An aliquot of serum was analyzed, and the total serum Ca^{45} was estimated using the value of 2.4 percent of body weight reported by Berlin[3].

Results. The results of these experiments are shown graphically in Figs. 1-5. Fig. 1 shows the percent of the dose of radio-calcium in the skeleton from 0-4 hours after administration; Fig. 2 shows the percent in the skeleton during the first 16 days. Fig. 3 gives the total serum Ca^{45} during the 16 day period.

Skeletal Uptake. (Figs. 1 and 2.) From Fig. 1 it is evident that the uptake of radio-calcium by the skeleton of young animals, both normal and rachitic, is very rapid. However, while the isotope remains fixed in the bones of the normal animals, it is quickly lost from the skeletons of the animals with low phosphorus rickets. This agrees with the previous findings of Jones and Copp[1] with radio-strontium. The uptake of radio-calcium by the mature adult skeleton is much slower.

Serum Level. (Fig. 3.) The level of radio-calcium in serum falls much more slowly in the adult animals, and remains at a consistently higher level. This reflects the slower initial uptake by the skeleton as compared to the young and rachitic rats.

Urineary Excretion. (Fig. 4.) The excretion of radio-calcium in the urine is similar in both young and adult normal animals, but is tremendously increased in the rats with low phosphorus rickets. "Renal serum clearances" were calculated 12 hours after injection by dividing the rate of urinary excretion by the total serum radio-calcium, and expressing the result as percent of the total serum in the body "cleared" of the isotope by urinary excretion per minute. For the adult animals, this value was 2.0 percent; for the young normal rats it was 0.6 percent; and for those with low phosphorus rickets it was 14 percent.

Fecal Excretion. (Fig. 5.) There is a relatively high rate of fecal excretion in the adult rats, while it is rather low in the young normal animals, and is almost insignificant in the rachitic group.

Discussion and Conclusions. In the adult rats, the relatively slow uptake of radio-calcium by the skeleton probably reflects ion exchange with the calcium in the bone salt, since there is little or no new bone formation in these animals. The initial rapid uptake in the normal and rachitic young rats is associated with the metabolically active tissue in these animals. However, while the calcium becomes fixed in the skeleton of the normal animals, it is rapidly lost from the rachitic skeleton, suggesting that it is initially taken up in a very labile form.

The high urinary excretion and renal serum clearance in the rats with low phosphorus rickets, despite a normal level of blood calcium, suggests that there is a direct effect of rickets on the calcium clearance by the kidney. This may be associated with the low level of blood phosphate in these animals.

In the adult rats, the renal serum clearance is almost the same as in young normals, and the urinary excretion is low, but fecal excretion is relatively high. The loss of radio-calcium from the body in these animals is not due to the kidney, but to fecal excretion.

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[1] D. C. Jones and D. H. Copp, University of California Radiation Laboratory Report UCRL-873.

[2] Coleman, R., Becks, H., Kohl, F. Van Nouhuys, and Copp, D. H., Arch. Path., 50, 209 (1950).

[3] Berlin, N. I., Huff, R. L., Van Dyke, D. C., and Hennessy, T. G., Proc. Soc. Exp. Biol. Med., 71, 176 (1949).

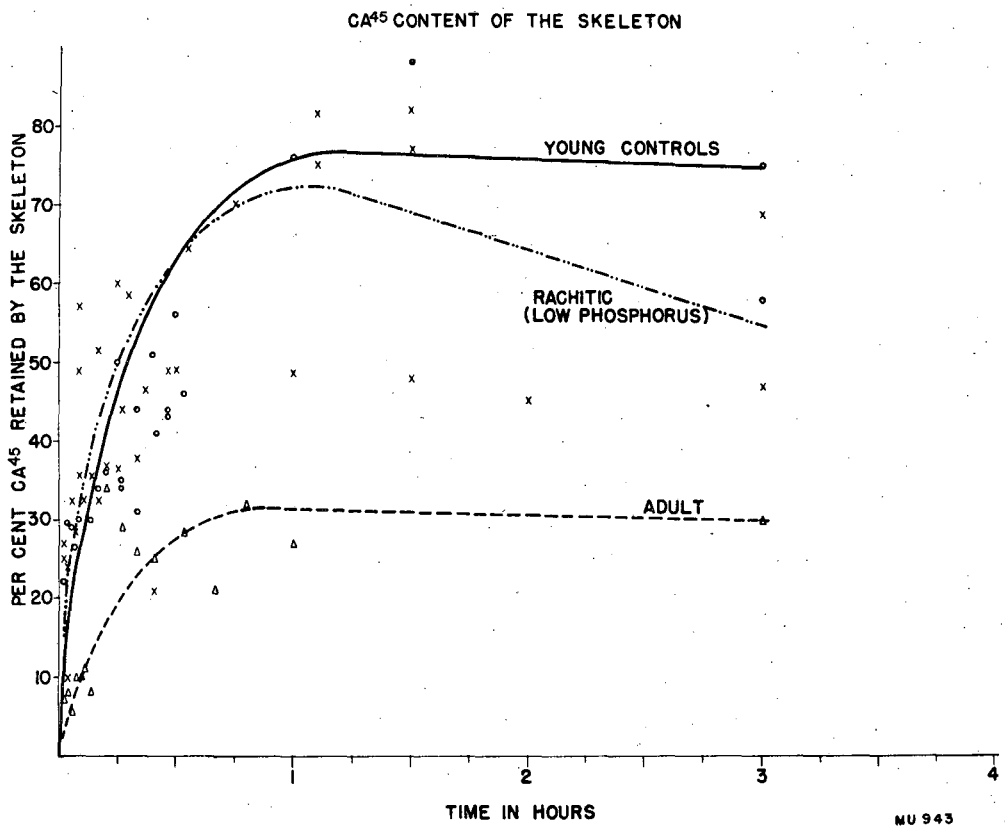
CA45 CONTENT OF THE SKELETON
PER CENT CA45 RETAINED BY THE SKELETON
80
70
60
50
40
30
20
10
YOUNG CONTROLS
RACHITIC
(LOW PHOSPHORUS)
ADULT
1
2
3
4
TIME IN HOURS
MU 943

Fig. 1

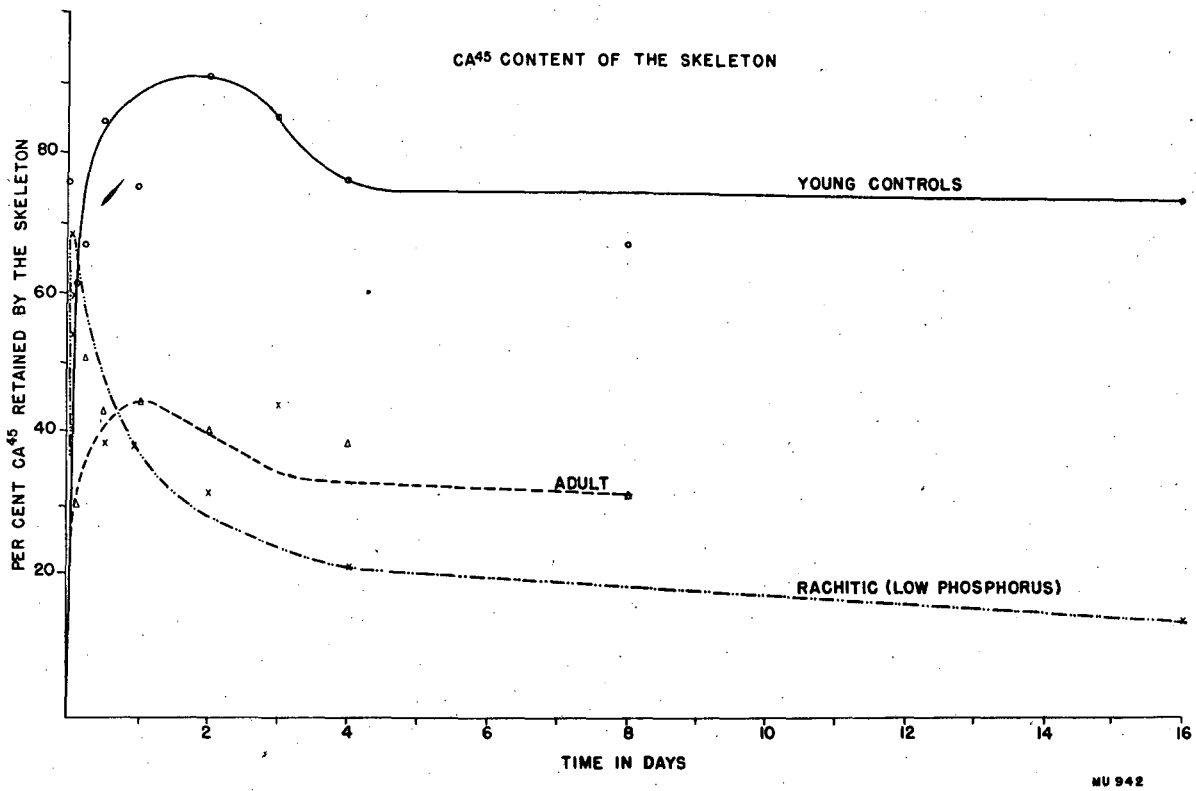
CA45 CONTENT OF THE SKELETON
PER CENT CA45 RETAINED BY THE SKELETON
80
60
40
20
YOUNG CONTROLS
ADULT
RACHITIC (LOW PHOSPHORUS)
2
4
6
8
10
12
14
16
TIME IN DAYS
MU 942

Fig. 2

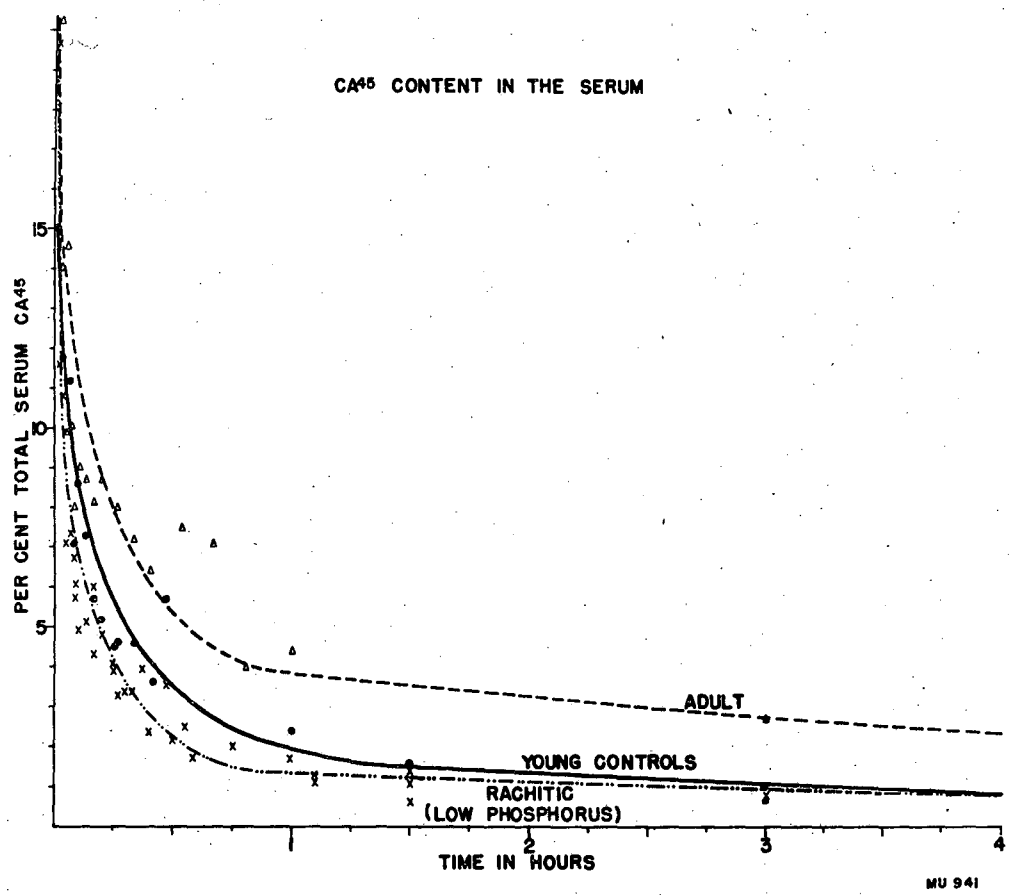
CA45 CONTENT IN THE SERUM
PER CENT TOTAL SERUM CA45
15
10
5
ADULT
YOUNG CONTROLS
RACHITIC
(LOW PHOSPHORUS)
1
2
3
4
TIME IN HOURS
MU 941

Fig. 3

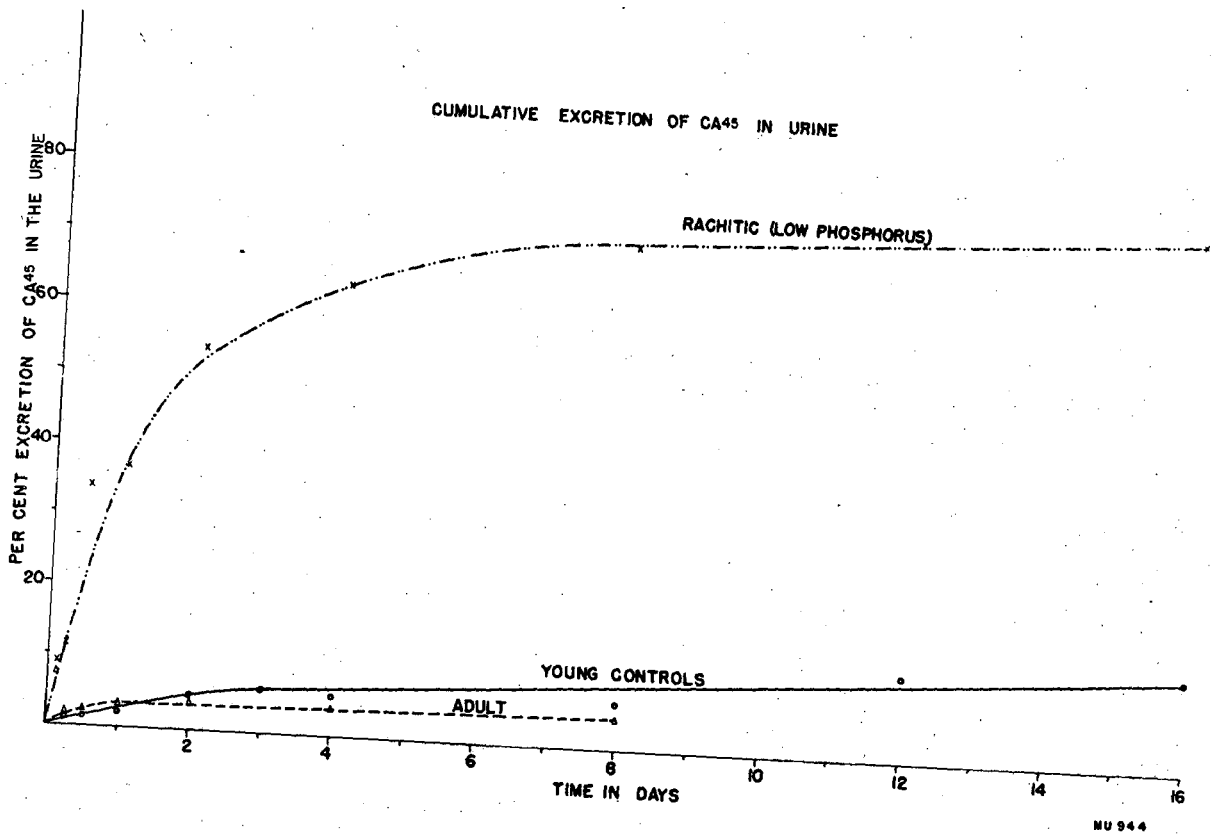
CUMULATIVE EXCRETION OF CA45 IN URINE
RACHITIC (LOW PHOSPHORUS)
YOUNG CONTROLS
ADULT
PER CENT EXCRETION OF CA45 IN THE URINE
80
60
40
20
2
4
6
8
10
12
14
16
TIME IN DAYS
MU 944

Fig. 4

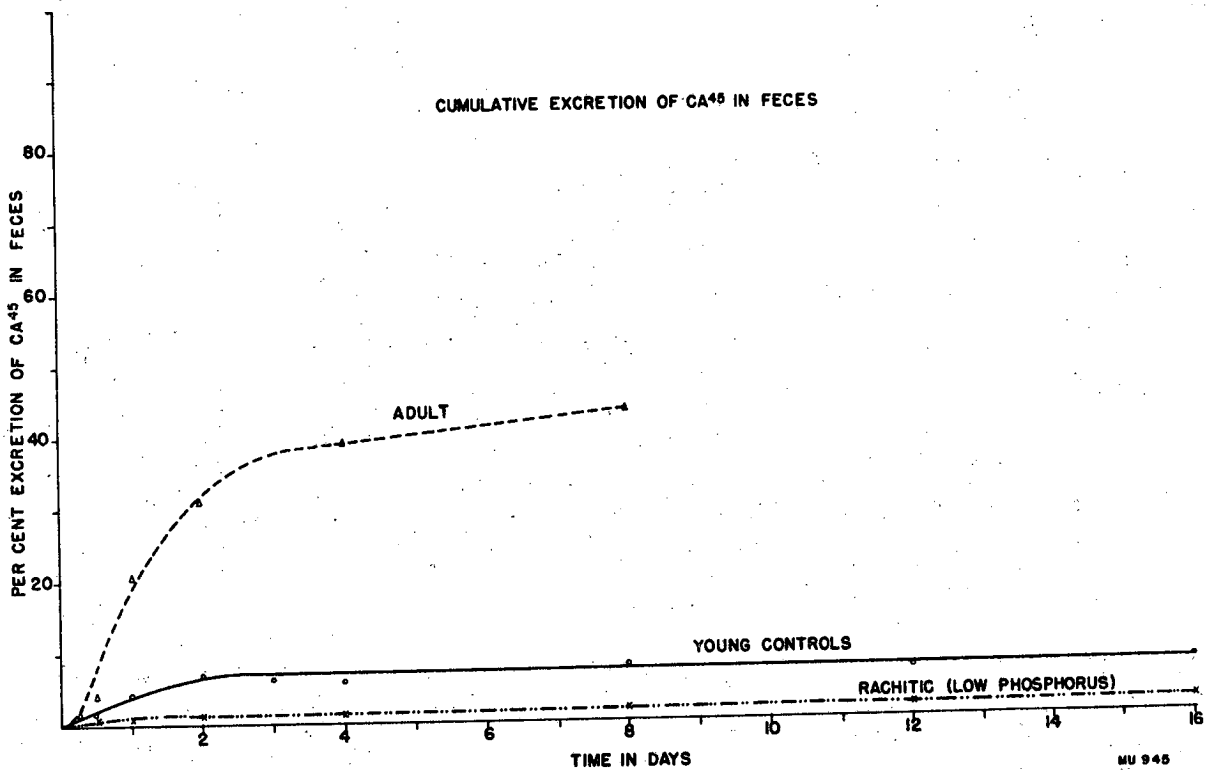
CUMULATIVE EXCRETION OF CA45 IN FECES
PER CENT EXCRETION OF CA45 IN FECES
80
60
40
20
ADULT
YOUNG CONTROLS
RACHITIC (LOW PHOSPHORUS)
2
4
6
8
10
12
14
16
TIME IN DAYS
MU 945

Fig. 5

Radiochemistry

W. M. Garrison

Carrier-Free Cr^{51} from Vanadium. The 26- day Cr^{51} was prepared by (d,2n) reaction on vanadium. The bombarded vanadium metal was dissolved in concentrated HNO_3 and the resultant solution was taken almost to dryness, diluted with water to approximately 1 normal and saturated with SO_2 to reduce chromium to Cr^{+++}. The vanadium, also reduced under those conditions, was reoxidized by concentrated HNO_3 obtained by evaporating to dilute acid solution. This solution containing the carrier-free chromium as Cr^{+++} and vanadate was diluted to approximately 3 normal and neutralized with Na_2CO_3 after the addition of 10 mgm of La^{+++}. The $La(OH)_3$ precipitate scavenged over 90 percent of the Cr^{51}. To separate traces of co-precipitated vanadium, the $La(OH)_3$ was dissolved in acid and reprecipitated. After three such cycles, the $La(OH)_3$ containing the carrier-free Cr^{51} was dissolved in a minimum volume of HCl and reprecipitated with the addition of $NaOH$-Br_2 mixture which oxidized the carrier-free chromium to chromate. Under these conditions the Cr^{51} activity remained in the supernatant. The alkaline solution of Cr^{51} was acidified with dilute HCl and saturated with SO_2 which reduced the chromium to Cr^{+++}. Ten milligrams of Fe^{+++} carrier were added and precipitated with excess NaOH which co-precipitated the Cr^{51} quantitatively. The $Fe(OH)_3$ containing the Cr^{51} was dissolved in 6 N HCl and extracted with several volumes of ether. The dilute HCl solution of carrier-free Cr^{51} was evaporated to dryness on an amount of NaCl which on the addition of 5 ml of water gave an isotonic saline solution for animal injection.

Carrier-Free Sc^{46} from Titanium. The radio-scandium was prepared by bombardment of titanium with 20 Mev deuterons. The bombarded titanium metal powder was dissolved in 40 ml of 18 N H_2SO_4 containing 5 percent 16 N HNO_3. A small amount of undissolved inactive material was removed by centrifugation. The supernatant solution was slowly added to 200 ml of 8 N NH_4OH containing 15 ml of 30 percent H_2O_2 to give a clear yellow solution. This solution was then passed through two consecutive Whatman No. 42 filter papers which retained over 95 percent of the scandium activity as absorbed radio-colloid. After washing with 10 ml of water, the scandium activity was quantitatively removed in 10 ml of 1 N HCl which after neutralization with NH_4OH-H_2O_2 solution was again passed through filter paper. Three such cycles gave a hydrochloric acid solution of carrier-free scandium containing less than 2 γ of titanium.

Carrier-Free $Bi^{204,206}$ from Lead. The $Bi^{204,206}$ was prepared by (d,n)(d,2n) reaction on lead. The bombarded lead foil was dissolved in a minimum volume of concentrated HNO_3 which was evaporated almost to dryness and diluted to approximately 1 normal with the addition of water. This solution was treated with excess NaOH (until the precipitate of $Pb(OH)_2$ had redissolved) and passed through two consecutive Whatman No. 42 filter papers. The carrier-free $Bi^{204,206}$ was quantitatively retained on the filter paper presumably as adsorbed radio-colloid. Residual sodium plumbate was washed from the filter paper with 1 percent sodium hydroxide solution. After washing with water, the $Bi^{204,206}$ was removed from the filter paper with dilute HCl. The resultant solution was neutralized with NaOH to give an isotonic solution of $Bi^{204,206}$ for animal

injection. The activity was identified by half-life measurements, absorption measurements and by chemical separation with added carriers.

Carrier-Free Mn^{52} from Chromium. The 6.5-day Mn^{52} was prepared by (d,2n) reaction in chromium. The bombarded chromium metal was dissolved in concentrated HCl, 10 mgm of Fe^{+++} carrier were added and the resultant solution was slowly added with stirring to a solution of $NaOH-Br_2$ mixture. Under these conditions, the chromium is oxidized to chromate and the carrier-free Mn^{52} is oxidized, presumably, to MnO_2 which quantitatively co-precipitates on the $Fe(OH)_3$. The $Fe(OH)_3$ containing the Mn^{52} was dissolved in a minimum volume of HCl and the oxidation-precipitation cycle was repeated. Three such cycles were required to separate the small amount of chromate which co-precipitate. The precipitate from the last cycle was dissolved in 6 N HCl and Fe was extracted with ether. The resultant HCl solution of carrier-free Mn^{52} was evaporated to dryness on NaCl. The activity was quantitatively dissolved in 5 ml of water.

Other Activities. Solutions of Oak Ridge Cb^{95} in millicurie amounts have been prepared for biological studies.

II BIOLOGICAL STUDIES OF RADIATION EFFECTS

J. H. Lawrence - in charge

Project 48A - 1

Evidence of a Combined Target Intermediate Action Mechanism of Radiation Effects

Cornelius A. Tobias*

The Target Hypothesis. As is well known, the target theory of biological effect of ionizing radiations is based on the idea that there exists a sensitive volume somewhere within the cell and that one or more "events" have to occur within this volume as a result of irradiation to produce a lethal effect, a mutation, or some other measurable change. A number of authors, particularly Lea[1] have associated the "event" with the production of a single ion pair. A recent review of the target theory has been published by Atwood[2]. Early success of the target theory was due to finding survival curves for various organisms, which were exponentially decaying functions of the dose (one ion pair in sensitive volume) and others which followed the multi-hit curves as shown in Fig. 10. However, closer examination a number of years ago revealed some discrepancies not easily explainable in the original form of the theory. For example, the theory predicted a sharp decrease in biological effects of radiations when radiations of high specific ionization were used. There were many experiments available however[1] which showed opposite dependence on REL from the one expected.

Some of the proponents of the target theory have identified the target with the size of a gene[18, 1]. Calculations based on dose-effect relationships have come within a small factor from the size of objects which resemble genes. However, as early as 1936 Timofeeff-Ressovsky and Delbruck[3] questioned this hypothesis. Sommermeyer[4] has postulated that ionization within a gene may produce mutations with a probability considerably less than unity. Lea and Catcheside[5] assumed that an ionization outside a gene may also produce mutation. Fano[6] reasoned that if the dose-effect relationship is a single exponential, the passage of a single ionizing particle must be sufficient to cause mutation; therefore, a single ionization, or at most two, or a cluster of ions, are sufficient to cause mutation. The question to be resolved then remains the probability with which this process may occur. At the Oberlin Conference, Fano gave a lucid presentation of the present status of the theory of ion cluster formation.

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*Part of this work was carried out in association with Professor R. E. Zirkle, of the University of Chicago. Other phases were done in collaboration with B. Stepka and H. Anger. More detailed accounts will be reported later.
A portion of this material was presented at the Oberlin Conference, June, 1950

Intermediate Action Theory. Independent of the target theory, certain biochemical effects on enzymes may be explained on the basis of the "intermediate action" theory of Dale[7]. He and others, notably Barron and his associates, have conclusively shown that the biochemical action of radiations in aqueous solutions depends greatly on the interaction of radiations with water. Physical chemistry of the radiation effects on solutions has taught us that water ions themselves last for very short-time intervals after their production. Dissociation occurs, giving rise to H and OH radicals; these in turn may combine with each other and with cellular constituents. Dale attempted to explain the general shapes of dose effect curves as well. He showed that monomolecular reactions lead to exponential dose effect relationships, curves similar to those one obtains in the one hit hypothesis; further, he has shown that if there are two substances competing for ionization products, the dose effect relationship becomes very similar to the multiple hit type functions of the target theory.

Comparison of Two Theories in the Light of Experiments on Yeast Cells. In the experiments described here the dose dependence of the survival of haploid colonies was compared to those of diploid colonies. If the indirect action theory were true, one would expect the two survival curves to be qualitatively the same. Since the biochemical constitution of the haploid and diploid cells is assumed to be similar, the survival curve of both colonies might show monomolecular reactions or both might exhibit the presence of some protective substances. Actually the haploid cells showed the simple exponential type survival vs dose relationship (monomolecular reaction) in a wide range of REL. The survival curve of diploid cells showed some kind of "protection" effect over the whole range of ionization. For typical survival curves, see Figs. 1 and 2. For the moment one would be thus inclined to prefer the target theory for simultaneous explanation of haploid and diploid cell survival curves, were it not for the fact that the comparison of haploid and diploid survival repeated at different REL yielded data which were not very well in agreement with the classical target idea either. The radiations at high REL were more effective than a low REL. The apparent shape of the survival curve for both haploid and diploid, however, remained approximately the same irrespective of the REL within the entire ionization region tested. In the course of this investigation it became clear that the two different theories may both apply to certain aspects of the same irradiation problem. In fact it seemed desirable to attempt the simultaneous use of both models of the radiation effect. In some respects this view is similar to some of the concepts advanced by others, particularly by Barron and Zirkle.*

Diffusion Model. The physicist in radiobiology should be interested in the dynamics of all processes involved, even beyond the mechanism for formation of ion pairs. He should be able to make contributions to the formation, distribution and absorption of ion products, and the fate of excited molecules. In a complex system such as the cell one has to be satisfied with the crudest of approximations. The inhibition of cell division is almost certainly a chain reaction initiated by changes in a few molecules. How such chains of events develop in the cell we

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*Proceedings of the Oberlin Conference, June 1950, to be published by the National Research Council.

do not know. All one may do is to trace out a few of the initial steps that occur between irradiation and inactivation of essential molecules. In organisms having high percentage of water one may draw an analogy between radiation effects on water and on the cell.

The physical basis of the diffusion model is very simple. In the process of ionization the lifetime of the ion pairs and excited atoms formed is very short. The primary initial positive ion and negative electron and some of the excited molecules may within a very short time interval give rise to radicals or more or less stable intermediate "oxidants". The exact chemical properties of these ionization products are of no importance at the moment, except it is important to find out how many ion pairs were needed to form each intermediate ionization product. This depends on the spacing of individual ion pairs of the positive and negative ion columns, and of the chemical composition of the medium.

The intermediate ionization products are usually longer lived than the ion pairs themselves and this is one reason why they are conceivably of importance. Due to their thermal Brownian motion, they will migrate through the medium until they find suitable molecules for interaction, molecules from the cell medium or other ionization products. Even if it is accepted that free radicals and other intermediates are the most frequent immediate result of ionization, one immediately gets into serious difficulties. The intermediates can obviously migrate; but what are the laws of such migration? Even in pure water this is a serious problem. Dissolved substances are in a "solvent cage". When they migrate through the medium they carry some water molecules along. When they find another solute molecule in their migration, the two solute molecules may stay together in the solvent cage for a reasonably long time, which they would be unlikely to do if the approach of the molecules were in the gas phase. In living protein, the laws of migration might be much more complex than those for water. If one accepts some of the views of Delbruck[8] one is forced to admit that protoplasmic structure and behavior may be very different in live cells and <u>in vitro</u>. Not knowing the mechanism of migration and of interaction of solutes in cellular matter, one might proceed by assuming the simplest admissible relationships and making predictions based on these. Thus we might assume that in cells the intermediate products of ionization are much like those in water, that they migrate, diffuse freely through the cellular medium and that when they interact, such interactions are of the oxidation-reduction type. Such interactions may give rise to biochemical effects and some grossly observable physical cytoplasmic effects of radiation. When intermediates migrate close to nuclear material genic and in some cases lethal effects are assumed to occur. These effects are thus intermeiate effects of radiation. One may also admit that similar effects might occur as a primary result of ionization produced in the immediate vicinity of the same cellular components. Such effects are direct hit type.

Table I indicates the parallelism of the mechanism of effect for extragenic and genic components of living cells. The two sets of effects may develop simultaneously to each other and with a given organism either type may dominate the other. However, the comparative importance of these effects is indicated by

TABLE I

Mechanism of Extragenic and Genic Effects of Radiation

Extragenic Effects are result of:	Genic Effects are result of:
1. Direct ionization or excitation of molecules. The chance for this is usually small.	1. Direct hit. Ionization or excitation of essential sites. The chance for this is usually small.
2. Indirect mechanism; chemical interation with ionization products. This occurs frequently but many molecules have to be inactivated before measurable biochemical deficiency occurs. Recovery may follow if essential genes are still intact. Lethal effect may result if too many molecules become inactivated.	Indirect action. Some of the ionization products may diffuse to the proper site through extragenic medium and interact, leading to inactivation of genes. The inactivation of a single molecule may lead to lethal or inheritable changes. Ionization products causing genic effects may have originated from ion pairs located at a distance from the essential sites.

the following statements:

A. In genes essential to cell division, only a single event needs to occur for inhibition of cell division.

B. The mean dose at which a single genetic effect will occur depends on extragenic composition of tissue.

Having outlined the plausibility of similarity between radiation action on genes and that on extragenic factors, we may now proceed to formulate the diffusion model of radiation effects in simple mathematical terms. Assume given a cell with a single, genic "site" to be affected by radiation, mediated by a known intermediate ionization product I (eg. OH, HO_2, H_2O_2). Fig. 3 will give a description of its path through the cell medium. I will migrate through the fluid medium of the cell along an irregular Brownian path until it has a chance to interact with some cytoplasmic constituent R, forming a compound to be designated RG; this will happen at a radial distance r from the point where the ion pair and shortly thereafter I was formed. According to procedures of statistical mechanics, the probability p (r) that the intermediate will diffuse at least to a distance r will be

$$p(r) = e^{-\frac{r^2}{\rho^2}} \qquad (1)$$

where ρ is a constant, $\rho^2 = 4\delta\tau$; τ is the mean life of the radical and δ is its diffusion constant through the medium.

Assuming a stationary sensitive site, a gene for example, it is easy to calculate the mean number of intermediate ionization products to diffuse to the site of the gene when ionization was produced at random in the medium. If a dose of D ev/cm^3 is given, and the energy per ion pair is w ev and if β fraction of the ion pairs produce the intermediate I, then the mean number of radicals M (D) diffusing to the sensitive site of cross section σ becomes:

$$M(D) = \frac{\beta\sigma\rho}{w} \qquad (2)$$

If a single molecule of the intermediate I is sufficient to inactivate a site, essential to cell division, then the number N of surviving cells is expressed by the equation:

$$N = No\ e^{-\frac{D\beta\rho\sigma}{w}} \qquad (3)$$

The right side of Equation 3 is a simple decaying exponential function of the dose, resembling the single hit survival curve of the target theory, and the monomolecular reactions in the intermediate theory. If there are two kinds of intermediates with different ionic yields β_1, β_2 and mean action radii ρ_1, ρ_2 the survival curve may be expressed as

$$N = No\ e^{-\frac{D}{w}(\beta_1\rho_1\sigma_1 + \beta_2\rho_2\sigma_2)} \qquad (4)$$

Multiple hit forms of the survival formula are also readily obtained. Examination of Equation 3 is worthwhile because this simple equation gives precise and possibly measurable definition to certain quantities often mentioned or described in radiobiology.

The expression $D\beta/w$ is the number of ionization products formed per unit volume in the medium, when exposed to D/W ion pairs; β is then the "ionic" efficiency of formation of intermediates such as radicals H, OH, O_2H, molecules H_2S_2 or other compounds capable of migration. If the ions themselves are direct causes of the radiation effects, β may be taken equal to one. The ionic efficiency obviously depends on the chemical composition of the medium and on the mean rate of energy loss ε of the ionizing particles; $\beta = \beta(\varepsilon)$. (Some people prefer to express the ionic yield in terms of the energy absorbed).

The product $\sigma\rho$ is analogous but not identical to the sensitive volume of the target theory. In the diffusion model σ is the "cross section" of the sensitive site. If inactivation occurs every time an intermediate finds itself at the sensitive site, then σ corresponds to the true, geometrical cross section. In other cases σ will be smaller than the geometrical cross section. The concept of σ is analogous to the term cross section as it is used in nuclear physics.

σ may include the "cage factor", or even conceivable a delayed recovery effect. ρ has the dimension of a distance; it expresses the mean radius to which the radicals diffuse from the site of their formation before they disappear due to chemical interaction. We have called ρ the "mean action radius" of an intermediate. Equation 1 shows the connection between the mean lifetime, the diffusion constant and ρ. As a rule in wet tissues $\sigma\rho$ is greater than V, the volume of the "sensitive" site of the target theory.

Both the ionic efficiency B of an intermediate I and its mean action radius ρ are functions of the composition of the medium. In the limiting case of dry organisms, or viruses, crystalline enzymes, etc., very little migration will take place; the mean action radius will then for all practical purposes define the size of the target volume in the sense of the classical target theory. As water is added, the mean action radius may increase, so that the slope of the survival curve will not immediately correspond to the true "sensitive volume". The sensitive volumes obtained in some earlier work for various organisms should be re-examined in terms of the diffusion model. There are some cells, among them yeasts, that may be dried and irradiated in that form. Some work along this line was done by Failla[9] and suggestive data were given by Dale at this symposium for enzymes with different water dilution. In the diffusion model most ion pairs or their products, the intermediates, end their life by extragenic interaction. As long as the intermediates originate reasonably close to a sensitive site of the cell they will have some chance to reach this site in the course of their migration.

It seems possible that the diffusion model can be intelligently used for evaluating changes in the radiosensitivity of cells due to their state of division, or to changes in the external medium. For example, the introduction of dissolved oxygen into an oxygen free medium may change the ionic yield and mean action radius of H_2O_2, OH and O_2H. At the same time the presence of oxygen may have no influence on peroxide-like intermediates. The use of the variables β, ρ, σ, should be helpful even in the absence of detailed chemical knowledge to predict protective effects of added substrates.

There is a continuity of procedure between evaluating the magnitude of radiation effects on isolated sensitive sites and extragenic effects on cytoplasmic constituents, for example enzymes. In the latter case a fairly large number of individual enzyme molecules may be present in the cell, and a known or measurable fraction of these may be inactivated by the radiation.

Calculations based on the diffusion model could provide the shape of survival curves, usually a type of multiple hit curves.

Recently much emphasis was placed on the findings that some externally applied chemical agents have biological effects qualitatively similar to radiation, particularly as far as inhibition of cell division and production of genetic effects are concerned. Such situations may be also handled similarly to the above treatment, using the diffusion model. The chief difference is in the boundary values of the diffusion problem. Fig. 4 shows a crude representation of this problem. When a cell is placed in a medium containing the external agent, diffusion through the cell membrane into the interior of the cell begins;

the density of the blackening in Fig. 4 shows a plausible concentration distribution of the poison in the process of diffusing to the nucleus of the cell. Consideration of the figure shows that due to larger volume of the cytoplasm to be crossed by the poison the shape of the "survival" curve as a function of the amount and duration of poisoning might be different from the radiation survivals and also, that in some cases the cell wall and cytoplasmic constituents might effectively protect the nucleus even at the expense of their own destruction. Some German workers[10] have recently applied the target hypothesis to this problem. More quantitative experiments are needed to uncover the mechanism of action of poisonous agents applied externally to living cells.

Diffusion Model and Dependence of Biological Effects on Specific Ionization. The above considerations introduce two additional constants in the radiation survival formulas. One reason for allowing these additional constants in the formulas was to allow variation of the biological effectiveness of radiations at different environmental conditions and at different mean rates of energy loss. From data obtained under widely varying conditions one may possibly determine the constants β, ρ, σ. As an example of the type of data one obtains, consider the comparison of the relative effectiveness of deuteron ions, x-rays, helium ions and low energy alpha particles on yeast cells, as shown in Fig. 5. The curves show an increase in relative biological effectiveness paralleling an increase in rate of energy loss of the radiations used. These data themselves are not striking since the majority of the experiments available show such an effect.

We should now define relative biological effectiveness ϕ of a radiation with REL ε to a standard radiation, for example 200 kv x-rays with REL ε_0. The same biological effect is caused by dose D of ε, and dose D_0 of ε_0.

$$\phi = \frac{D_0}{D} \tag{5}$$

In the simplest case, and neglecting the distribution of ions in tracks the criterion might be the survival of a given fraction of cells having a single sensitive site. For this case from Equation 3

$$\phi = \frac{\beta \rho \sigma}{\beta_0 \rho_0 \sigma_0} \text{ or with } \sigma = \sigma_0 \quad \phi = \frac{\beta \rho}{\beta_0 \rho_0} \tag{6}$$

The mathematical considerations involved in predicting the RBE with radiations of different REL becomes involved since one should remember at this point that ionizing radiations produce entire tracks of ions simultaneously - not single ion pairs as it was assumed up to the present. It is necessary to calculate the probability of diffusion of intermediates to a certain distance from the center of the track. This can be done, however. It turns out that if a sensitive site is close to densely ionizing tracks, then there is a high probability for it becoming inactivated. However, if the ion density becomes very high, some of the ions in the track will be wasted since a single track cannot be responsible for more than the inactivation of a single cell.

It is possible to obtain approximate mathematical expressions for the relative biological effectiveness using the diffusion model and assuming values for the ionic yield of different intermediates that are likely to be present; further one has to consider the heterogeneous distribution of the ionization along the tracks.

If intermediates due to formation of single ion pairs only are considered the diffusion model does not explain a rise in biological effectiveness of radiations when the rate of energy loss is increased. In order to account for the numerous older and for the present experimental findings, one is forced to assume the action of intermediates, the yield of which increases with specific ionization. In the example under discussion at present since the water content of the cell is important one might draw a cautious analogy with the example of decomposition of water. At low REL the ionic yield of peroxide in pure unoxygenated water is low. At high REL the ionic yield of peroxide is high.

For the purpose of quantitative comparisons it seems worthwhile to assume a simple mathematical expression for the ionic yields of the intermediates requiring ion pairs. Exact derivation of the yield is not an easy matter when ion clusters and diffusion theory are taken into account. Progress is being made in this field by Landau[11] and Wijsman[12].

Lind[13] has shown that the ionic yield of H_2O_2 in oxygen free pure water is close to unity in a range of energies where alpha rays are used. Toulis[14] has studied the yield as a function of proton energy in the absence of dissolved material. While more extensive studies are desirable, the data available indicate that H_2O_2 yield remains low at proton energies above 6 Mev; below this it rapidly rises until a plateau is reached with ionic yield of 1/2 with low energy alpha particles. A formula was obtained for the H_2O_2 yield B_2 by assuming that the probability of peroxide formation in water is one if the distance between two ion pairs formed is less than a critical distance r_o, and the probability is zero if the distance between ion pairs is greater than r_o.

$$\beta_2 = \frac{1 - e^{-\frac{\varepsilon r_o}{w}}\left(1 + \frac{\varepsilon r_o}{w}\right)}{2} \qquad (7)$$

where ε is the rate of energy loss, w the energy required per ion pair. This formula is admittedly poor, and there is no doubt that further refinement is needed when more exact knowledge of ionic spacing (clusters), cage factors, and back reactions are available. However, until something better comes along the use of this formula may be helpful in qualitative studies of the mechanism of radiation effects. When the ion spacing is large, a more exact formula has been derived by Wijsman, based on diffusion considerations. This yields the probability for H_2O_2 formation in oxygen free water as

$$\beta_2 = \frac{1}{2}\ \frac{r_o^2\,\varepsilon^2}{w^2}\left(1 - \mathrm{Exp}\left(\frac{\frac{w}{\varepsilon} - r_o}{2\sqrt{\delta_\tau}}\right)\right) \qquad (8)$$

where δ is the diffusion constant and τ the mean life of OH radicals.

Both of the organisms tested indicate that the mean action radius of an H_2O_2 like product in the cells is much greater than that of the ions or radicals themselves. Assuming for the OH radicals a lifetime akin to that in pure water of 10^{-7} sec., one may calculate that the cross section of a sensitive site might be only of the order of 10^{-16} cm^2 in the yeast cell. The radius computed from this reminds one more of the size of a bond than the size of a molecule. However, the cross section may include some unknown factors. There is a possibility that when an intermediate arrives at a sensitive site, the probability of its reacting is less than unity. In any case, our hypothetical model of a sensitive site in the yeast cell also gives some information on the mean action radius of H_2O_2 like radicals which should be of the order of 10^{-4} cm. Dimensions of the order of 10^{-6} cm result for the mean action radius of OH radicals.

Although the above outlined ideas represent an attempt to put biological observations on a semi-quantitative basis, it is clear that with the availability of better data more detailed and informative physical models could be constructed. The insight in the mechanisms would be materially helped if survival data were available in detail over a wide range of energy loss on several organisms, in particular: (a) with certain dissolved substrates, e.g. oxygen, nitrogen, hydrogen; (b) at different temperatures; (c) with different amounts of water in the cells; (d) at different dose rates; (e) at rates of energy loss higher than those commonly used. The mechanism of biological effects will not be clear until enough of these experiments have been done. Preferably all these data should be available for a number of different organisms.

Number and Meaning of Sensitive Sites in Cells. In all of the above discussion the existence of a single sensitive site* was assumed without clearly stating the recent evidence for such sites. The advantage of using the diffusion model for fitting survival curves of different kinds is that formally it can be used much like the target theory when interactions of single sites are involved. Since the observed curves were exponential type for the haploid and multiple action type for the diploid cells, the curves were fitted next assuming that one sensitive site exists in the haploid cells (nuclear material damaged anywhere) and two for the diploids. It may be definitely stated that this idea did not fit the data. Next a model originally proposed by Luria[15] for ultraviolet ray induced effects was tried. This model was used when lethality of ultraviolet rays was tested on bacteriophage, attached singly or doubly to bacteria. Applied to the cell we may calculate the number of cells N that survive and form large colonies, when initially N_0 are irradiated by dose D.

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*The name "site" was chosen to distinguish the present form of theory from previous forms. Words like "target" and "hit" were avoided, since the radiation according to the concepts outlined does not often produce "hits" in "targets". Since we do not know the exact nature of "sites", they are not further specified. A site may correspond to one of several bonds, to a molecule, a gene, chromosome arm, or something else.

$$N = N_0 e^{-n\alpha D} \tag{9}$$

n = number of independent sites essential to cell division and inactivated by a single intermediate molecule of radical.

$\alpha = \frac{\beta \rho \sigma}{W}$ = constant (see Equation 3).

For similar cells of a ploidy m

$$N = N_0 \left[1 - (1 - e^{-\alpha D})^m\right]^n \tag{10}$$

which for the diploid cell becomes

$$N = N_0 (2e^{-\alpha D} - e^{-2\alpha D})^n \tag{11}$$

For graphic explanation see Fig. 6. With the survival data as shown in Figs. 1 and 2, it was possible to plot the theoretical haploid-diploid survival curves as done in Fig. 7 for different values of n. One may notice that the shape of the curve and the LD_{50} is a sensitive function of n. The theoretical ratio of Diploid LD_{50}/Haploid LD_{50} is plotted in Fig. 8. Even if the survival curves are not very accurate, as in the case of the present experiment, the value n may be obtained. At the present time we believe $n = 16 \pm 5$ for S. cerevisiae. Thus if the model used were true, one might make the following statement: "Haploid yeast cells under the experimental conditions applied exhibit approximately 16 radiation sensitive sites essential to cell division. If any one of the sites is inactivated, the cell will not form macrocolonies". Notice that "site" has very little to do with target; ions do not have to hit the site.

A pair of corresponding sites have to be inactivated out of about 16 pairs of sites before inhibition of colony growth occurs in diploid yeast cells. When development of the yeast cells is observed under the microscope, it is found that inhibition of cell division occurs only after a number of cell divisions have taken place. Microcolonies develop; inhibited haploid cells divide usually only once after irradiation; inhibited diploids may divide several times before growth of the microcolony stops. The rate of growth of inhibited cells and also of some cells which will grow eventually into macrocolonies is slowed down considerably. It is thought that there are important cytoplasmic effects along with the damage to the essential sites. In addition there may be damage of a nonlethal nature to a number of genes in the cell. With only the haploid and diploid strains available, the above advanced theory of inhibition of cell division seemed plausible but not conclusive. More evidence was recently added in favor of this theory by Mortimer[16] who isolated, following a method given by Subramanion[17] some tetraploid yeast cells. Such cells were so far obtained by two different methods: treatment with acenaphthene, and isolation from preirradiated diploid yeasts. These appeared morphologically like the tetraploid yeasts of Subramanion, although we have not so far succeeded in seeing the chromosomes in the microscope. The inhibition of cell division

in these cells of higher ploidy follows reasonably well to what is expected for tetraploid yeasts on the basis of Equation[10]. In fact, the experimental data seem rather amazing as shown in Fig. 9: the polyploid yeast cells need 140,000 rep units of x-rays for 50 percent inhibition of cell division, which is four times the dose required by the diploid, and twenty times the dose required by the haploid cells. Morphologically, and as far as general viability is concerned, there seems very little difference in the yeast cells of different ploidy. These experiments indicate that at least in yeast cells radiation injury of the genetic mechanism, though mediated by the cytoplasm, is a much more important factor than extragenic radiation injury.

What is the nature of the sixteen essential sites of radiation injury? Although no direct evidence is available, it is plausible to assume that the sites are part of the chromosomes or genes. The damage might well be chromosome break or gene mutation. Further work is needed to identify the nature of the sites and to find out whether or not there is the same probability for inactivating each of the sites. One of the requirements for a satisfactory theory of radiation effects is that the explanation offered should stand up when the experiments are repeated under different conditions. Already data are available which indicate at least limited invariance of the relative shape of survival curves. There is a set of experiments available at different rates of energy loss. The relative shapes of haploid and diploid survival curves in all these experiments are substantially the same even though the relative biological effectiveness, that is the amount of dose required, did change as a function of REL. Further these organisms were tested with x-rays when they had dissolved helium, air or oxygen gas present in their cytoplasm. In oxygen much less dose was required to produce inhibition than in helium, but the relative shapes of survival curves, thus the apparent number of essential sites, remained the same in each experiment.

Having established the shape of survival curves, further methods were searched for in an effort to test the theory of inactivation. The study of cells damaged but surviving the radiation offers a convenient step in this process. In order to explain the mechanism of action of radiation it was assumed that diploid cells with unpaired defects survive. These cells are thus damaged but viable. If the damage is genetic as assumed above it is likely to inherit in a vegetative colony as a recessive defect. Colonies grown from preirradiated single cells with unpaired recessive defects may be re-irradiated. The sites of pairs where unpaired defects occur should be more sensitive to radiation than undamaged pairs of sites. Fig. 10 graphically illustrates the presence of weak spots in the damaged cells. A diploid cell with n essential sites and r unpaired recessive defects will have its survival curve described by the equation:

$$N = N_0 \left(2e^{-\alpha D} - e^{-2\alpha D}\right)^{n-r} e^{-r\alpha D} \qquad (12)$$

A family of such survival cures is shown in Fig. 11. Further, if our hypothesis is true, the frequency with which defective cells occur in a preirradiated diploid colony may be also calculated (Fig. 12). For the last six months experiments were carried out on diploid colonies grown from preirradiated single diploid cells. A number of colonies were found to show defective survival

curves. These are easy to demonstrate because the initial slope of their radiation survival curve differs from zero which is the slope of normal diploid colonies. An example is shown in Fig. 13. However, none of these colonies retained its defective properties for more than five weeks. Some mechanism seems to be present which allows regeneration of normal diploid cells which then outgrow in numbers their recessive sisters. Nevertheless, there is hope that stable and recessively defective diploid yeast colonies will be available for future study. It is interesting that preirradiated haploid cells show the same survival curves when irradiated again as normal haploids, a finding that strengthens the explanation given. In other words for haploid cells, inactivation of a single site leads to complete inhibition of cell division. At the present time it is not known whether the probability of inactivating each of the n essential sites is the same or not. It is likely that the probability will be different for each site, the overall effect being a small deviation in the shape of the diploid survival curve. The deviations in the shape will also show up in the cells with recessive defects. Detailed and statistical studies are needed to obtain the exact shapes of the survival curves. One might ask what the survival curves would look like if the medium on which the cells grow is changed in composition. There is some preliminary evidence that the shapes of the survival curves change on a medium different from the one used in this study. Such a change is expected because it is assumed that a cell may have more than one mechanism available to produce the essential component for division. One would expect the minimum number of essential sites on a minimum medium for survival and one would expect that on a more complex medium the number of essential sites might be increased. There is hope that the study of such cells will furnish important clues for the biochemical defects present in each cell. This information should be of value in the interpretation of the basic mechanism of cell division itself.

Conclusions. A parallelism is demonstrated between the so-called indirect mechanism of radiation effect and the target theory.

The apparent contradiction in the two theories may be eliminated by using the "diffusion model" of radiation effects. This model assumes the formation of intermediates by the ions of the primary radiation. These may migrate in the cell and chemically interact with genic and extragenic components.

Evaluation of the ionic efficiency in a given example allows approximate calculation of the magnitude of biological effects as a function of specific ionization.

Experimental test of the diffusion model are expected to clarify some radiation mechanisms in detail. The formulation of the diffusion model allows for variation in radiation sensitivity with substrates, state of cell division, water content, etc.; it furnishes clues for study of the quantitative effects of externally applied cell poisons.

In the modified theory the size of the target loses significance. Individual sensitive "sites" may exist in the cell. They are important because of their biological role, not because they form "targets".

Using the diffusion model the mechanism of inhibition of cell division

by radiation may be quantitatively accounted for in haploid, diploid and tetraploid yeast cells. There appear to be in the haploid cells 16 ± 5 independent sites essential to cell division. These sites appear to be of genic nature.

The production of yeast cells with unpaired recessive radiation induced defects should stimulate biochemical and biophysical study of the basic mechanisms involved in cell division.

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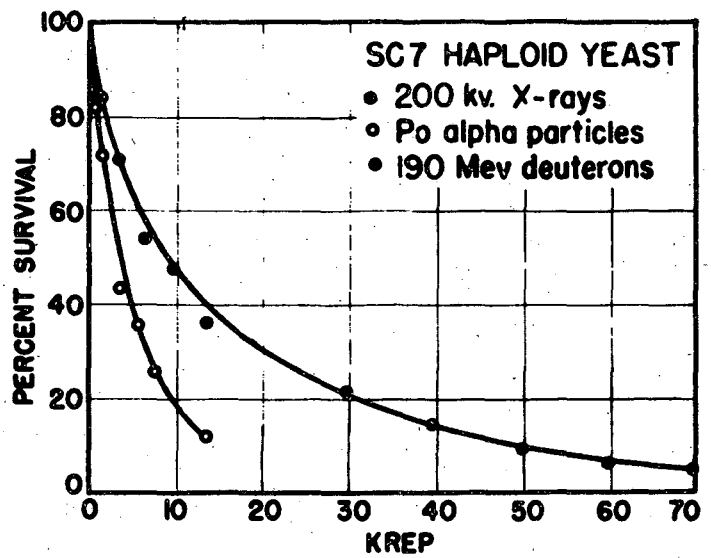
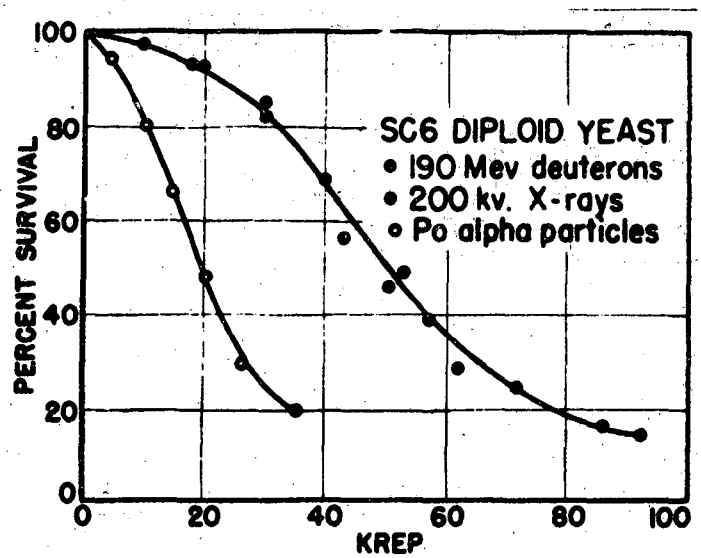


MU-954

Fig. 1

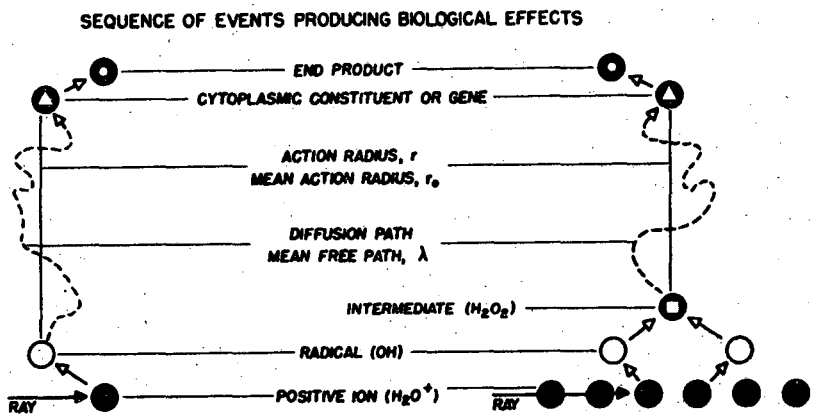
Survival of haploid yeast cells as a function of dose when x-rays and alpha particles are used. The curves indicate the percentage of cells that divides more than once after irradiation. Single hit type curves.



MU-955

Fig. 2

Survival of diploid yeast cells exposed to deuterons, x-rays and alpha particles. Cells are taken as survivals if they divide more than once after exposure to radiation. Multiple hit curves are obtained.



MU-956

Fig. 3

Graphic presentation of the sequence of events in the diffusion model. Left side: The positive ions after their production by the ionizing rays decompose into radicals and other ions. The radicals chemically responsible for the radiation effect diffuse through the medium of the cell along an irregular path. Their mean free path for chemical interaction is λ. Most of the time these radicals are annihilated in a reaction with some extragenic molecule. Occasionally they interact with a genic molecule. Right side: When densely ionizing beams are available, or in ion clusters, different types of intermediates might be produced; for example: H_2O_2 is formed in water. The intermediate molecules may then diffuse and act similarly to the radicals.

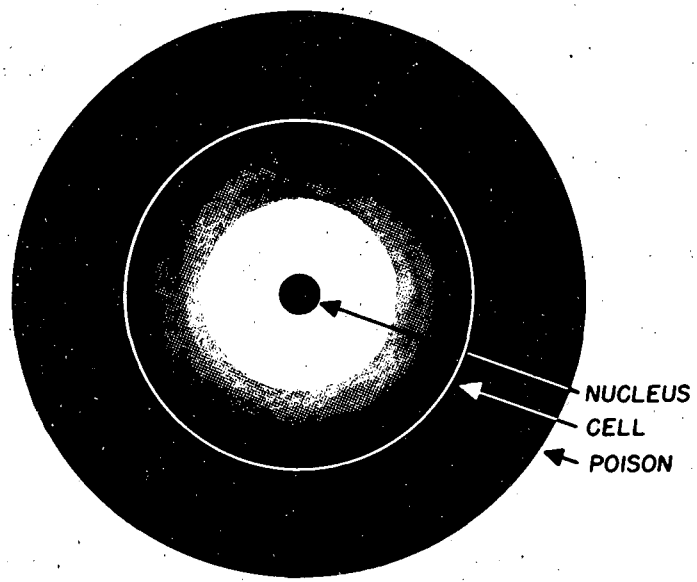


Figure 4. Diffusion model of the action of a poison on the cell. When the cell is placed in a medium containing a uniform concentration of poison, migration of the poison through the cell wall and cytoplasm begins toward the nucleus. This figure is a grphic representation of the concentration gradient of the poison in the cell. Whether or not the effect is genic, dose effect relationships may be calculated using the diffusion model with the proper boundary conditions.

OZ 992

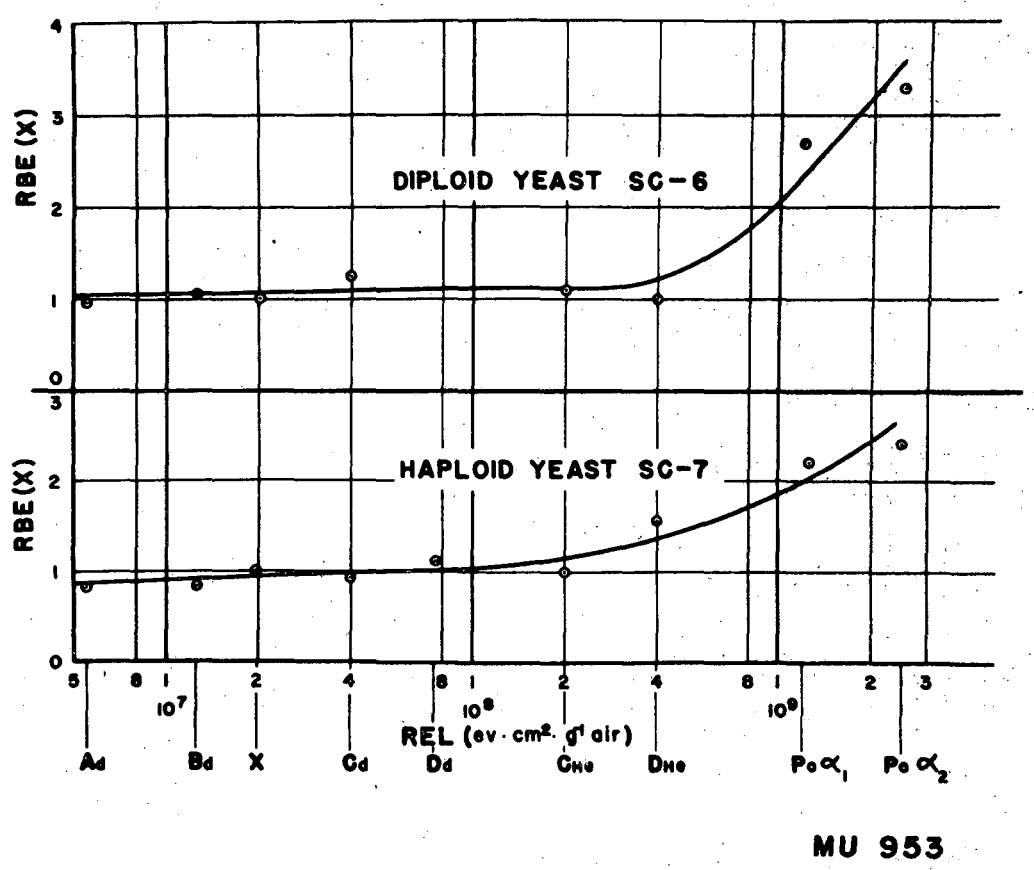
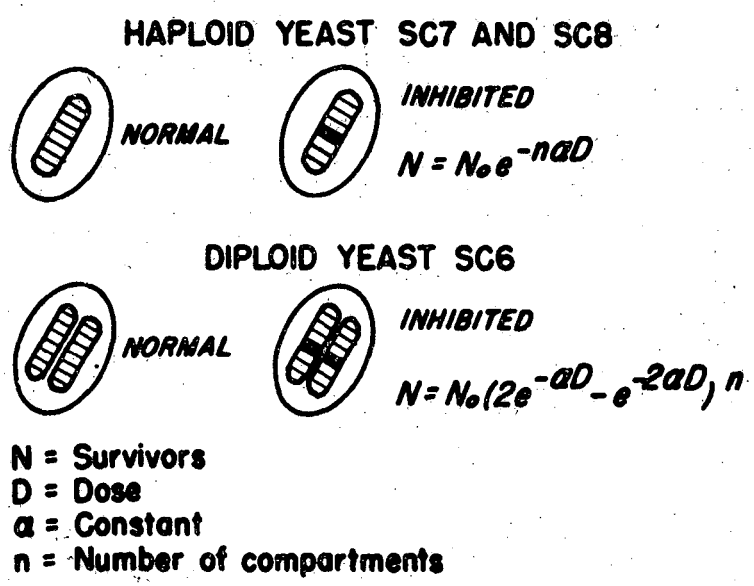


Fig. 5

Experimental data on the relative biological effect of various radiations on haploid and diploid yeast cells. Along the horizontal axis the rate of energy loss is plotted, and along the vertical axis the relative biological effect refers to 200 kv x-rays. Four experimental points were obtained with high energy deuterons, two with high energy helium ions, and two with polonium alpha particles. (Ref. 19)



MU-957

Fig. 6

Schematic presentation of model for inhibition of haploid and diploid yeast cells by radiation. It is assumed that the haploid cell has "n" independent sites essential to cell division. If any one of these sites is inhibited as shown by the black spot in the haploid cell in the upper right part of the figure, the cells would stop dividing. In the diploid yeast cells the number of essential sites is doubled; here a pair of essential sites has to be inhibited before cell division stops.

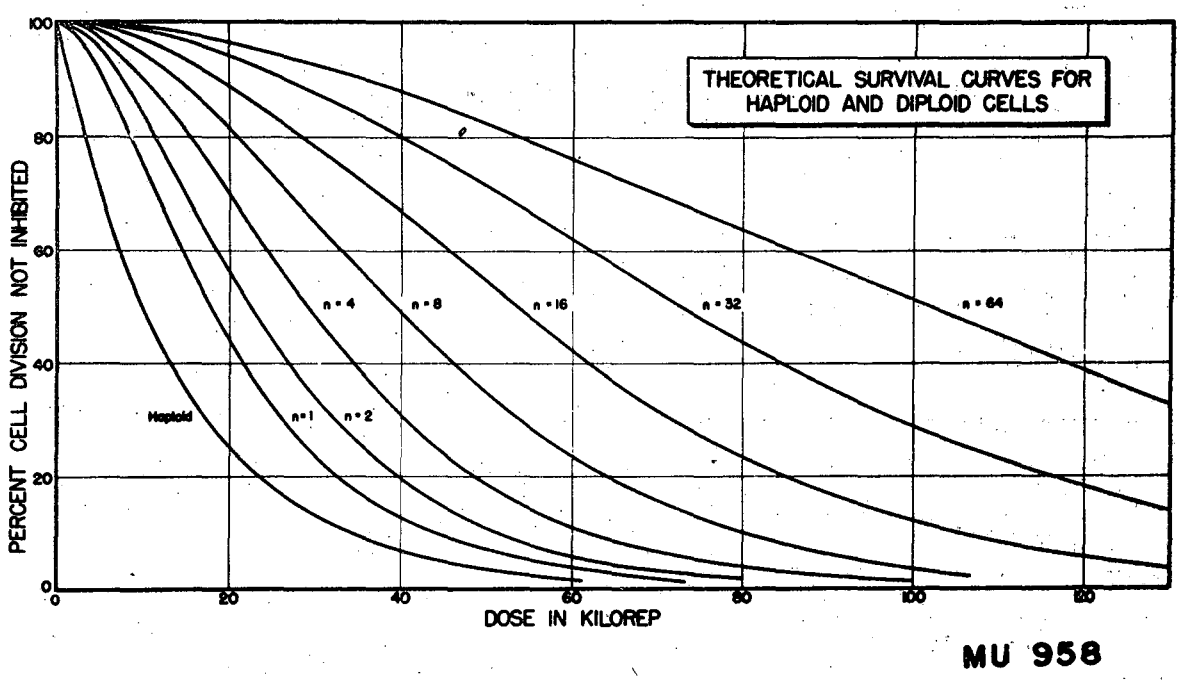


Fig. 7

Theoretical survival curves for haploid and diploid yeast cells adjusted to fit the experimental curve for haploids. The possible diploid survival curves are plotted for n = 1, 2, etc., up to n = 64.

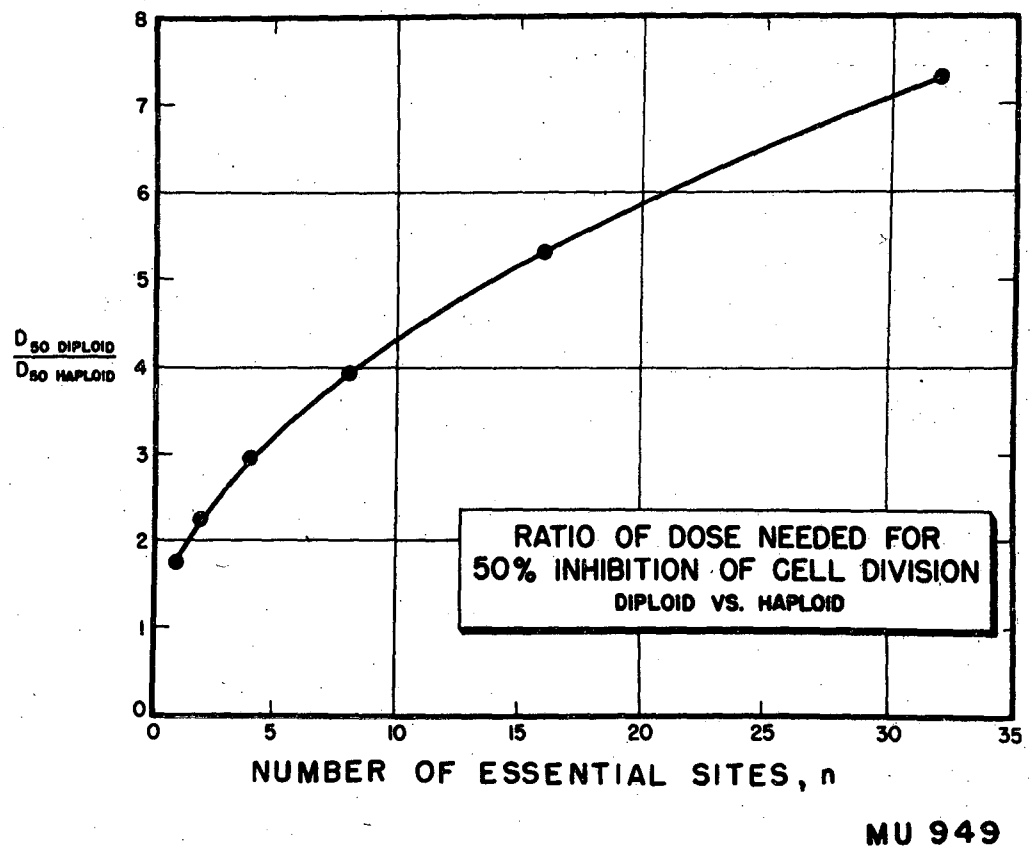
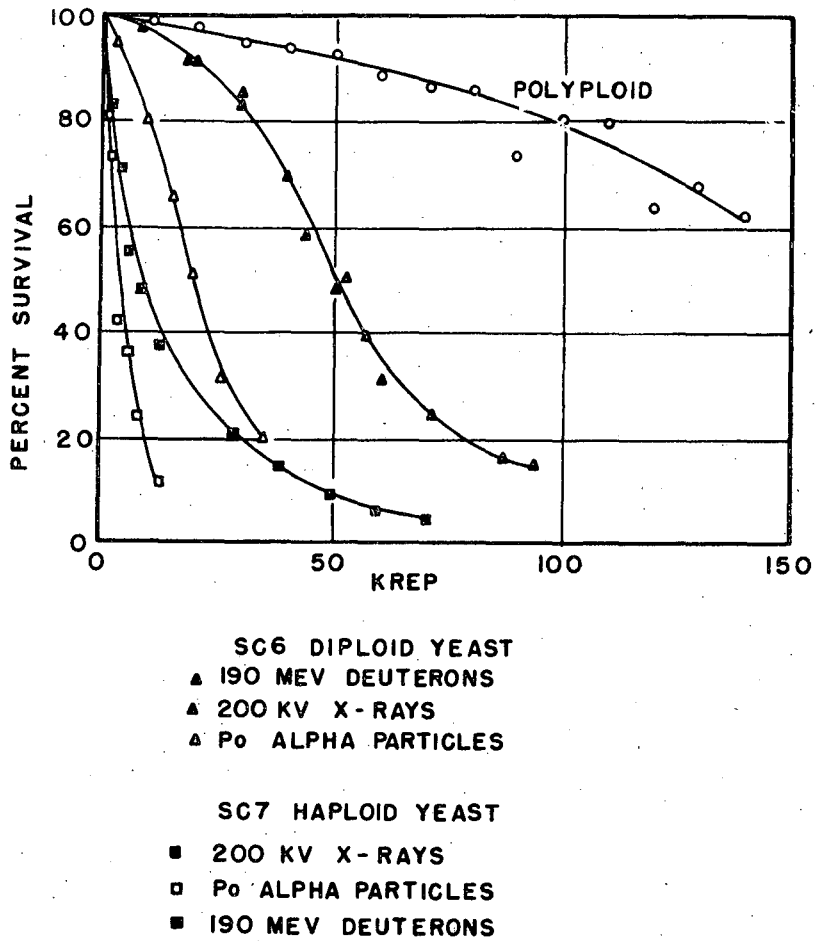


Fig. 8

The ratio of doses needed for 50 percent inhibition of cell division D_{50} diploid/D_{50} haploid is plotted here as a function of the number of essential sites "n". As it may be seen from the curve this ratio is quite sensitive for the number of essential sites.

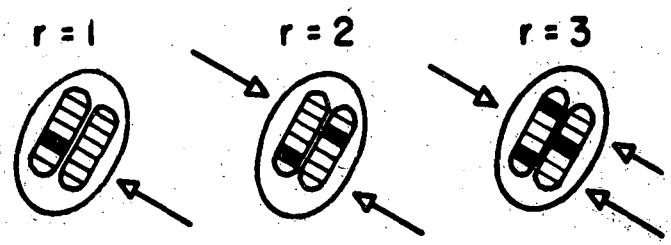


MU 952

Fig. 9

Recently, a polyploid yeast colony was isolated and tested for survival with x-rays. The respective haploid, diploid and polyploid survival curves are shown for cells which divided more than once. The polyploid curve comes reasonably near to the theoretical relationship based on the assumption that a quadruplet of essential sites out of about 16 quadruplets of sites has to be inactivated before the cell division of polyploid cells is inhibited.

DIPLOID YEAST WITH DEFECTS



$$N = N_o(2e^{-\alpha D} - e^{-2\alpha D})^{n-r} e^{-r\alpha D}$$

N = Survivors
D = Dose
n = Number of compartments
r = Number of defects
α = Constant

MU-960

Fig. 10

In the diploid yeast cells which survive, the radiation produces some unpaired defects, but no paired ones. The graph shows different types of diploid cells having unpaired defects in a schematic fashion. The weak spots in the defective cells are indicated by arrows.

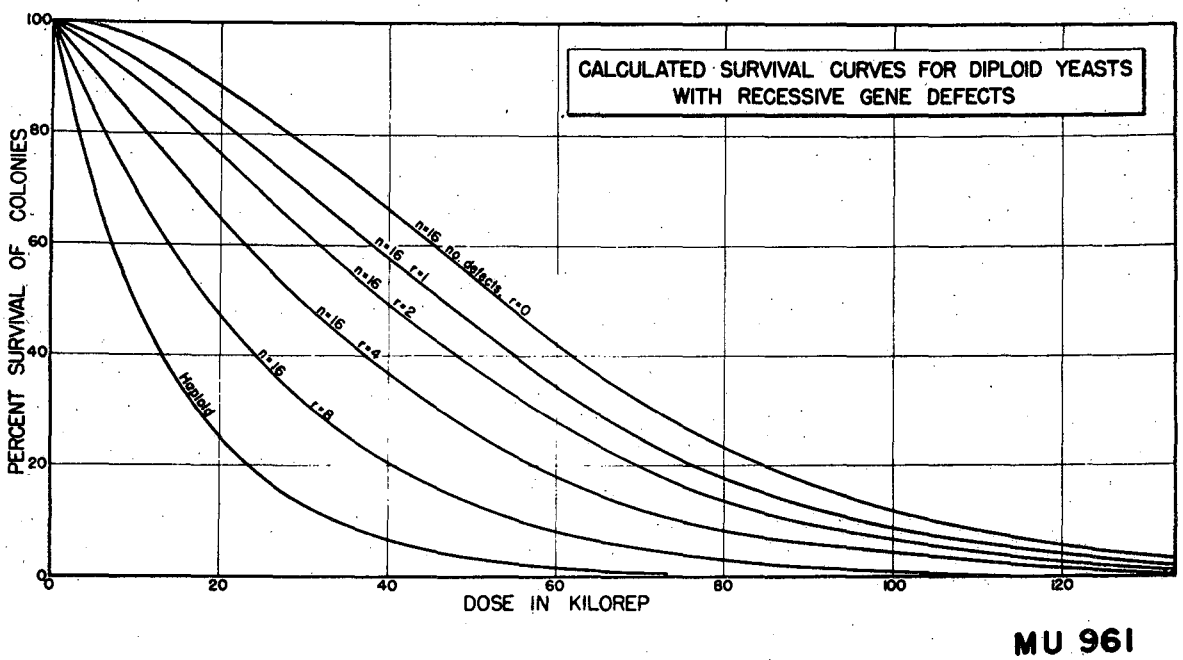


Fig. 11

Theoretical survival curves for diploid yeast cells with unpaired defects and normal diploid and haploid survival curves.

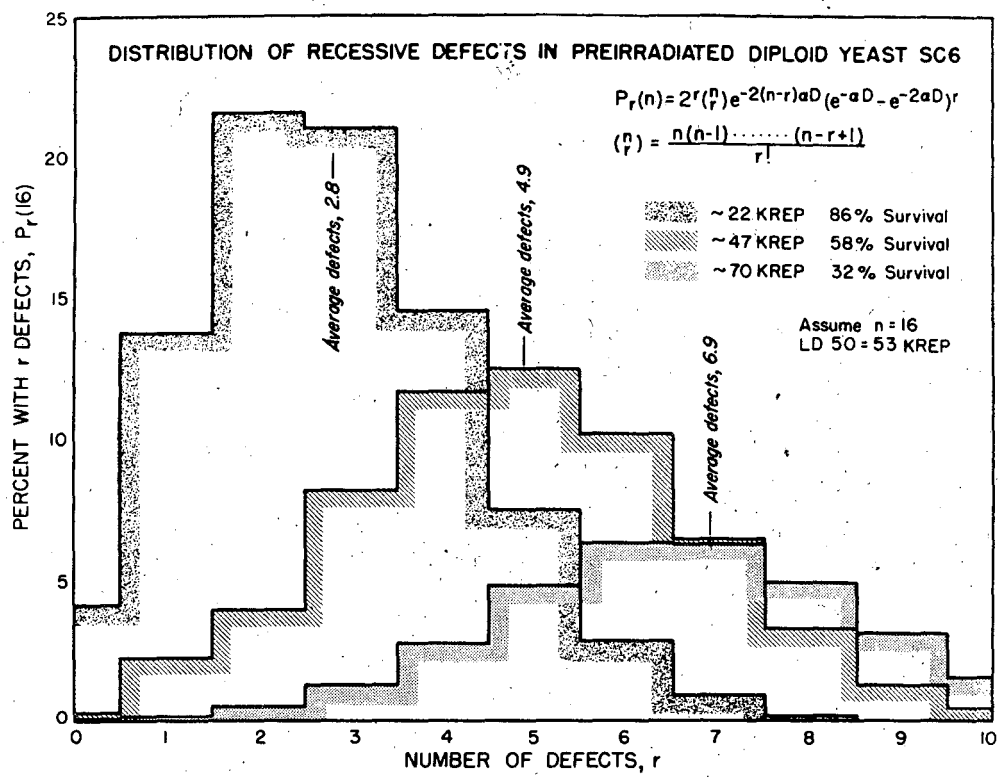
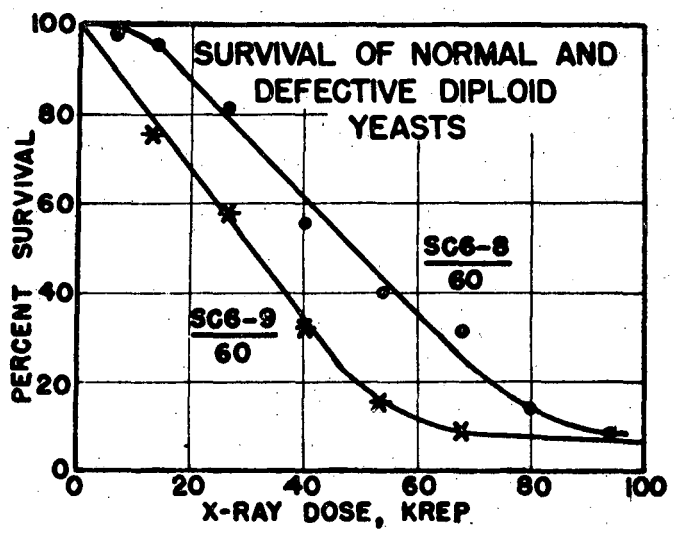


Figure 12. Theoretical distribution of diploid yeast cells with unpaired defects produced after single irradiation of normal diploids.



MU-1075

Fig. 13

Experimental survival curves of a diploid colony with about three unpaired defects. This colony was obtained by pre-irradiation subsequent to isolation of a single cell and its growth into a vegetative colony. The survival of a normal diploid colony is also shown.

III HEALTH CHEMISTRY AND PHYSICS

Health Chemistry

N. Garden

Monitoring. Routine monitoring of laboratories, areas and materials has continued. Other regularly executed duties include a new routine servicing of filter queens and a modified hood filter change schedule. New survey meters acquired include six long awaited Pee-Wees for alpha surveys and two alpha foot counters. Improvements were made in the box described in the last Quarterly Report for injecting animals with plutonium and subsequent treatment.

Transportation, Decontamination, Disposal and Storage. Transportation of radioactive materials, disposal of radioactive waste, checking of shipments in and out of the area, storage of active materials not being currently used and decontamination of equipment continued as usual. The new decontamination chamber described in the last Quarterly report, was tried out with some success. The motors driving the mechanized dolly however proved to be too light and must ultimately be replaced with heavier-duty types. The decontamination of platinum has been discontinued in favor of a central decontamination service offered by the Atomic Energy Commission. Decontamination of the six-inch straight-type lead cave has begun, following the processing of a Hanford bombardment described previously. Two beta manifolds from Oak Ridge have been decontaminated for Project use. Surplus and unused uranium holdings on the area are being packaged for shipment to Oak Ridge.

Research and Development. Two transuranic bombardments from Chalk River have been processed, one for the Radiation Laboratory and one for Los Alamos. These specimens were treated by remote operation in two-inch lead boxes. Other major projects included preparation of equipment for a proton bombardment of uranium, improvement of the liquid transfer system for work with Hanford dissolver solution, and standardization of Health Chemistry equipment and drawings.

General. The health Chemistry group has expanded during this period, to increase Health Chemistry services and to afford training to groups needed elsewhere. This department has been acting in a contamination capacity for non-project work. Calls and inquiries are being placed in increasing amounts.

Health Physics

B. J. Moyer

The work which has been pursued during the last quarterly period has concerned the radiation field of the 60-inch cyclotron under various types of operation and also a study of the fast neutron field produced by the syncrhotron.

Synchrotron. Measurements taken at the synchrotron with a monitor reading 67 micro Coulombs per minute, long beam, and a 20 mil platinum target, showed a maximum fast neutron intensity of 300 Mev per square centimeter per second. This maximum reading was obtained 12 feet from the target and in the general azimuth region of the x-ray beam. The distance of 12 feet was about as close as the apparatus could conveniently approach the target under the conditions of the experiment going on.

In all the synchrotron working areas outside the radiation shielding there was no measurable fast neutron flux above the usual background. At the door of the enclosed area in the azimuth of the x-ray beam the neutron intensity was about 80 Mev per square centimeter per second.

It is apparent that the neutron fields outside of the radiation shielding are completely negligible unless the beam is considerably increased in which case some consideration should be given to the area outside the shielding in the general azimuth of the beam.

60-inch Cyclotron. Recent surveys at the 60-inch cyclotron have been performed under the following types of operation:

1. Deuteron beam 20 Mev energy, 21 microamperes and beryllium target.
2. Alpha beam 40 Mev energy, 5 microamperes and silver target.
3. Proton beam 10 Mev energy, 7-1/2 microamperes bismuth target.

The results of these surveys are most clearly seen by reference to Figs. 1, 2, and 3 accompanying this report. The "T"-unit employed is the maximum permissible fast neutron energy flux of 86 Mev per square centimeter per second. Measurements of the fast neutron energy flux are made by the hydrogen recoil proportional counter method. The measurements in units of mr per hour are made with a plastic walled ionization chamber.

It is apparent that under the high intensity deuteron operation shown, the radiation field over a considerable region is out-of-bounds for continuous operation. The region which is especially high is just outside a shielding aperture through which the deflected deuteron beam can be guided. The aperture is filled with an array of five gallon water cans and is manifestly weak in its attenuation of the neutrons. Because of these conditions such deuteron operation is restricted to the owl shift and Sundays.

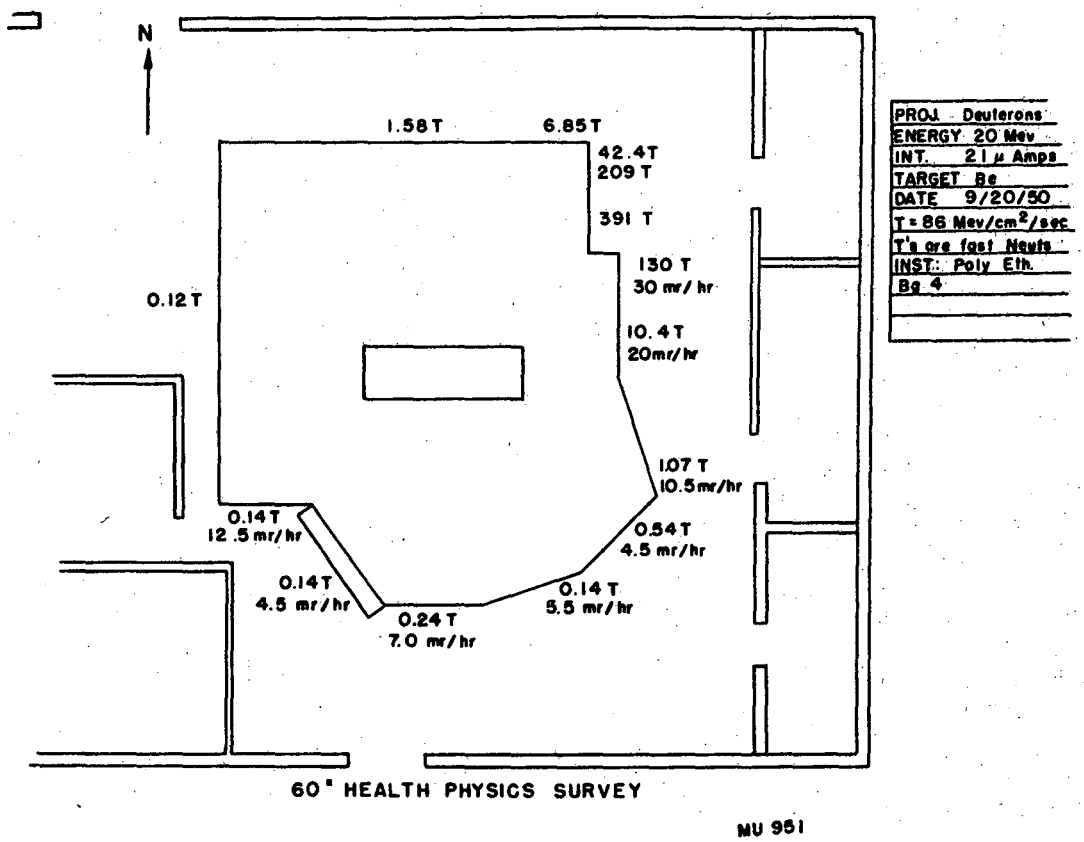

N
1.58 T
6.85 T
42.4 T
209 T
391 T
130 T
30 mr/hr
10.4 T
20mr/hr
1.07 T
10.5mr/hr
0.54 T
4.5 mr/hr
0.14 T
5.5 mr/hr
0.24 T
7.0 mr/hr
0.14 T
4.5 mr/hr
0.14 T
12.5 mr/hr
0.12 T
PROJ. Deuterons
ENERGY 20 Mev
INT. 21 μ Amps
TARGET Be
DATE 9/20/50
T = 86 Mev/cm²/sec
T's are fast Neuts
INST: Poly Eth.
Bg 4
60" HEALTH PHYSICS SURVEY
MU 951

Fig. 1

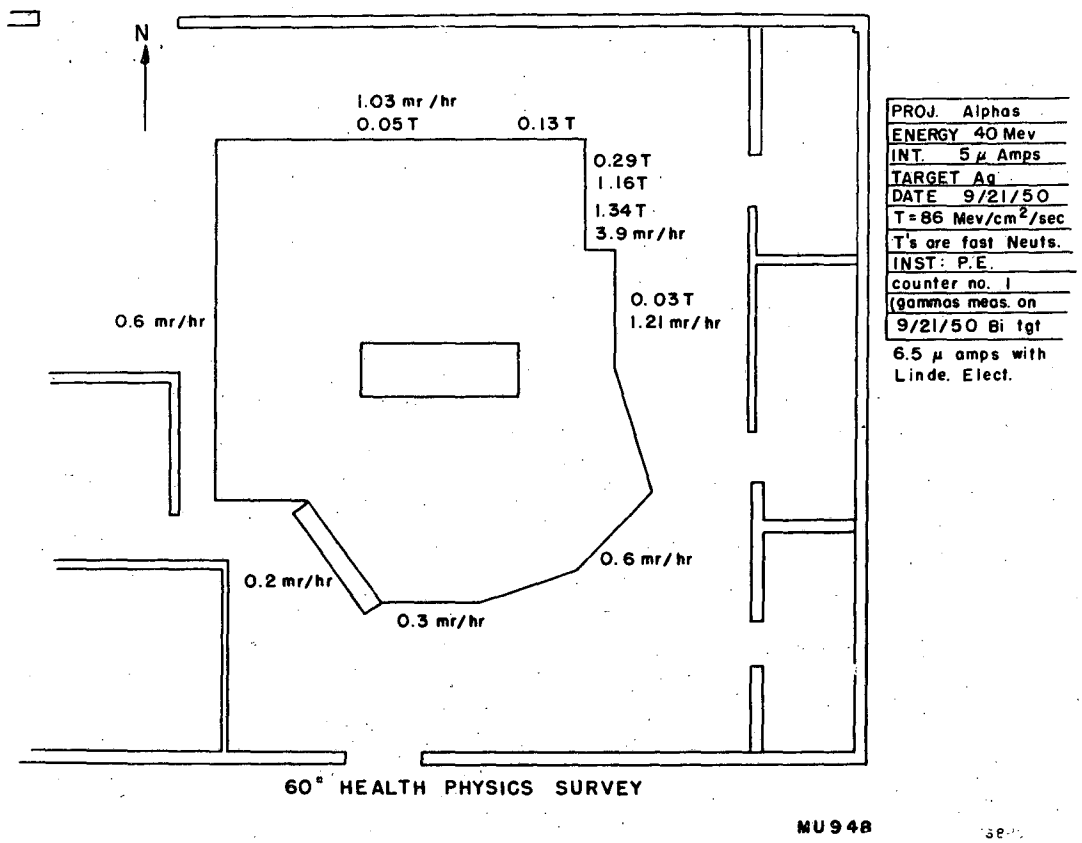

N
1.03 mr/hr
0.05 T
0.13 T
0.29 T
1.16 T
1.34 T
3.9 mr/hr
0.03 T
1.21 mr/hr
0.6 mr/hr
0.2 mr/hr
0.3 mr/hr
0.6 mr/hr
PROJ. Alphas
ENERGY 40 Mev
INT. 5 μ Amps
TARGET Ag
DATE 9/21/50
T = 86 Mev/cm²/sec
T's are fast Neuts.
INST: P.E.
counter no. 1
(gammas meas. on
9/21/50 Bi tgt
6.5 μ amps with
Linde. Elect.
60" HEALTH PHYSICS SURVEY
MU948

Fig. 2

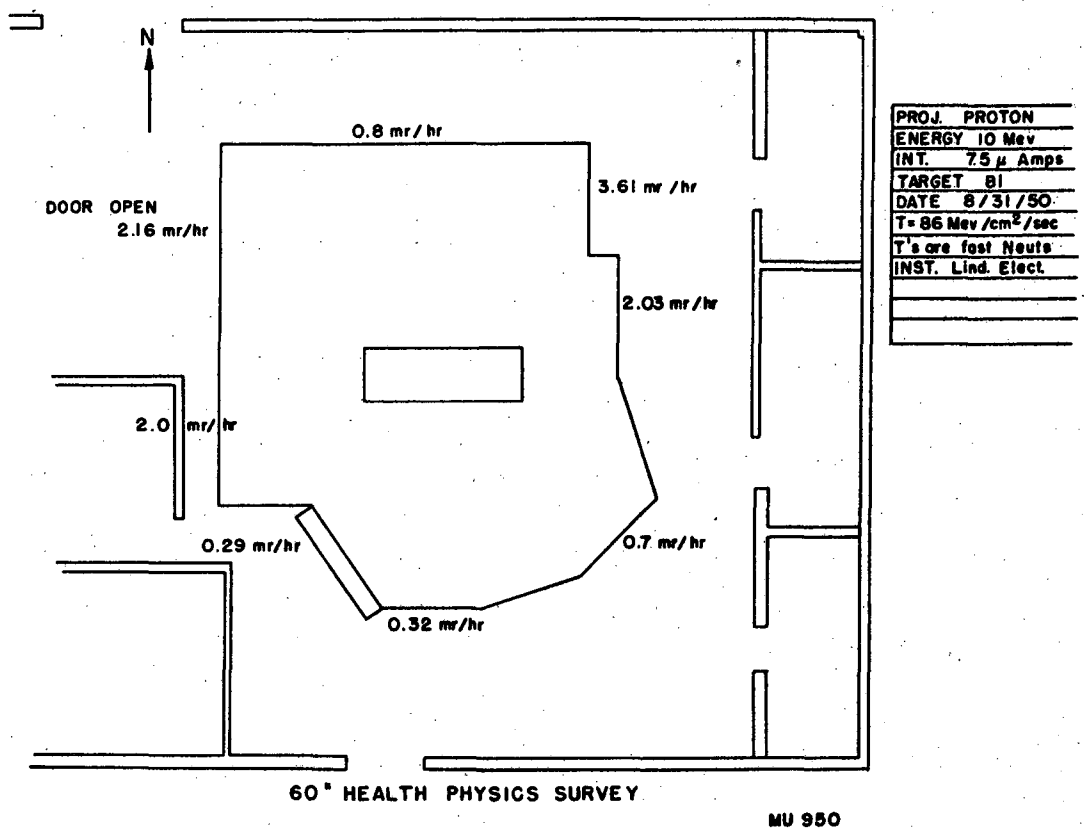

N
0.8 mr/hr
3.61 mr/hr
DOOR OPEN
2.16 mr/hr
2.03 mr/hr
2.0 mr/hr
0.29 mr/hr
0.7 mr/hr
0.32 mr/hr
PROJ. PROTON
ENERGY 10 Mev
INT. 7.5 μ Amps
TARGET Bi
DATE 8/31/50
T= 86 Mev/cm²/sec
T's are fast Neuts
INST. Lind. Elect.
60" HEALTH PHYSICS SURVEY
MU 950

Fig. 3

Statistical Summary of Monitoring Program. Survey Instruments Maintained:

1.	B-γ ionization chambers	28
2.	Victoreen 263 meters	19
3.	I.D.L. portable survey meters	18
4.	Cutie Pies	3
5.	Recording γ-intensity meters	11
6.	Victoreen proteximeters	3
7.	Fast neutron proportional counters	5
8.	Slow neutron proportional counters	8
9.	Balanced chamber (slow neutron survey instrument)	2
10.	Balanced chamber (fast neutron survey instrument)	1
11.	Special tissue wall survey instrument	1

Personnel Meters in Use:

1.	Total people covered with film badges	1751
2.	Total man days coverage with pocket chambers	1276
3.	Total man days coverage with pocket dosimeters	3061
4.	Total man days coverage with pocket chambers(SN)	2846

Cases of weekly exposures above .3r:

Weekly film exposure above	184-in. area	60-in. area	Linear Accelerator	Synchrotron	Chemistry	Total
.3r	0	12	6	0	6	24
.5r	0	4	4	0	4	12
1.0r	0	0	1	0	0	1
1.5r	0	-	1	0	0	1

LMB/11-13-50
Information Division