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UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE
TENNESSEE

BIOLOGICAL ACTION OF GAMMA AND X-RAYS

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Date of Manuscript: December 22, 1944

Document Declassified: April 30, 1947

This document consists of 34 pages.

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BIOLOGICAL ACTION OF GAMMA AND X-RAYS

I. Exposure of Mice to Daily Doses of Gamma Radiation at Two Rates: 5.5 r hr and 0.11 r/8 hr.

By E. Lorenz, A. Eschenbrenner, M. Derringer, and W. E. Heston

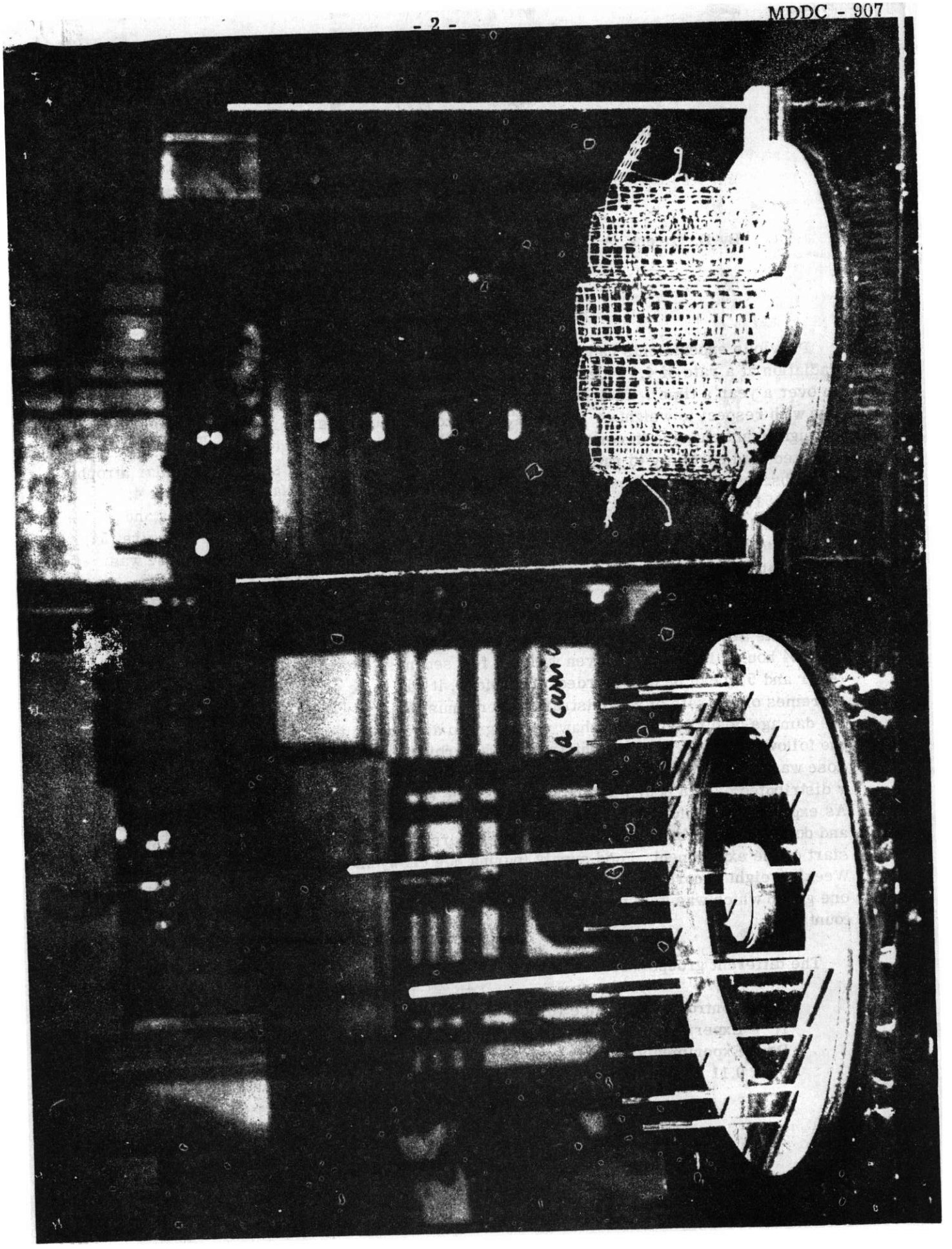
INTRODUCTION

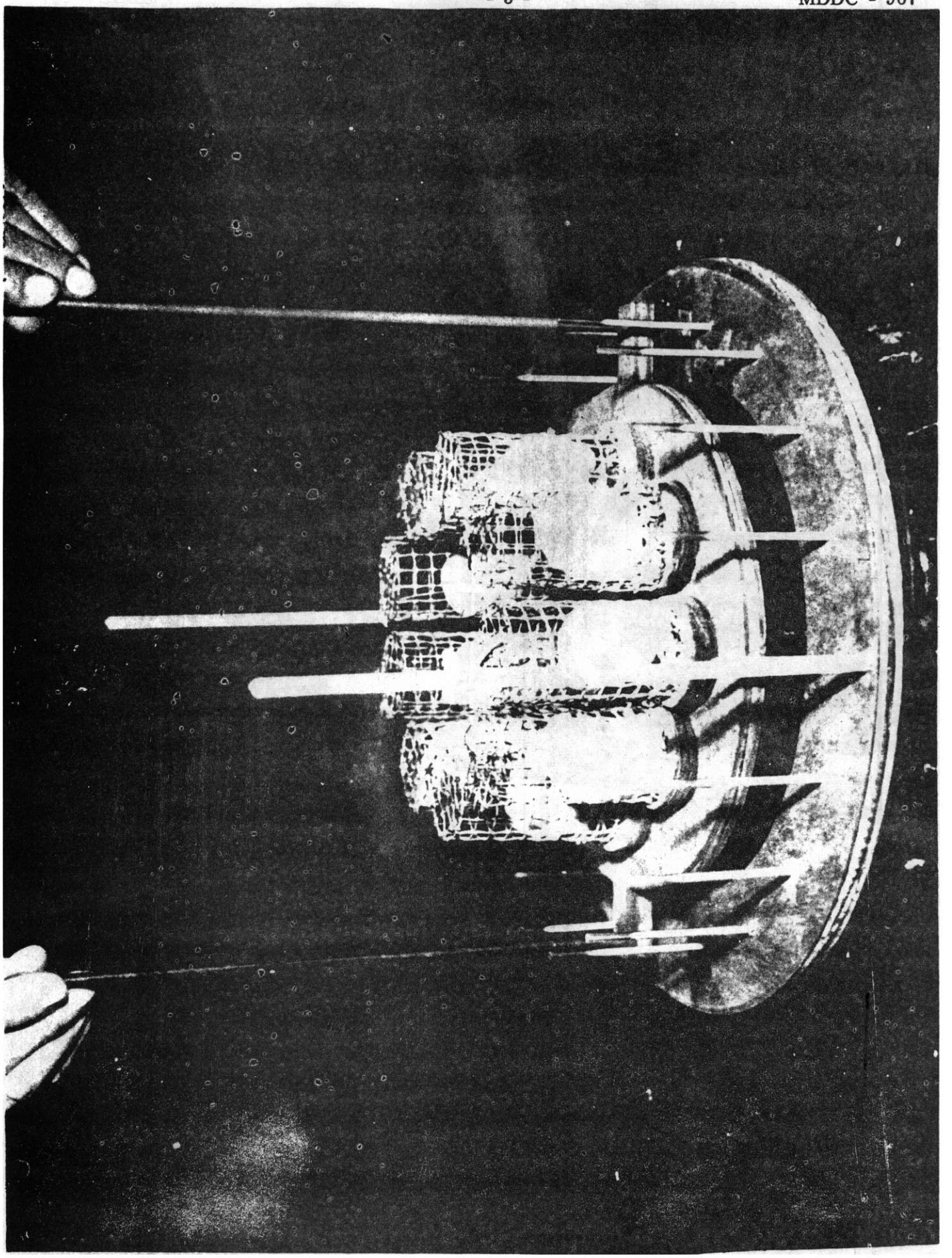
Previous experiments had shown that male C3H mice when exposed continously to γ radiation at a rate of 4.4 r per day would survive total doses of more than 1600 r (given in over a year's time). They appeared in no way different from the controls of the same age with respect to weight or activity. Blood counts which were done occasionally showed no significant changes in comparison to controls. The only damage that could be attributed with certainty to radiation was the histological finding of severe testicular atrophy with absence of mature sperms. On the other hand, Henshaw (J. Nat. Cancer Inst. 4: 513-522, 1944) reported pronounced histological damage in Hematopoetic organs and testes, and an appreciable shortening of life span in C3H mice after a daily exposure (5x weekly) to 5 r of x-rays given within a few seconds. The total average lethal dose was somewhat below 1000 r.

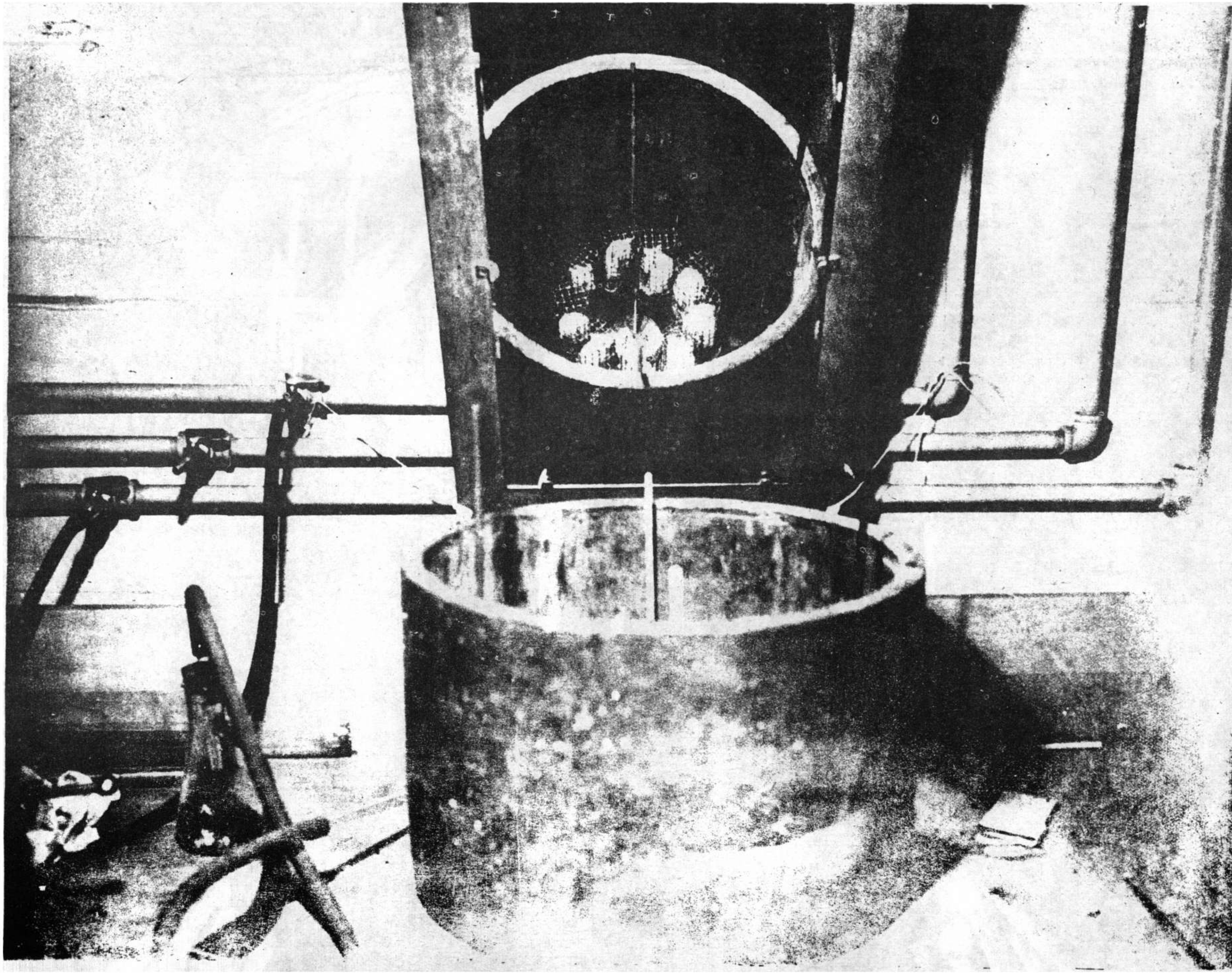
The discrepancy between these 2 experiments can only be attributed to the difference in the rate at which the daily dose was administered; in one experiment it was distributed over 24 hours, in the other given within a few seconds. The difference in the daily dose (4.4 r and 5 r) can be disregarded. Therefore, it has to be expected that between the extremes of the rate of administration there must exist a rate of administration at which the damage described by Henshaw will begin to appear. In the experiments described in the following, the rate of administration was arbitrarily chosen as one hour, and the daily dose was 5.5 r. In addition, one batch of mice was given a daily dose (tolerance?) of 0.11 r distributed over 8 hours to study any possible enhancing effects of this additional dose. As experimental mice, female LAF_1 hybrids were chosen as they are vigorous animals and do not develop breast tumors. All mice were approximately 2 months of age at the start of the experiment. Food supply (purina dog chow) and drinking water were unlimited. Weekly weight records were kept. Blood counts were taken biweekly with the exception of one group which was kept for breeding purposes. Controls were given 4 weekly blood counts.

The different groups were as follows:

- A_3 - Control female mice (8)
- I_1 - Experimental female mice (9) exposed daily to 5.5 r given in one hour.
- D_7 - Experimental female mice (9) exposed daily to 5.5 r given in one hour and 0.11 r given in 8 hours.







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I_2 - Experimental female mice (9) exposed daily to 5.5 r given in one hour (breeding experiment).

S_1 - Experimental female mice (8) given a single dose of 300 r in 7-1/2 minutes (breeding experiment).

EXPERIMENTAL SETUP

It did not seem practical to use x-rays for these experiments; the reasons being mainly the tie-up of an x-ray machine and an assistant for at least one hour daily. Therefore γ rays were chosen. The experimental set-up is given in Figures 1, 2 and 3. Figure 1 shows the radium carrier and the mice holders. The outer radium carrier consists of a wooden ring carrying 18 glass tubes at equal distances. 5 mg radium tubes (filter 0.5 mm of Pt) are inserted into the top of the glass tubes at a height corresponding to the middle of the little wire cylinders holding the mice. There are 9 mice holders, one radium tube is opposite each wire cage and one tube opposite the space between the wire cages. The central (inner) radium carrier has a 5 mg tube on top at about the same height as the top of the wire cages and another 5 mg tube at the bottom, at the same height as the bottom of the wire cage. Figure 2 shows the wire cages with the mice being lowered into the radiation field. Figure 3 shows the setup in a lead box with wall and bottom 2 cm thick. A 2 mm Al filter (not shown) lines the inner wall of the lead box. The radium carrier is permanently fixed in the lead box, the carrier with the mice being removable so that the operator is only exposed to the radiation for a few seconds. The daily dose received by the operator's hands is far below the safety dose, and the dose to the body is negligible.

The energy distribution at the place of the mice was calculated by assuming an equivalent of 8 r per hour at 1 cm distance from 1 mg of radium filtered by 0.5 mm of Pt. Measurements of the dose were carried out with a Victoreen 25 r chamber at different points inside the mice cages; the chamber was calibrated by the Bureau of Standards with x-rays. This calibration also holds for γ rays as a lucite thimble fitting snugly over the chamber gave readings within the error of the 25 r chamber being approximately $\pm$ 2%. (An increase in the measurement of 1% was observed with the addition of the lucite thimble.) The measurements showed an average value for the intensity in the center of a mouse cage of 5.5 r per hour; the variations within the mouse cage (sides, top and bottom) were approximately $\pm$ 5%, the values on top and bottom lower than the average; those at the wall opposite the radium carrier higher than the average. The mice usually moved around in the little cages so that an average mouse dose of 5.5 r per hour $\pm$ 5% is the most probable. There is also a small variation ($\pm$ 2%) from cage to cage. Absorption within the mice is not taken into account as it can be neglected.

RESULTS

As will be seen in the following, the majority of the mice of experiment I_1 and D_7 suffered from a low grade chronic pneumonia which made necessary the termination of

the experiment after nine months. The experiment was started in early summer of 1943 and the daily moving of the animals from an air conditioned room to the irradiation room, which was not air conditioned, may have been the cause for the animals catching the disease. Unfortunately this condition was not recognized until several months had elapsed. At the beginning it expressed itself in a slower gain of weight of the experimental animals than of the controls. At that time, this was attributed to the radiation effects. It is believed, however, that this disease does not make the experiments without value. This is evident from the data presented in the following. It only terminated the experiments at a lower total dose (approximately 1500-1600 r) than might have been obtained with healthy animals.

All pertinent data are given in Tables 1 to 4 and Charts 1 to 18.

I. Blood counts. Blood counts were only taken of the control and experimental animals of Groups A_3, I_1 and D_7.

III. The controls were counted every four weeks; the experimental animals every two weeks. Charts 1 to 8 give the data on the control mice. These animals also serve as controls for other experiments and are in age several months ahead of the experimental animals. However, the data are comparable as counting was begun in all animals at approximately two months of age. All control animals were alive at the age at which the last experimental animal was killed. Approximately 50% of them are still alive at present, at an age of approximately 24 months. The charts, however, go only to approximately 18 months of age. In comparing Charts 1 to 8 (control animals A_3) and Charts 9 to 18 (experimental animals I_1 and D_7) there appears to be a greater frequency of fluctuations in the experimental animals. This however is of no importance as the experimental animals were counted twice as often as the control animals. Red counts, hemoglobin and platelet counts (the latter being taken a number of months after the experiment was started show no significant differences between experimental and control animals. Likewise, the total white count of the experimental animals is within the limits of the controls. There is a difference, however, in the differential count, the neutrophil count of the experimental animals being usually higher than that of the controls. This, however, has to be attributed to the chronic pneumonia and not to the irradiation. Animals of other experimental series which received much higher doses did not show an increase in neutrophil count. The following table gives the terminal (or near terminal) counts of the experimental mice and those of the controls at comparable age.

PATHOLOGICAL OBSERVATIONS

The pathological data available for experiments I_1, D_7, I_2 and S_1 are given in Tables I to IV. Complete data are given on experiments I_1 and D_7 (Tables I and II) in which the mice were exposed to the irradiation until death. In the experiments I_2 and S_1 the animals received not only considerably smaller doses than those of experiments I_1 and D_7, but also were killed and autopsied a considerable time after termination of the irradiation. Tables III and IV, therefore, give mainly the pertinent pathological data on the ovaries.

Table I

EXPERIMENT NO. I_1 ANIMAL SPECIES: MOUSE

Animal Number	Sex	Age at Start	Age at Death	Died or Killed	Autopsy Number	Exposure Data: Total Time of Exposure and Age Range	Exposure Data: Level	Exposure Data: Total Chronic Dose	Exposure Data: Total Acute Dose (daily)	Exposure Data: Total Chronic and Acute Dose	Data on Terminal Blood Counts: RBC	Hgb	WBC	%N	%L	Platelets	Lymphoma: Lymph Nodes	Lymphoma: Intestine	Lymphoma: Spleen	Lymphoma: Thymus	Lymphoma: Liver	Ovaries: Follicles	Ovaries: Down Growth	Ovaries: Tumor	Ovaries: Cysts	Estrous	Testes	Hepatoma	Lung Tumors	Lymph Nodes	Bone Marrow	Infections	Kidneys	Miscellaneous
14319	♀	68 d.	215 d.	D	C6937	147 d. 3/17/43 to 10/18/43	5.5 r per 1 h. per day		808 r				4850 counted 14 days before death	22	75		-	-	-	-	-	Primordial Smell Medium Large	-	-	-			-	-	R.C. L.N.	-	Pneumonia		
14313	♀	68 d.	237 d.	D	C7394	169 d. 3/17/43 to 11/9/43	5.5 r per 1 h. per day		930 r		10.6 x 10^6	17.0 gms.	10200 counted 8 days before death	25	74		-	-	-	-	-	Primordial	-	-	-			-	-	R.C. L.N.	-	Pneumonia		
14330	♀	65 d.	240 d.	K	C7469	175 d. 3/20/43 to 11/15/43	5.5 r per 1 h. per day		961 r		9.7 x 10^6	15.2 gms.	counted 7 days before death 6350	54	39		-	-	-	-	-	Lerge & Primordial		-	-			-	-	R.C. L.N.	-	Pneumonia		
14320	♀	68 d.	289 d.	D	C8254	221 d. 3/17/43 to 12/31/43	5.5 r per 1 h. per day		1215 r		9.6 x 10^6	15.8 gms.	10800 counted 4 days before death	36	61	100,000																Pneumonia		
14326	♀	67 d.	321 d.	D	C8748	254 d. 3/18/43 to 2/2/44	5.5 r per 1 h. per day		1397 r		12.8 x 10^6	20.2 gms.	6950	33	64	670,000						-		-	-						Pneumonia		
14325	♀	67.d	322 d.	K	C8758	255 d. 3/18/43 to 2/3/44	5.5 r per 1 h. per day		1403 r		10.3 x 10^6	18.7 gms.	4800	57	39	620,000	-	-	-	-	-	-		-	-			-	-		-	Pneumonia		
14318	♀	68 d.	326 d.	D	C8804	258 d. 3/17/43 to 2/6/44	5.5 r per 1 h. per day		1419 r		11.0 x 10^6	16.2 gms.	3800 counted 13 days before death	31	55	900,000	-	-	-	-	-	-		-	-			-	-		-	Pneumonia		
14317	♀	68 d.	341 d.	K	C8932	273 d. 3/17/43 to 2/21/44	5.5 r per 1 h. per day		1502 r		10.9 x 10^6	16.4 gms.	5000	49	46	800,000	-	-	-	-	-	-		-	-			-	-	R.C. L.N. R.E.	-	Pneumonia		
14321	♀	68 d.	341 d.	D	-	273 d. 3/17/43 to 2/21/44	5.5 r per 1 h. per day		1502 r		11.0 x 10^6	15.4 gms.	10800 counted 2 weeks before death	32	52																		

R.C. - Reaction Centers
L.N. - Large Nodules
R.E. - Reticulo-endothelial hyperplasia, medulla

Table II

EXPERIMENT NO. D_7 ANIMAL SPECIES: MOUSE

Animal Number	Sex	Age at Start	Age at Death	Died or Killed	Autopsy Number	Total Time of Exposure and Age Range	Exposure Data: Level	Exposure Data: Total Chronic Dose	Exposure Data: Total Acute Dose (daily)	Exposure Data: Total Chronic and Acute Dose	Data on Terminal Blood Counts: RBC	Hgb	WBC	%N	%L	Platelets	Lymphoma: Lymph Nodes	Lymphoma: Intestine	Lymphoma: Spleen	Lymphoma: Thymus	Lymphoma: Liver	Ovaries: Follicles	Ovaries: Down Growth	Ovaries: Tumor	Cysts	Estrous	Testes	Hepatoma	Lung Tumors	Lymph Nodes	Bone Marrow	Infections	Kidneys	Miscellaneous
14308	♀	69 d.	181 d.	D	-	112 d. 3/16/43 to 9/13/43	0.11 r per 8 h. per day 5.5 r per 1 h. per day	12 r	616 r	628 r	9.0 x 10^6	-	2650	14	79																			
14305	♀	69 d.	279 d.	D	-	210 d. 3/16/43 to 12/10/43	0.11 r per 8 h. per day 5.5 r per 1 h. per day	23 r	1155 r	1178 r	9.6 x 10^6	16.0 gms.	6100 Counted 11 days before death.	39	54	770,000																Pneumonia		
14311	♀	68 d.	284 d.	D	C8197	216 d. 3/17/43 to 12/26/43	0.11 r per 8 h. per day 5.5 r per 1 h. per day	24 r	1188 r	1212 r	10.3 x 10^6	16.8 gms.	4350 Counted 6 days before death	49	47	910,000	-	-	-	-	-			-				-	R.C. L.N. R.E.	-	Pneumonia	-	
14225	♀	72 d.	307 d.	D	C8448	235 d. 3/13/43 to 1/14/44	0.11r per 8 h. per day 5.5 r per 1 h. per day	26 r	1292 r	1318 r	9.1 x 10^6	14.7 gms.	5800 Counted 4 days before death	44	51	660,000	-	-	-	-	-	-	-	-			-	-	R.C. L.N. R.E.	-	Pneumonia	-	
14304	♀	69 d.	330 d.	D	C8816	261 d. 3/16/43 to 2/9/44	0.11 r per 8 h. per day 5.5 r per 1 h. per day	29 r	1436 r	1465 r	7.3 x 10^6	12.3 gms.	6250 Counted 2 days before death	41	57	340,000	-	-	-	-	-	-	-	-			-	-	R.C. L.N. R.E.	-	Pneumonia	-	
14306	♀	69 d.	344 d.	D	-	275 d. 3/16/43 to 2/23/44	0.11 r per 8 h. per day 5.5 r per 1 h. per day	30 r	1503 r	1533 r	8.1 x 10^6	15.5 gms.	11850 Counted 2 days before death	50	45	920,000																Pneumonia		
14260	♀	72 d.	353 d.	K	C9095	281 d. 3/13/43 to 3/3/44	0.11 r per 8 h. per day 5.5 r per 1 h. per day	31 r	1546 r	1577 r	11.7 x 10^6	18.4 gms.	3850	46	51	340,000	-	-	-	-	-	-	-	-	-			-	-	R.C. L.N. R.E.	-	Pneumonia	-	
14307	♀	69 d.	350 d.	K	C9094	281 d. 3/16/43 to 3/3/44	0.11 r per 8 h. per day 5.5 r per 1 h. per day	31 r	1546 r	1577 r	7.0 x 10^6	16.0 gms.	5550	22	75	1,060,000	-	-	-	-	-	-	-	-				-	-	R.C. L.N. R.E.	-	-	-	
14331	♀	65 d.	346 d.	K	C9093	281 d. 3/20/43 to 3/3/44	0.11 r per 8 h. per day 5.5 r per 1 h. per day	31 r	1546 r	1577 r	7.0 x 10^6	15.5 gms.	4350	40	57	970,000	-	-	-	-	-	-	-	-	-	Met-estrous		-	-	R.C. L.N. R.E.	-	-	-	

R.C. - Reaction Centers
L.N. - Large Nodules
R.E. - Reticulo-endothelial hyperplasia, medulla

Table III

EXPERIMENT NO. I_2 ANIMAL SPECIES: MOUSE

Number	Sex	Age at Start Days	Age at Death Days	Died or Killed	Autopsy Number	Exposure Data: Level	Exposure Data: Total Dose	Ovaries: Follicles	Ovaries: Down Growth	Ovaries: Cysts	Estrous	Lung Tumors	Mammary Gland Tumors	Uterus	Breeding Results Litters 1: No. Born	1: No. Weaned	2: No. Born	2: No. Weaned	3: No. Born	3: No. Weaned	4: No. Born	4: No. Weaned	5: No. Born	5: No. Weaned	Miscellaneous -- Age at Mating (days)
14771	♀	68	321	Killed	C9376	5.5 r/1 h. per day	330		-	-	Metestrus 2	♀ Primary 11 Metastatic		-	9	9	10	10	9	9	8	3	-	-	128
14776	♀	68	412	"	D1108	"	330	(few)		Small cyst in 1 ovary	Praestrus to Estrous	-	-	Growth resembling a fibro-Myoma	10	7	10	0	13	12	4	4	-	-	128
14777	♀	68	412	"	D1112	"	330	(few)		Papillary cyst in 1 ovary	Estrous	-	-	-	4	4	8	8	12	12	13	12	3	3	128
14778	♀	68	412	"	D1109	"	440	(few)		-	Praestrus	-	-	-	7	7	7	7	8	7	1	0	-	-	148
14779	♀	68	412	"	D1110	"	440	(few)		-	Praestrus	1 Primary		-	9	9	6	6	6	6	2	0	-	-	148
14782	♀	66	410	"	D1111	"	440			-	Mucenous Cells (Pregnant)	-	-	-	10	0	11	0	8	8	3	2	-	-	146
14783	♀	66	410	"	D1113	"	770	-		-	Estrous(?)	-	-	-	2	0	-	-	-	-	-	-	-	-	175
14784	♀	66	410	"	D114	"	770	-		One ovary cystic	Atypical	-	-	-	1	0	-	-	-	-	-	-	-	-	175
14790	♀	66	410	"	D1115	"	770	-		-	Atypical	-	-	-	0	-	-	-	-	-	-	-	-	-	175

Table IV

EXPERIMENT NO. S_1 ANIMAL SPECIES: MOUSE

Animal Number	Sex	Age at Start Days	Age at Death Days	Died or Killed	Autopsy Number	Exposure Data		Ovaries			Estrous	Lung Tumors	Mammary Gland Tumors	Uterus	Breeding Results Litters										Miscellaneous	
															1		2		3		4		5			
						Level	Total Dose	Follicles	Down Growth	Cysts					No. Born	No. Weaned	No. Born	No. Weaned	No. Born	No. Weaned	No. Born	No. Weaned	No. Born	No. Weaned	Age at Mating (days)	
15711	♀	56	276	Killed	D586	40.7 r per min.	300 r	-		One ovary cystic	Estrous to Metestrus-1	-	-	-	5	5	-	-	-	-	-	-	-	-	56	
15712	♀	56	276	"	D587	"	300 r	-		One ovary cystic	Estrous	-	-	-	5	5	-	-	-	-	-	-	-	-	56	
15713	♀	55	275	"	D588	"	300 r	-		-	Metestrus-2	One Primary	-	-	9	9	-	-	-	-	-	-	-	-	55	
15714	♀	55	203	"	C9628	"	300 r	-		-	Atypical	-	-	-	8	8	-	-	-	-	-	-	-	-	55	
15715	♀	55	275	"	D589	"	300 r	-		-	Atypical	-	-	-	6	6	-	-	-	-	-	-	-	-	55	
15716	♀	55	275	"	D590	"	300 r	-		One ovary cystic	Estrous to Metestrus-1	-	-	-	6	6	-	-	-	-	-	-	-	-	55	
15717	♀	55	275	"	D591	"	300 r	-		-	Diestrus	-	-	-	5	4	-	-	-	-	-	-	-	-	55	

TABLE V

Group	Mouse Number	Age in days	R.B.C. x 10^6	Hgb. gms/100cc	Pl. x 10^5	W.B.C.	%N	%L
	14319	201	------	----	-----	4850	22	75
	14313	237	10.6	17.0	-----	10200	25	74
	14330	240	9.7	15.2	-----	6350	54	39
	14320	289	9.6	15.8	10.0	10800	36	61
I_1	14326	321	12.8	20.2	6.7	6950	33	64
	14325	322	10.3	18.7	6.2	4800	57	39
	14318	326	11.0	16.2	9.0	3800	31	55
	14317	341	10.9	16.4	8.0	5000	49	46
	14321	341	11.0	15.4	-----	10800	32	52
	14308	181	9.0	----	-----	2650	14	79
	14305	279	9.6	16.0	7.7	6100	39	54
	14311	284	10.3	16.8	9.1	4350	49	47
	14255	307	9.1	14.7	6.6	5800	44	51
D_7	14304	330	7.3	12.3	3.4	6250	41	57
	14306	344	8.1	15.5	9.2	11850	50	45
	14260	353	11.7	18.4	3.4	3850	46	51
	14307	350	7.0	16.0	10.6	5550	22	75
	14331	346	7.0	15.5	9.7	4350	40	57
		Approx.						
	13381	180	11.0	16.4	-----	8300	7	89
	13382	200	9.6	16.6	-----	3300	5	94
	13386	240	9.9	15.8	-----	7250	10	86
A_3	13387	280	10.6	18.2	-----	3800	10	90
	13388	300	9.8	16.4	-----	4250	22	78
	13389	320	10.8	18.4	-----	5050	12	86
	13395	340	7.4	13.4	-----	6650	22	73
	13396	360	8.6	17.7	-----	5350	10	89

The experimental groups I_1 and D_7 are discussed together as there is no indication that the additional dose of 0.11 r per 8 hours per day in the D_7 group had any effect whatsoever. Examination of the sections prepared from complete autopsies revealed the presence of pathological changes attributable to irradiation only in the spleen, lymph nodes and ovaries. All but two mice had extensive penumonia of a chronic type commonly seen in untreated animals. Differences in mice with and without pneumonia were observed only in the spleen. Descriptions of lymph nodes and spleens will follow the terminology used by Conway in her studies on the changes in these organs of the guinea pig and rabbit, following infection by Bact monocytogenes. No bone marrow atrophy was observed in any of the animals. No special cytological study was made of the marrow.

Lymph Nodes. The lymph nodes were slightly smaller than normal. They were composed of 1 to 3 very large nodules of medium and small sized lymphocytes without any peripheral zone of densely packed small lymphocytes. In these nodules there were scattered mitoses and foci of necrotic debris that were not concentrated in any particular zone. Some lymph nodes had one or two small nodules with pale central areas containing medium sized lymphocytes surrounded by a zone of densely packed small lymphocytes but these were conspicuously fewer in number than seen normally. Beginning with a total dose of 1212 r (not being present following a total dose of 961 r) a definite increase in the number of reticular cells was observed between the large lymphatic nodules. There was no associated increase of reticulum fibers (Laidlaw's stain).

Spleen. The spleens of the two pneumonia-free animals were of normal size (approximately 16 x 4 mm). They contained many medium sized lymphatic nodules that were composed of medium and small lymphocytes. Within the nodules were scattered mitoses and small foci of necrotic debris that were not concentrated in any particular zone. These nodules were very similar to the large nodules in the lymph nodes, except for size.

The spleens of animals that had pneumonia were slightly larger than normal (approximately 20 x 4-5 mm). Some of these contained numerous medium and large lymphatic nodules similar to those in the pneumonia-free animals, except for a prominent peripheral clear zone composed of large mononuclear cells with pale nuclei and abundant cytoplasm. In others, especially in animals that were found dead, the lymphatic nodules were very small without a peripheral clear zone. There appeared to be no increase of reticular cells in the medulla in contrast with the findings in the lymph nodes.

Ovaries. The ovaries were about normal size. Serial sections were made of ovaries of all animals but two in which there was advanced autolysis. After an exposure of 808 r, one mouse had follicles in all stages of development; after an exposure of 930 r, one mouse had only primordial follicles, and after an exposure of 961 r, one mouse had primordial and several large but no small or medium sized follicles. Higher doses up to 1577 r gave ovaries devoid of developing follicles. The highest dose at which primordial follicles were present was 1403 r. Above this total dose the organ was composed almost

entirely of luteal tissue but a few invaginative downgrowths of the surface epithelium were present.

The critical dose in this experimental arrangement for the development of follicles in the ovary appears to be in the region of 900 r. Although conclusions can be only tentative with the limited data available, it would appear that the stage of transformation of primordial into developing follicles is the most vulnerable one. After a follicle has begun to develop it proceeds to grow to maturity. Later, primordial follicles also disappear so that the organ is composed only of luteal tissue. Finally this tissue is displaced by invaginative downgrowths of the surface epithelium. In the last analysis these abnormalities of growth of the follicles are probably merely a reflection of a primary irradiation effect on the ova rather than a direct action on follicular cells.

The changes in the lymph nodes and spleen suggest repeated overlapping cycles of destruction and lymphopoiesis and with increasing dose this is accompanied by the appearance of proliferation of reticular cells in the medulla. It is assumed that the latter change represents further attempts at regeneration by proliferation and transformation of the reticular cells into lymphocytes.

From many observations of chronic pneumonia in untreated mice it is likely that in the present series of experimental animals this disease need not be considered to be a very great factor in interpretation of irradiation effects except in its terminal stages. It is a very slowly progressive disease that has no general systemic effects until more than half of the lungs are consolidated. It has no counterpart in the human but its systemic effects can be compared with those of mild bronchiectasis.

BREEDING EXPERIMENTS

The results of the breeding experiments on the I_2 mice (those receiving total doses of 330 r, 440 r and 770 r at a rate of 5.5 r per hour and per day) and the S_1 mice (those receiving a total dose of 300 r in 7 minutes 22 seconds) are presented in Tables III and IV. A study of the results indicates that a total dose of 300 r given in 7 minutes 22 seconds is sufficient to produce sterility in female LAF_1 mice. The results indicate a latent period since these females produced one litter, but no subsequent ones. All of these animals were mated on the day that they were irradiated. The vaginal epithelium of some of these animals, however, indicated an estrus cycle, despite the absence of follicles in the ovaries. The explanation of this is not apparent. Total doses of 330 r and 440 r given at the rate of 5.5 r per hour and per day are not sufficient to produce sterility, while a total dose of 770 r given at this rate is sufficient. Two of the three females receiving 770 r at the rate of 5.5 r per hour and per day each produced one small litter (consisting of 1 and 2 animals) but no subsequent litters. The reduction in litter size in the fourth litters produced by the females receiving 550 r at the rate of 5.5 r per hour and per day is probably an effect of age. The same situation prevailed in one of the females receiving 330 r at the rate of 5.5 per hour and per day. It should be noted that at that time the animals

in the two groups were of approximately the same age which would explain the similar results obtained. These data can be compared with data obtained in other experiments which will be discussed here.

The breeding results obtained in the 4.4 r per 24 hours and per day groups are in accord with those obtained for the I_2 mice. Females receiving up to 550 r on the 4.4 r/day level produced normal sized litters. Those receiving a total dose of 770 r at the rate of 4.4 r/day show a definite reduction in litter size, the average in this case being 2.6 (incomplete). The average litter size for controls to this group is 8.8. This reduction in litter size in the animals receiving 770 r at the rate of 4.4 r/day is probably in part an age effect since these animals were not mated until they were approximately 8 months of age. The first indication of any effect on the animals on the 8.8 r/day level was seen in the females receiving 880 r. Ten of the fifteen animals in this group produced litters with an average litter size of 2.6. The females which received 770 r at the rate of 8.8 r/day produced litters with an average litter size of 6.1. The average litter size for controls to this group is 8.1. The few results available at this time indicate an irradiation effect in the females which received a total dose of 880 r at the rate of 8.8 r/8 hours per day; the average litter size in this instance is 2.0 while that for controls is 8.6.

CONCLUSIONS AND SUMMARY

Haematology. Female LAF_1 mice have been exposed to daily doses of 5.5 r in one hour (I_1) and 5.5 r in one hour, plus 0.11 r in 8 hours. Biweekly blood counts were taken on these animals. They came to autopsy after having received total doses ranging from 600 to 1600 r. The blood picture of these animals is comparable to that of controls of the same age with the exception that the neutrophil count was higher than normal for most of the experimental animals. This increase in neutrophils was probably due to a low grade pneumonia and not due to the irradiation.

Pathology. Radiation effects were observed only in lymph nodes, spleen and ovaries while all other organs were within normal limits histologically.

Breeding. Breeding experiments showed that a single dose of x-rays of 300 r given in 7-1/2 minutes, will result in sterility after one litter of reduced size was born. Breeding experiments in which 330 and 440 r were given at the rate of 5.5 r per one hour per day gave litters of normal size and the mice remained fertile up to about 1 year of age, which is approximately the breeding end point of normal mice. Mice exposed to 770 r at the rate of 5.5 r per 1 hour per day gave one litter of greatly reduced size and were sterile thereafter. This finding is in agreement with other experiments, in which mice were exposed at the rate of 4.4 r per day, 8.8 r per day and 8.8 r per 8 hours per day. These animals when exposed to total doses of 770 and 880 r also became permanently sterile after one litter of reduced size was born. These breeding data are in agreement with the pathological observation of the I_1 and D_7 mice which showed that at a dose of approximately 900 r large follicles begin to disappear.

It can be concluded therefore that an exposure of mice to 5.5 r per hour per day up to total doses of approximately 1600 r produces radiation effects on the ovaries similar to and not more pronounced than those observed when similar doses are given at the rates of 4.4 r per day, 8.8 r per day and 8.8 r per 8 hours per day. The discrepancy between a single sterilization dose of 300 r and a dose of approximately 900 r given daily at the above rate seems to indicate that a certain amount of recovery of the ovary is possible when doses are subdivided. Whether the subdivision of the dose or the rate of administration of the dose is more important in producing sterility has to be decided by further experiments.

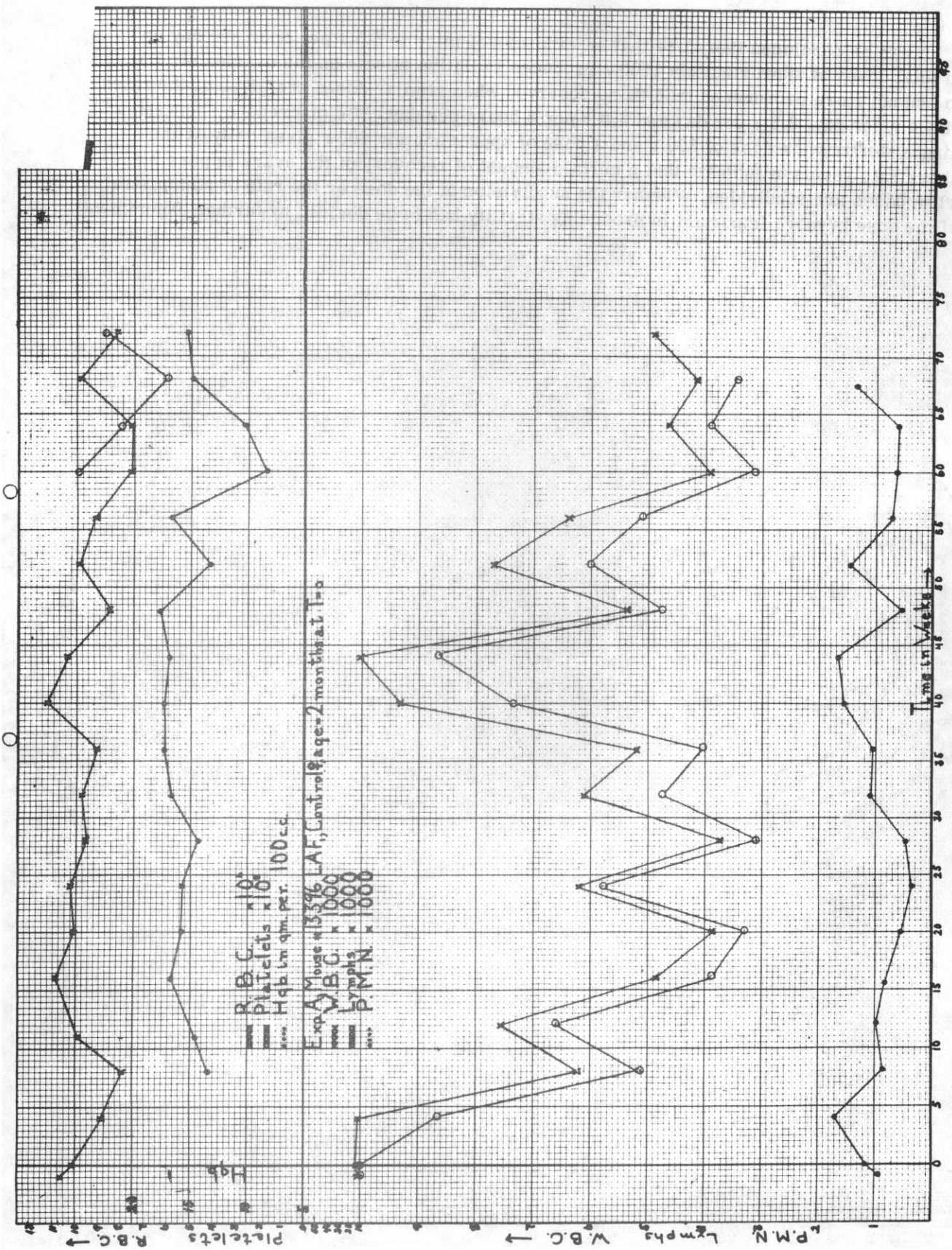

Exp. A Mouse #1356 LAF, Control (age = 2 months at T=0
R.B.C. x 10⁶
Platelets x 1000
Hgb. in gm. per 100 c.c.
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
R.B.C.
Platelets
Hgb.
W.B.C.
Lymphs
P.M.N.
Time in Weeks

Chart 1

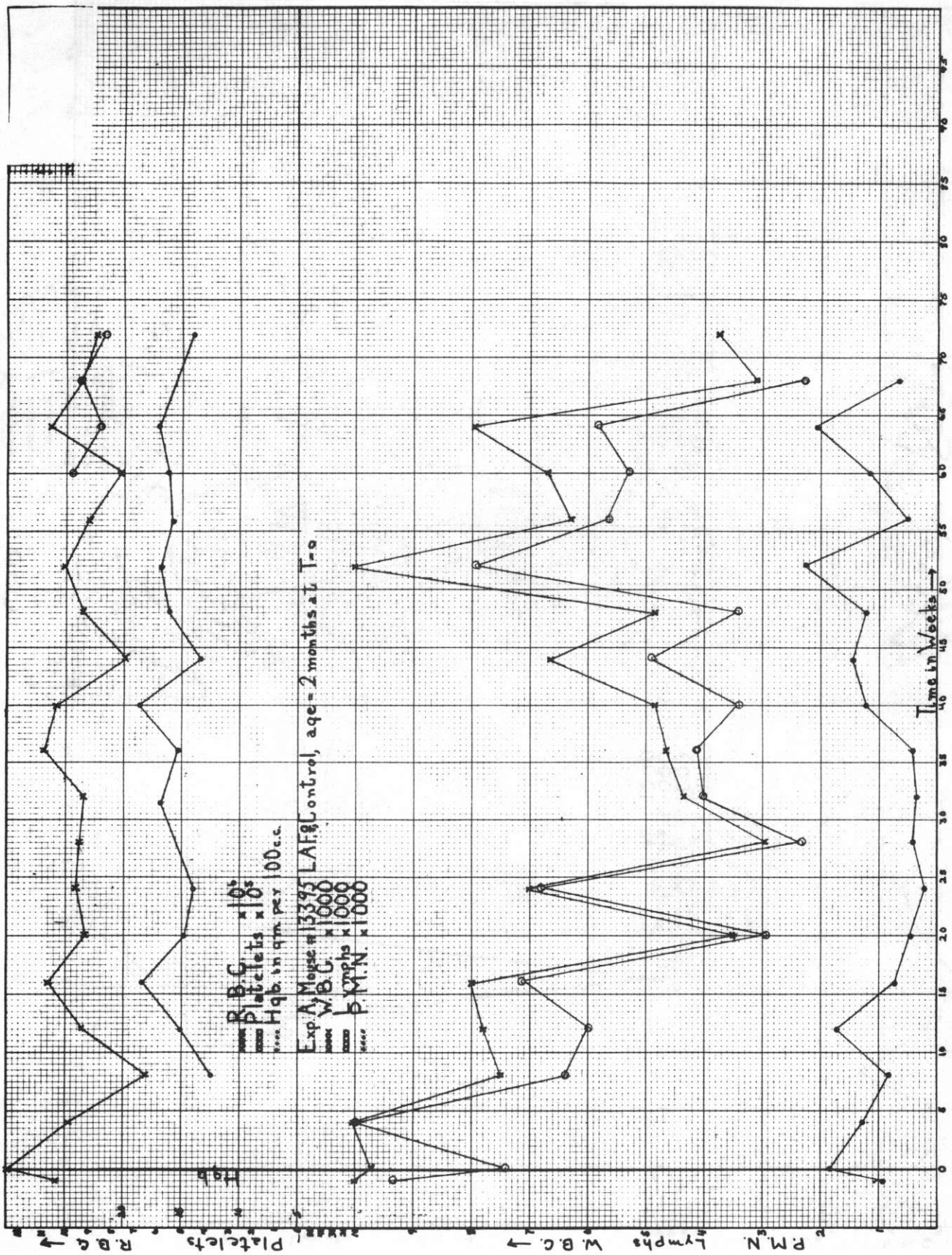

R.B.C.
Platelets
Hgb. in gm. per 100 c.c.
Exp. A, Mouse #13395 LAF1 Control, age = 2 months at T=0
W.B.C. ×1000
Lymphs ×1000
P.M.N. ×1000
Time in Weeks →

Chart 2

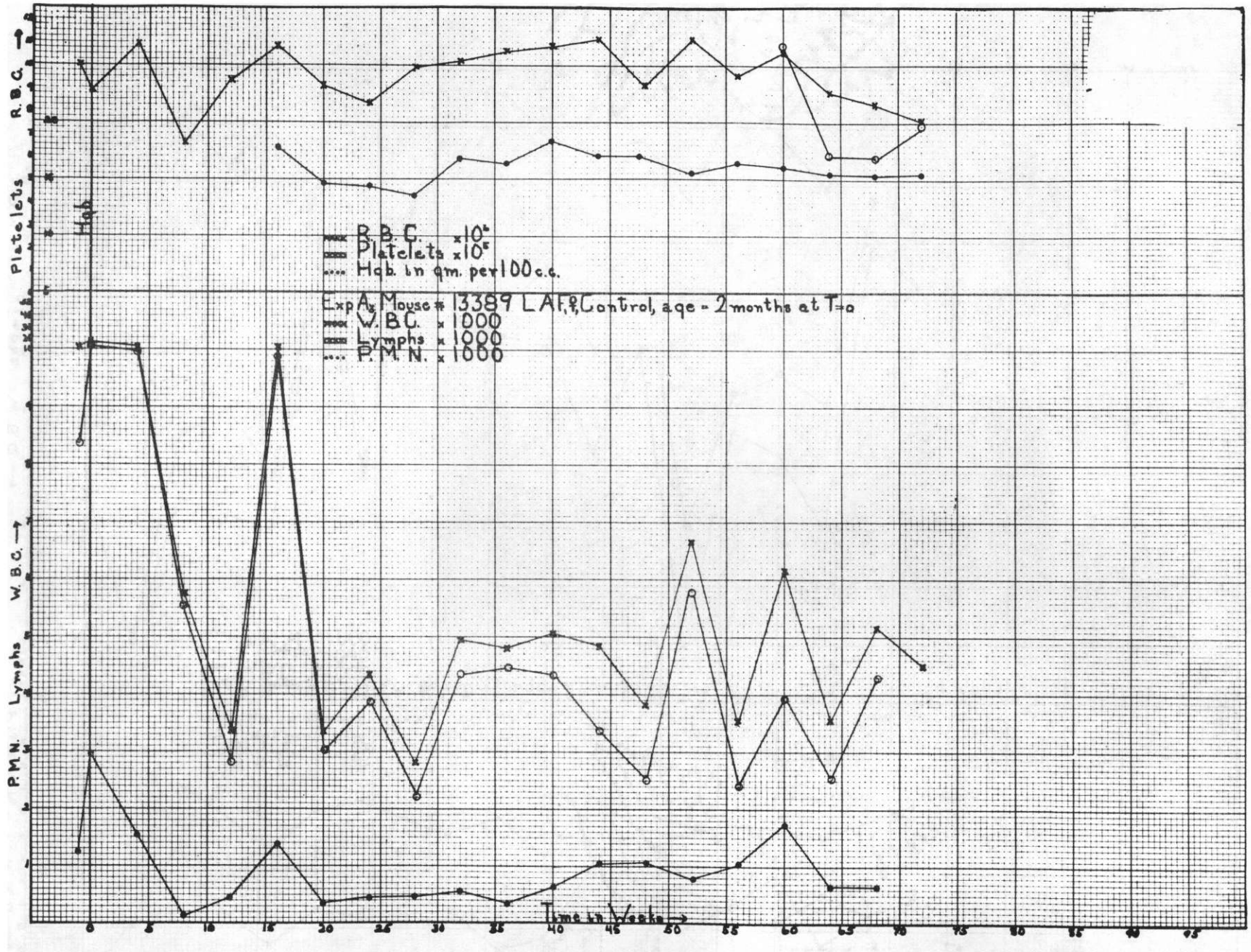

R.B.C. →
Platelets
Hgb.
R.B.C. x10⁶
Platelets x10⁵
Hgb. in gm. per 100 c.c.
Exp A₂ Mouse # 13389 L AF♀ Control, age - 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
W.B.C. →
Lymphs
P.M.N.
Time in Weeks →

Chart 3

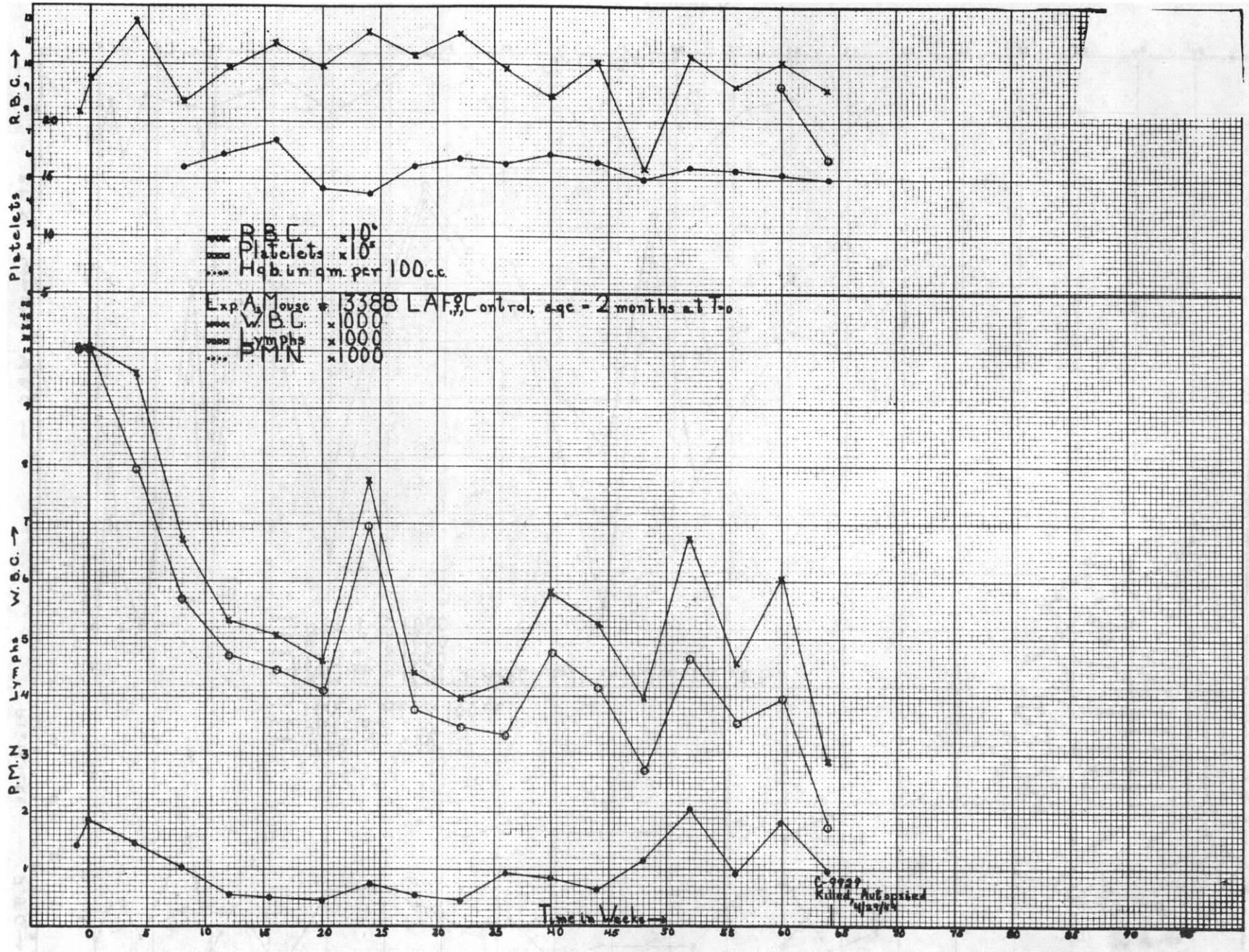

R.B.C. →
Platelets
W.B.C. →
Lymphs
P.M.N
R.B.C. x10⁶
Platelets x10⁵
Hgb. in gm. per 100 c.c.
Exp A₃ Mouse # 13388 LAF₁ ♀ Control, age - 2 months at T-o
W.B.C. x1000
Lymphs x1000
P.M.N. x1000
C-9727
Killed, Autopsied
4/27/45
Time in Weeks →

Chart 4

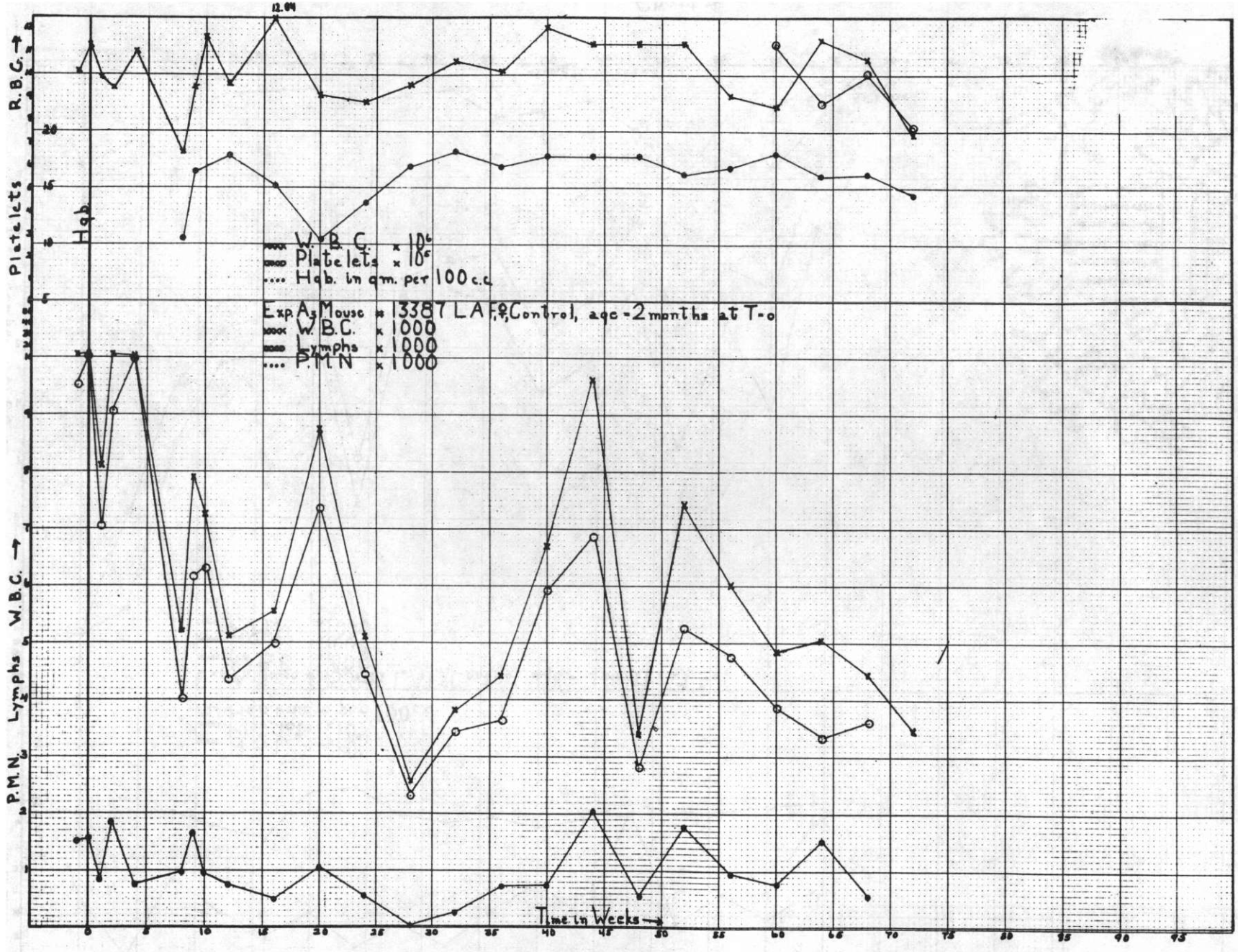

R.B.C.
Platelets
Hgb.
W.B.C.
Lymphs
P.M.N.
W.B.C. x 10⁶
Platelets x 10⁵
Hgb. in gm. per 100 c.c.
Exp. A, Mouse # 13387 LAF1 ♀ Control, age - 2 months at T-o
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
Time in Weeks

Chart 5

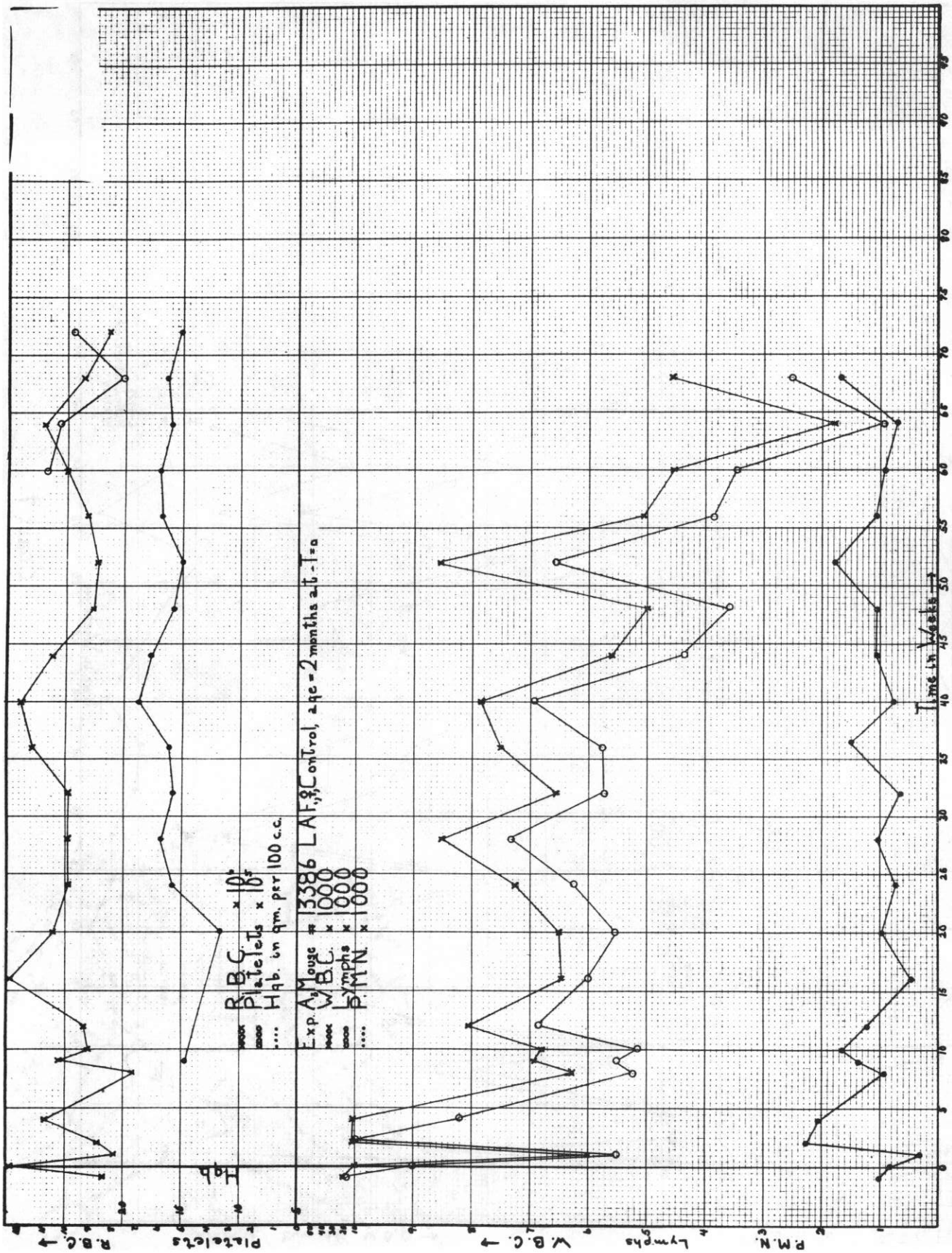

R.B.C.
Platelets x 10⁵
Hgb. in gm. per 100 c.c.
Exp. A₂ Mouse # 13386 LAF₁ Control, age = 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
Time in Weeks
R.B.C.
Platelets
W.B.C.
Lymphs
P.M.N.

Chart 6

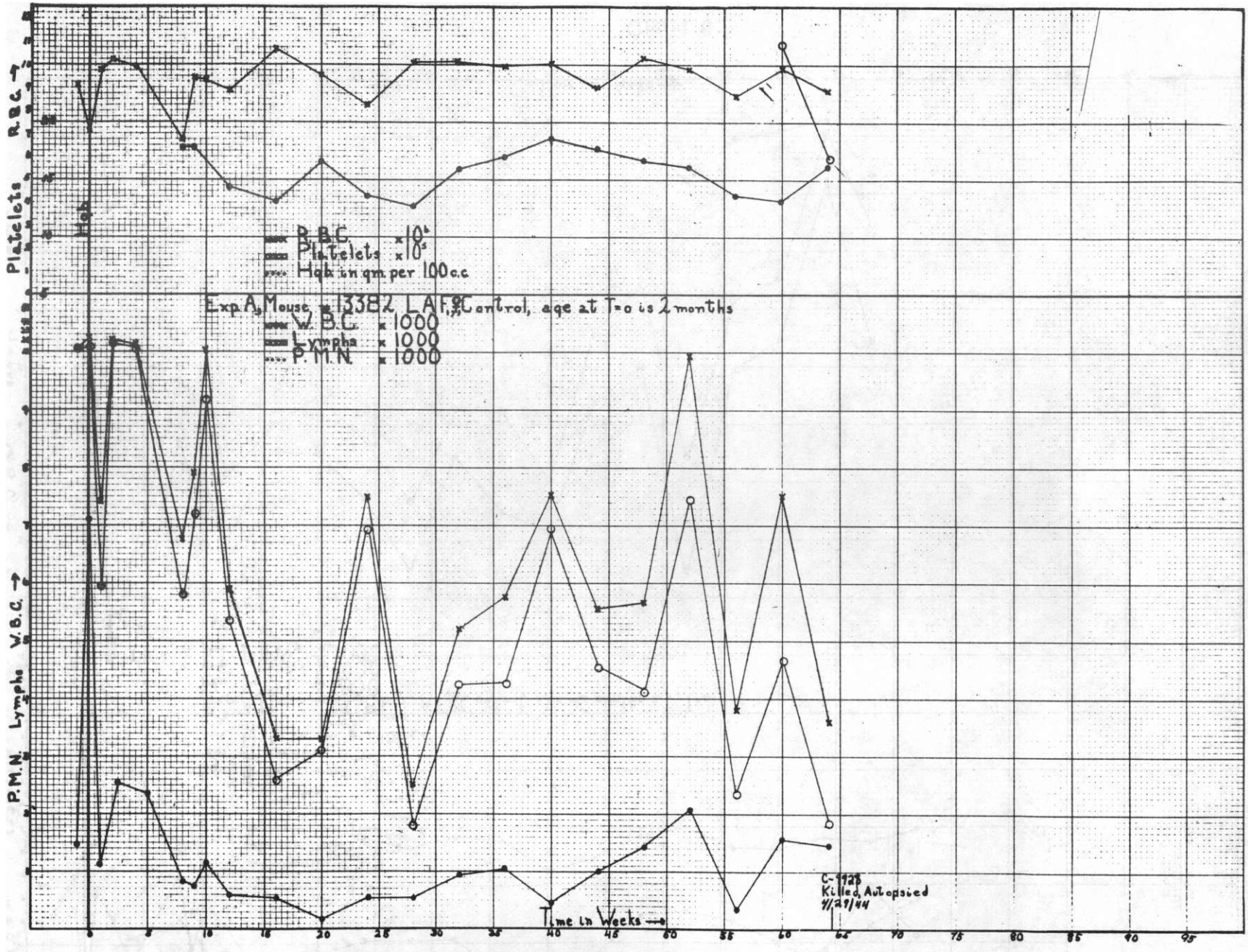

Platelets
R.B.C. →
Hgb
P.M.N.
Lympha
W.B.C. →
R.B.C. x 10⁶
Platelets x 10⁵
Hgb in gm per 100 c.c
Exp. A, Mouse # 13382 LAF♀ Control, age at T=0 is 2 months
W.B.C. x 1000
Lympha x 1000
P.M.N. x 1000
C-1925
Killed, Autopsied
11/29/44
Time in Weeks →
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95

Chart 7

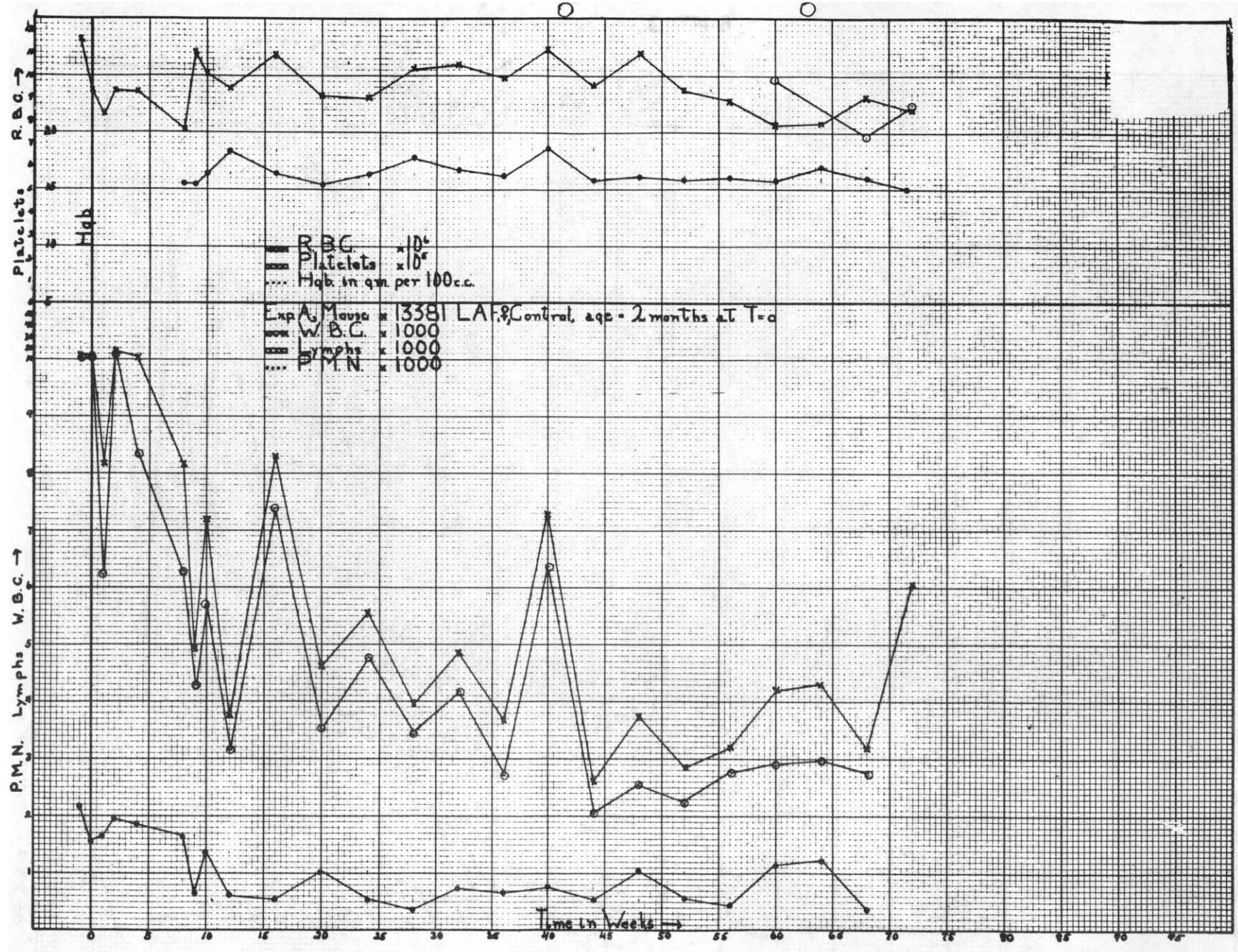

R.B.C. →
Platelets
Hgb
R.B.C. x 10⁶
Platelets x 10⁵
Hgb. in gm. per 100 c.c.
Exp. A, Mouse # 13381 LAF₁ ♀ Control, age - 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
P.M.N. Lymphs W.B.C. →
Time in Weeks →
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95

Chart 8

R.B.C. →
Platelets
Hgb.
W.B.C. →
P.M.N. Lymphs
R.B.C. x 10^6
Platelets x 10^6
Hgb. in gm per 100 c.c.
Total Dose → Dose rate: 5.5 r in 1 hr. Daily
Expt. Mouse # 14330 ♀ LAF, age - 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
C-7469
Killed Autopsied
11/18/43
Time in Weeks →

Chart 9

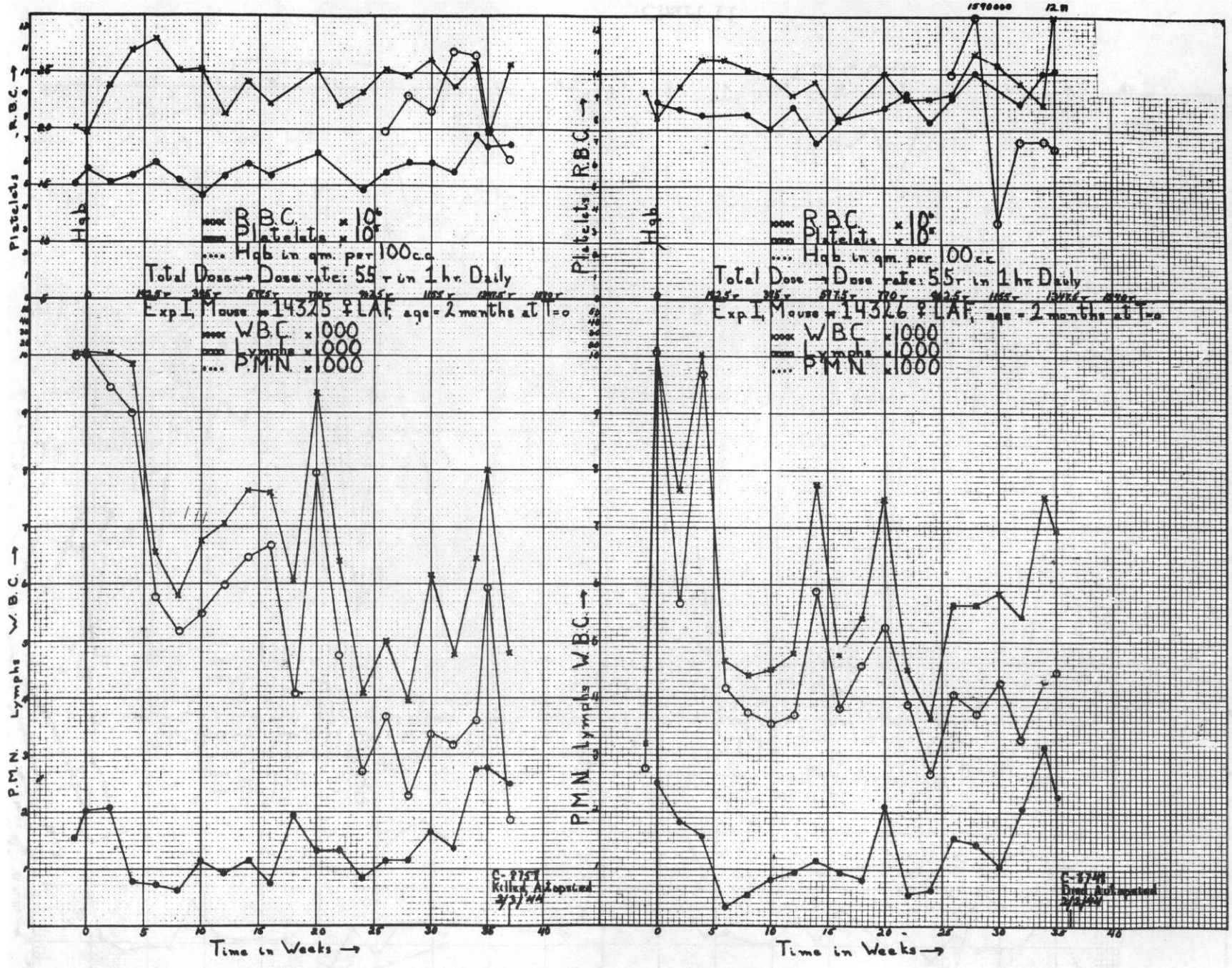

R.B.C. →
Platelets
Hab
···· R.B.C. x 10⁶
▬▬ Platelets x 10⁵
···· Hab. in gm. per 100 c.c.
Total Dose → Dose rate: 55 r in 1 hr. Daily
Exp I, Mouse # 14325 ♀ LAF, age - 2 months at T=0
···· W.B.C. x 000
▬▬ Lymphs x 000
···· P.M.N. x 000
W.B.C. →
Lymphs
P.M.N.
C-9757 Killed Autopsied 2/3/44
Time in Weeks →
Exp I, Mouse # 14326 ♀ LAF, age - 2 months at T=0
···· W.B.C. x 1000
▬▬ Lymphs x 1000
···· P.M.N. x 1000
C-9741 Died Autopsied 2/3/44

Chart 10

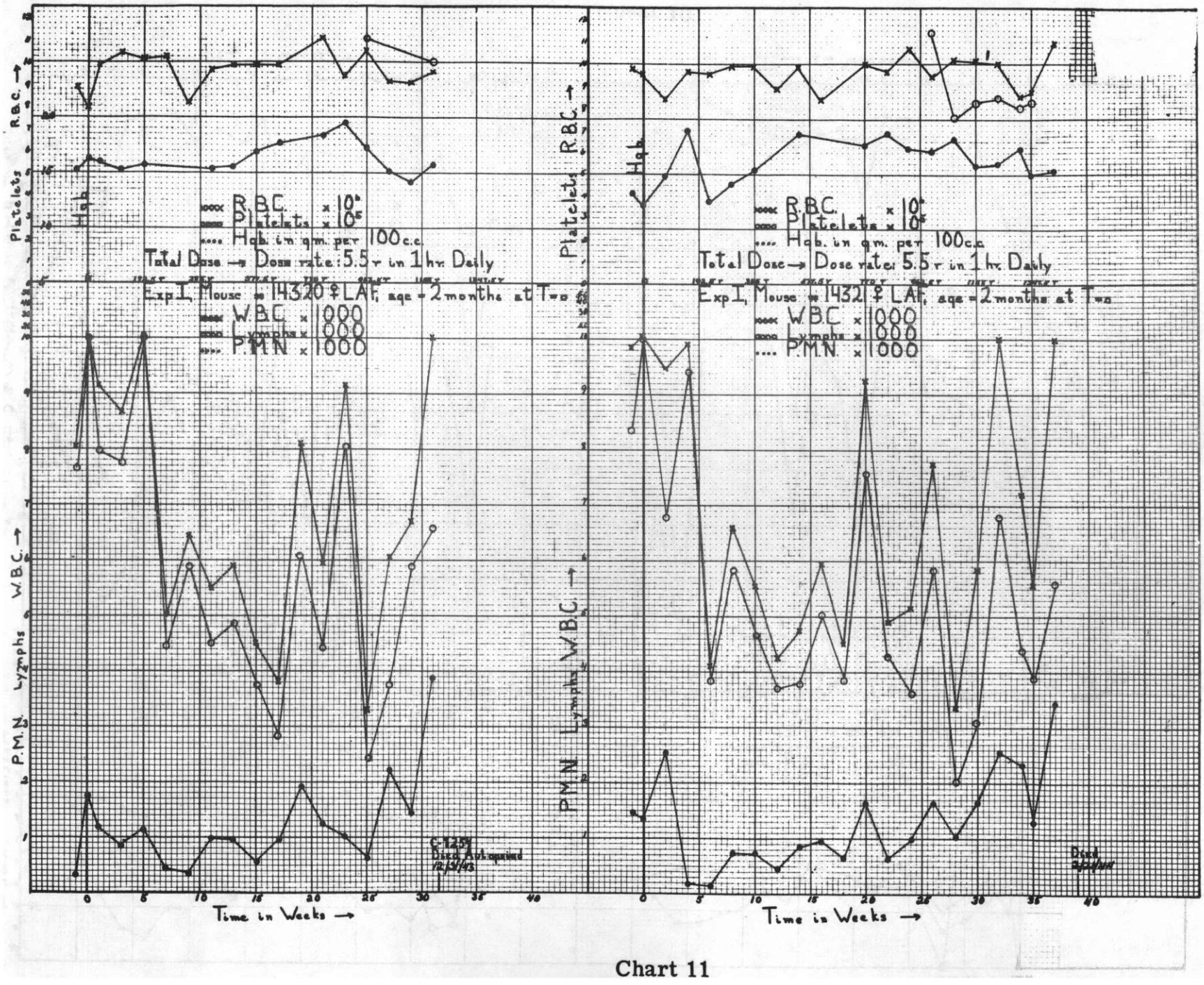

R.B.C. →
Platelets
Hab
R.B.C. x 10⁶
Platelets x 10⁵
Hab. in gm. per 100 c.c.
Total Dose → Dose rate: 5.5 r in 1 hr. Daily
Expt. I, Mouse # 1432 ♀ LAF, age = 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
W.B.C. →
Lymphs
P.M.N.
C-1259 Died Autopsied 12/31/43
Time in Weeks →
Platelets R.B.C. →
Hab
R.B.C. x 10⁶
Platelets x 10⁵
Hab. in gm. per 100 c.c.
Total Dose → Dose rate: 5.5 r in 1 hr. Daily
Expt. I, Mouse # 1432 ♀ LAF, age = 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
P.M.N. Lymphs W.B.C. →
Died 2/9/44
Time in Weeks →

Chart 11

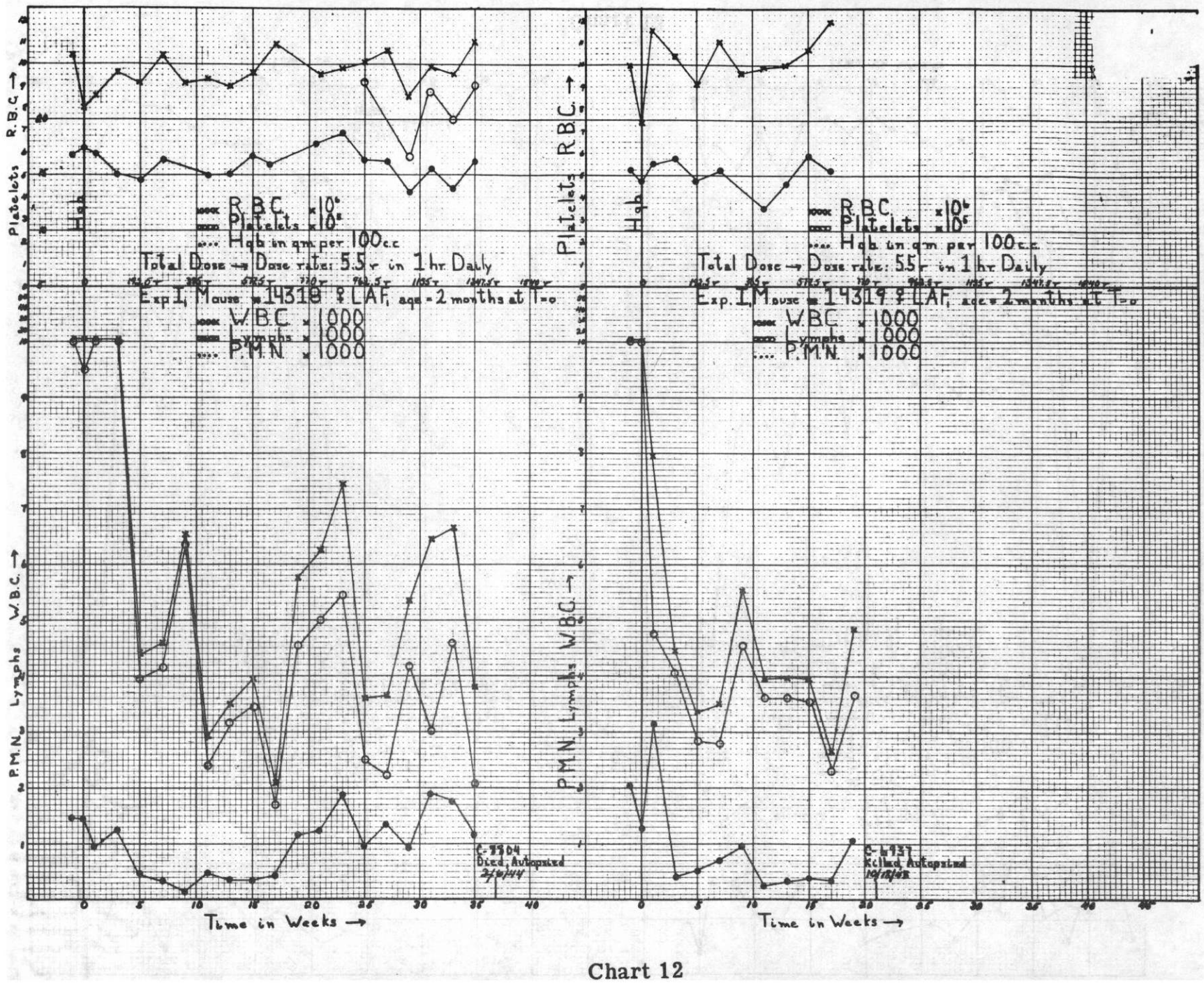

R.B.C. →
Platelets
Hgb
R.B.C. x 10⁶
Platelets x 10⁵
Hgb in gm per 100 c.c.
Total Dose → Dose rate: 5.5 r in 1 hr Daily
Exp. I, Mouse # 14318 ♀ LAF, age = 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
C-9304
Died, Autopsied
2/6/44
P.M.N. Lymphs W.B.C. →
Time in Weeks →
Exp. I, Mouse # 14319 ♀ LAF, age = 2 months at T=0
C-6937
Killed, Autopsied
10/12/43

Chart 12

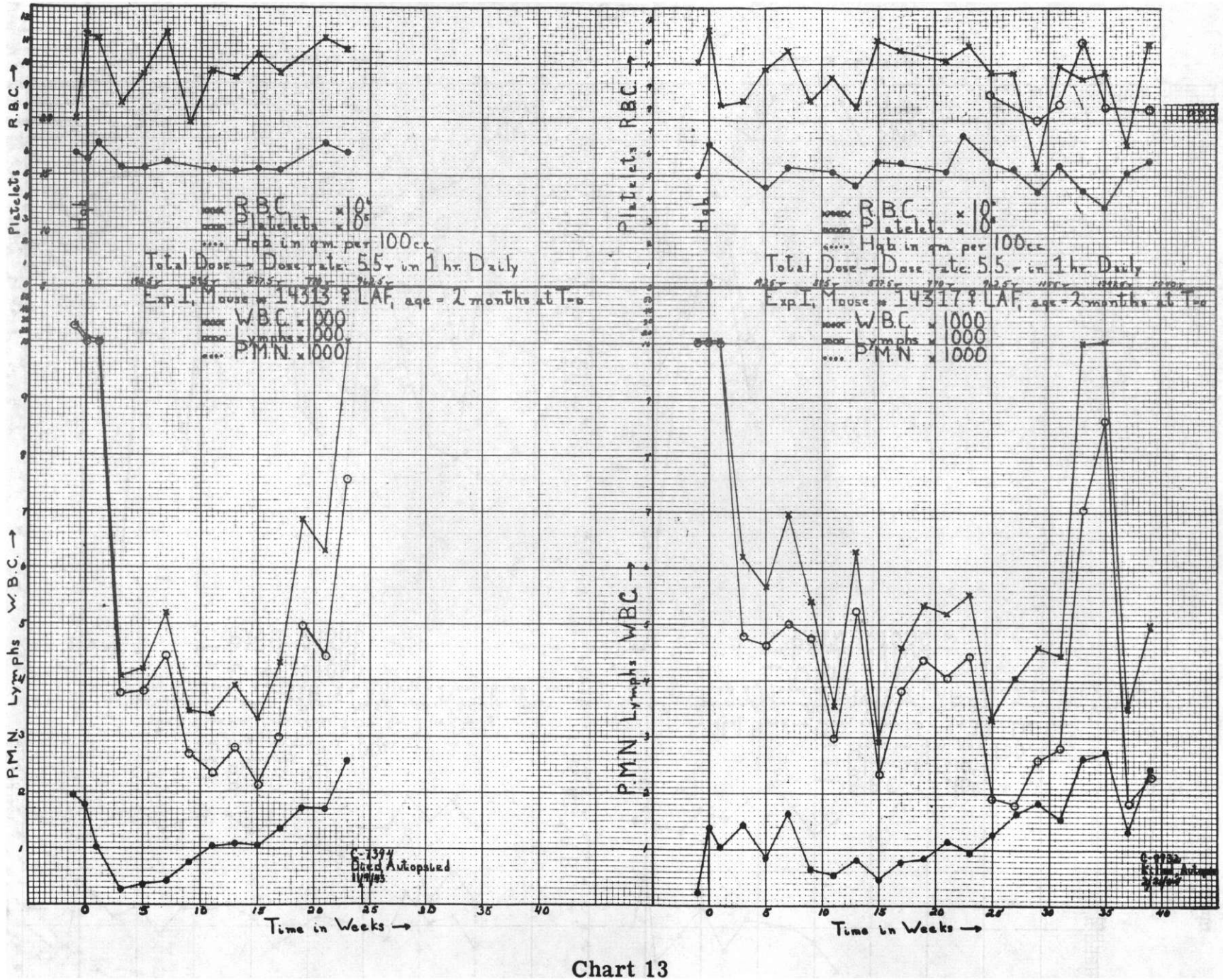

R.B.C. →
Platelets
Hgb
xxxx R.B.C. x 10⁶
xxxx Platelets x 10⁵
.... Hgb in gm. per 100 c.c.
Total Dose → Dose rate: 5.5 r in 1 hr. Daily
Exp I, Mouse # 14313 ♀ LAF, age = 2 months at T=0
xxxx W.B.C. x 1000
xxxx Lymphs x 1000
.... P.M.N. x 1000
P.M.N. Lymphs W.B.C. →
C-1394 Died Autopsied 11/19/45
Time in Weeks →
Platelets R.B.C. →
Hgb
xxxx R.B.C. x 10⁶
xxxx Platelets x 10⁵
.... Hgb in gm. per 100 c.c.
Total Dose → Dose rate: 5.5 r in 1 hr. Daily
Exp I, Mouse # 14317 ♀ LAF, age = 2 months at T=0
xxxx W.B.C. x 1000
xxxx Lymphs x 1000
.... P.M.N. x 1000
P.M.N. Lymphs W.B.C. →
Time in Weeks →

Chart 13

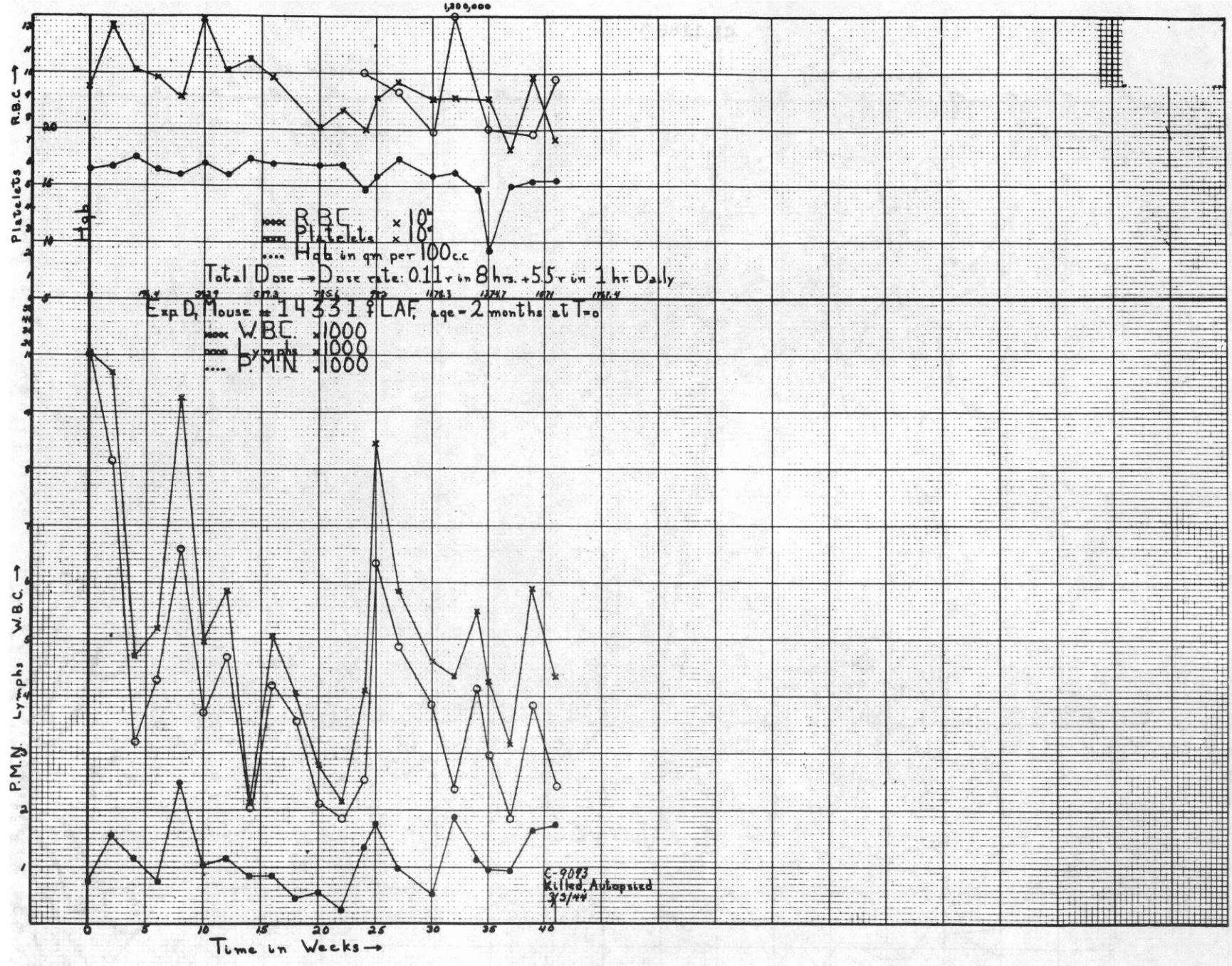

R.B.C. →
Platelets
Hgb
1,200,000
R.B.C. x 10⁶
Platelets x 10³
Hgb in gm per 100 c.c.
Total Dose → Dose rate: 0.11 r in 8 hrs. + 5.5 r in 1 hr. Daily
Exp D, Mouse # 14331 ♀ LAF, age - 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
W.B.C. →
Lymphs
P.M.N.
C-9043
Killed, Autopsied
9/3/44
0
5
10
15
20
25
30
35
40
Time in Weeks →

Chart 14

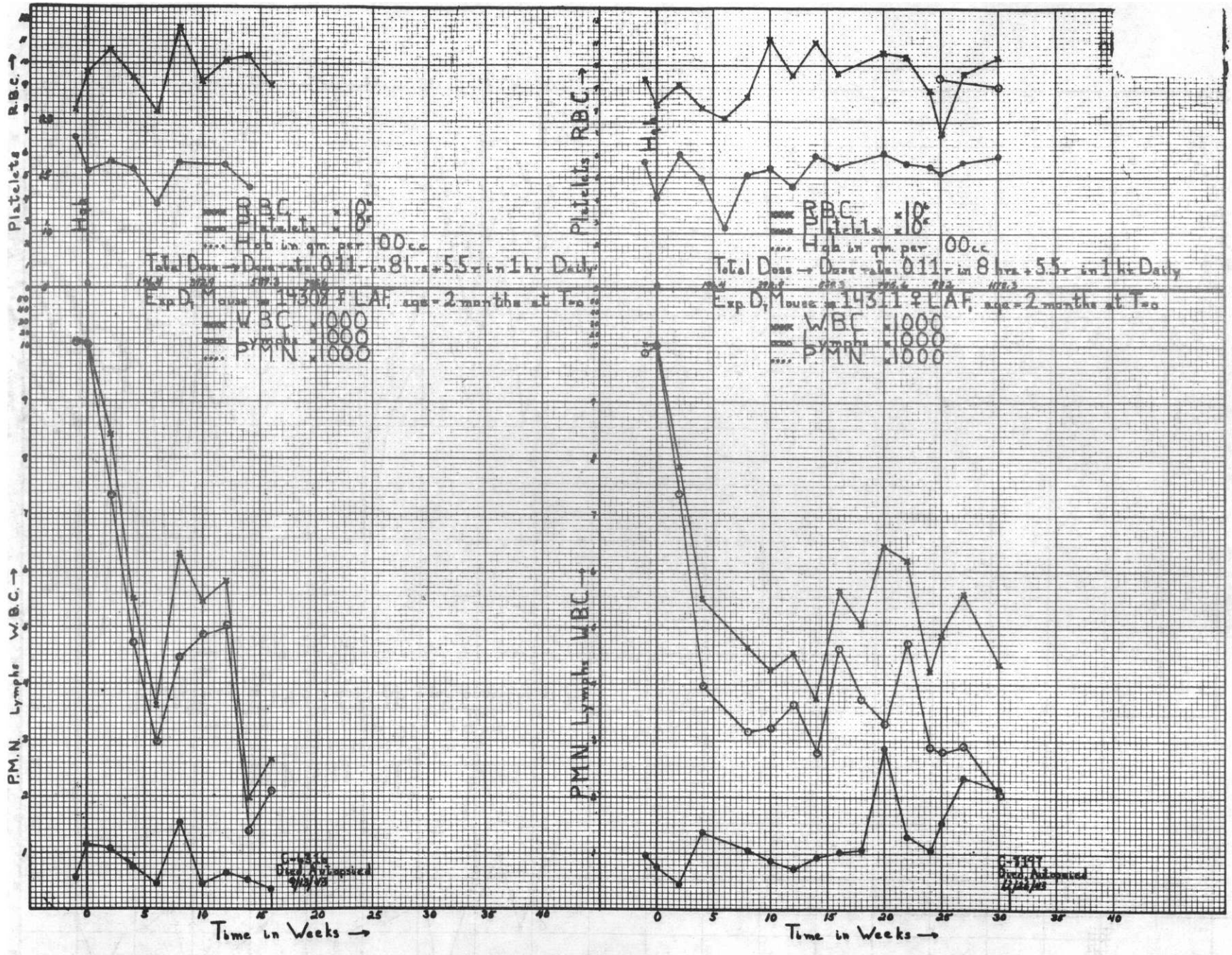

Platelets R.B.C.
Hab
P.M.N. Lymphs W.B.C.
RBC ×10⁶
Platelets ×10⁶
Hab in gm. per 100 c.c.
Total Dose → Dose rate 0.11 r in 8 hrs + 5.5 r in 1 hr Daily
Exp D, Mouse # 1430 ♀ LAF, age = 2 months at T=0
WBC ×1000
Lymphs ×1000
P.M.N. ×1000
Time in Weeks →
Platelets R.B.C.
Hab
P.M.N. Lymphs W.B.C.
RBC ×10⁶
Platelets ×10⁶
Hab in gm. per 100 c.c.
Total Dose → Dose rate 0.11 r in 8 hrs + 5.5 r in 1 hr Daily
Exp D, Mouse # 1431 ♀ LAF, age = 2 months at T=0
WBC ×1000
Lymphs ×1000
P.M.N. ×1000
Time in Weeks →

Chart 15

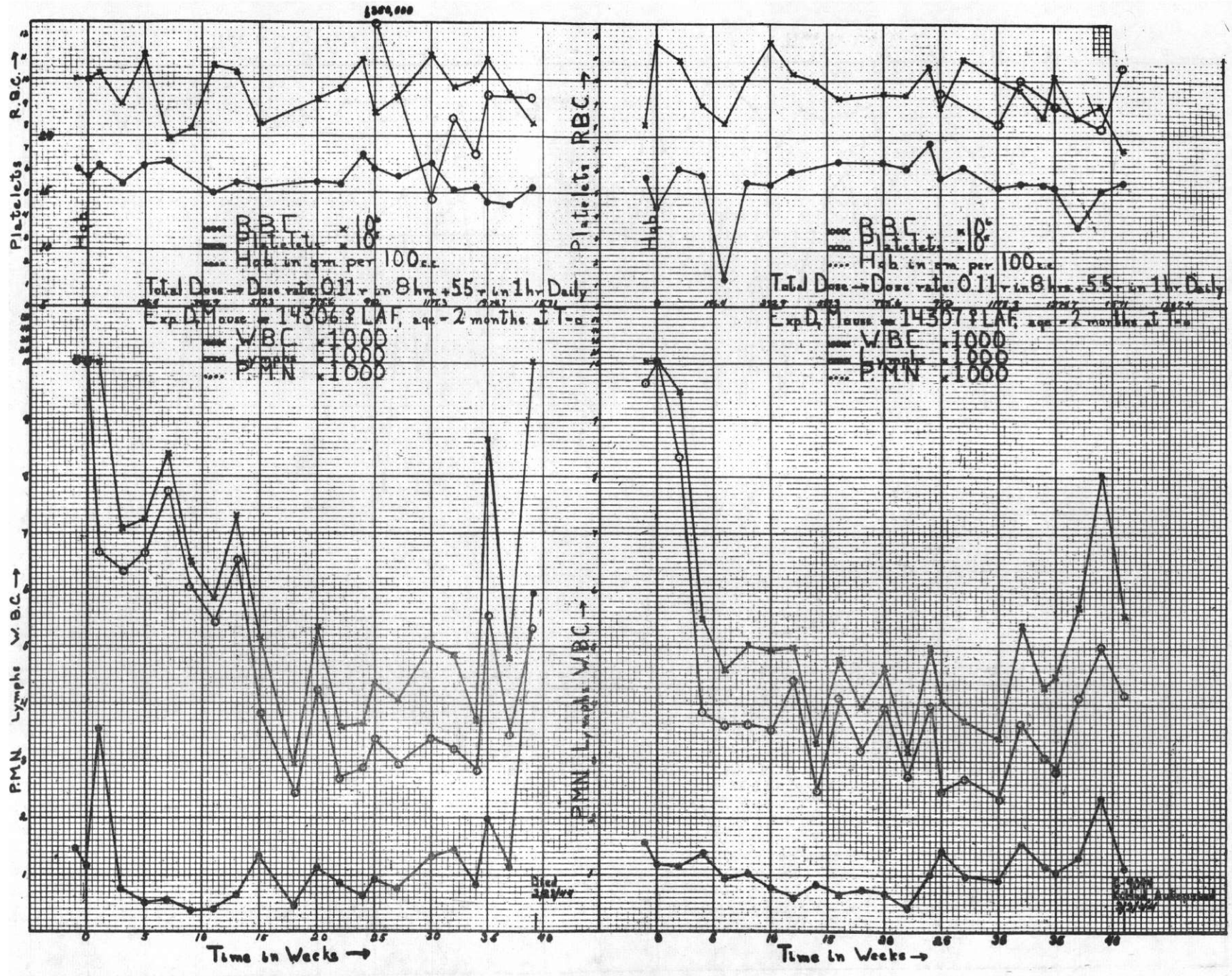
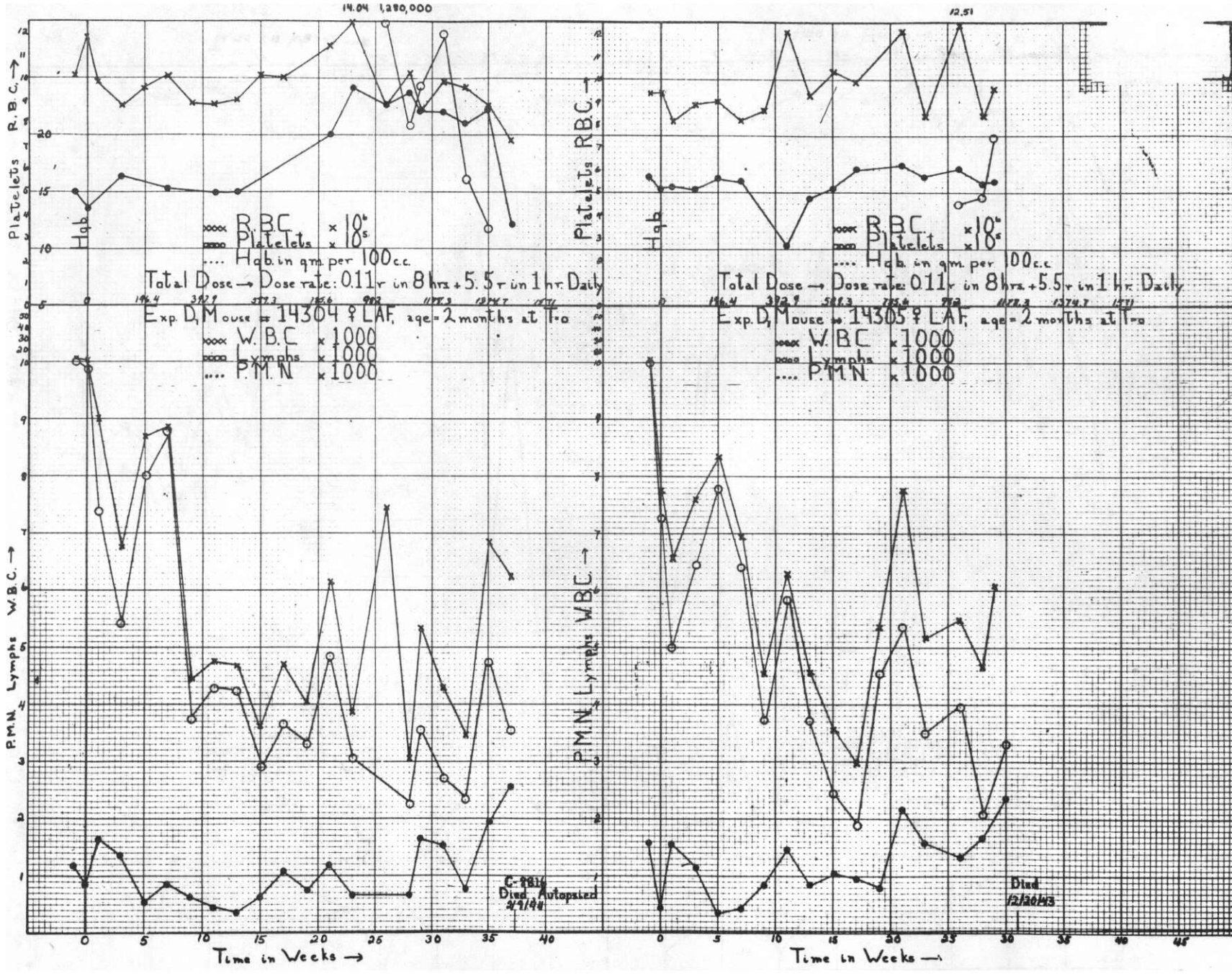

RBC
Platelets x 10
Hgb in gm. per 100 c.c.
Total Dose → Dose rate: 011 r in 8 hrs. + 55 r in 1 hr. Daily
Exp. D, Mouse # 14306 ♀ LAF, age - 2 months at T-o
WBC x 1000
Lymphs x 1000
P.M.N x 1000
Time in Weeks →
Exp. D, Mouse # 14307 ♀ LAF, age - 2 months at T-o

Chart 16


14.04 1,280,000
12.51
R.B.C. →
Platelets
Hgb
R.B.C. ×10⁶
Platelets ×10⁵
Hgb in gm. per 100 c.c.
Total Dose → Dose rate: 0.11 r in 8 hrs. + 5.5 r in 1 hr. Daily
Exp. D, Mouse # 14304 ♀ LAF, age = 2 months at T=0
Exp. D, Mouse # 14305 ♀ LAF, age = 2 months at T=0
W.B.C. ×1000
Lymphs ×1000
P.M.N. ×1000
W.B.C. →
P.M.N.
Lymphs
C-9814
Died Autopsied 2/9/44
Died 12/30/43
Time in Weeks →

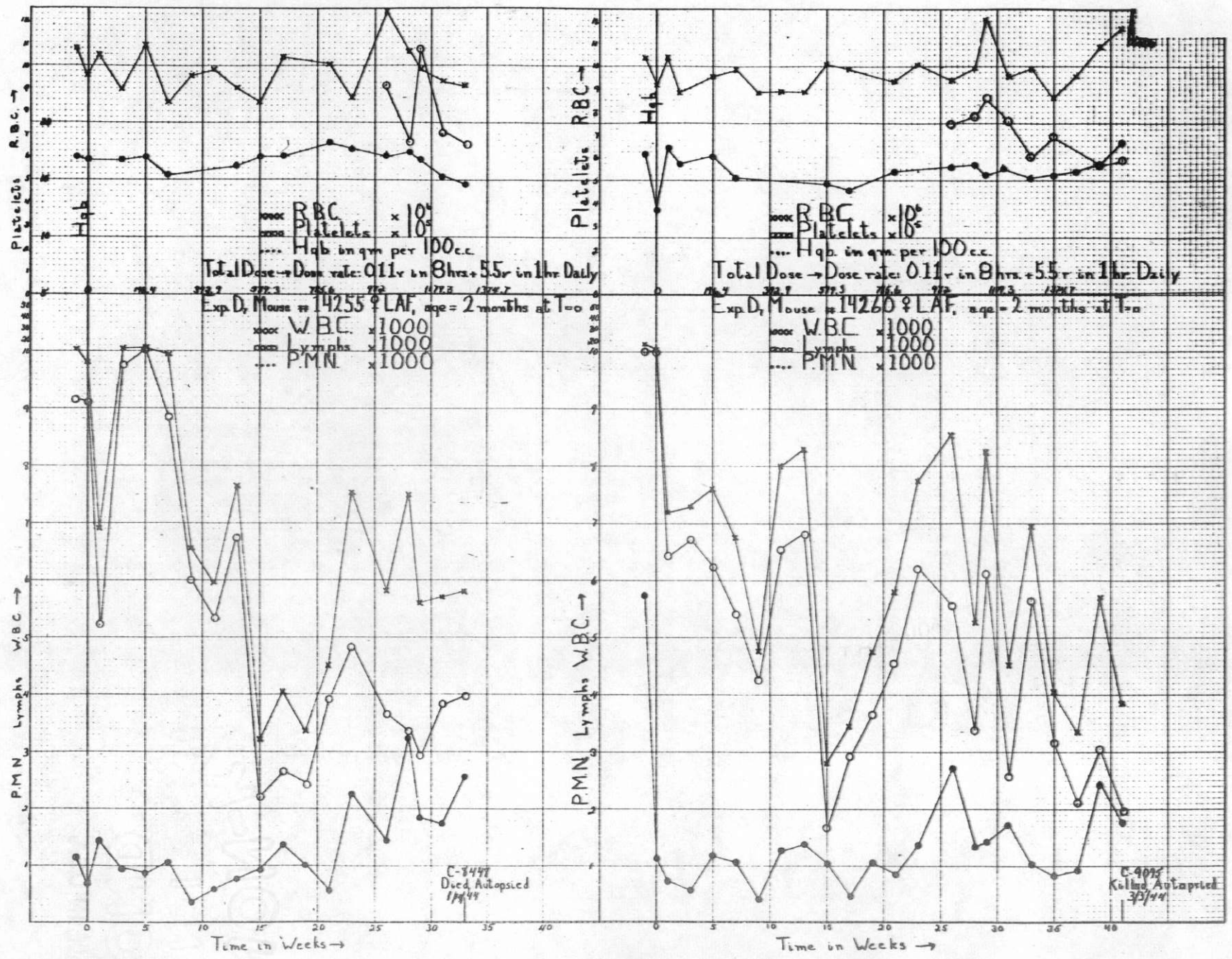

R.B.C. →
Platelets
Hgb
RBC x 10⁶
Platelets x 10⁵
Hgb in gm per 100 c.c.
Total Dose → Dose rate: 0.11 r in 8 hrs + 5.5 r in 1 hr Daily
Exp. D, Mouse # 14255 ♀ LAF, age = 2 months at T=0
W.B.C. x 1000
Lymphs x 1000
P.M.N. x 1000
P.M.N. Lymphs W.B.C. →
C-8447 Died Autopsied 1/4/44
Time in Weeks →
Exp. D, Mouse # 14260 ♀ LAF, age = 2 months at T=0
C-9015 Killed Autopsied 3/3/44

Chart 18