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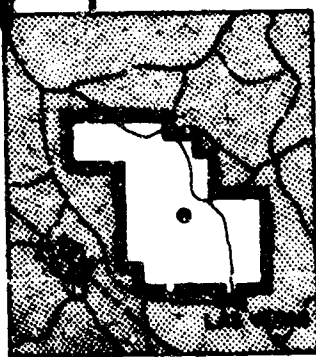
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BIOLOGICAL EFFECTS OF NUCLEAR RADIATION
ON THE MONKEY (Macaca Mulatta):
TWO-YEAR EVALUATION

Issuance Date: August 17, 1960

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Report to the Test Director

**BIOLOGICAL EFFECTS OF NUCLEAR
RADIATION ON THE MONKEY (*Macaca
Mulatta*): TWO-YEAR EVALUATION**

By

**J. E. Pickering, D. P. Williams,
G. S. Melville, Jr., A. A. McDowell,
T. P. Leffingwell, and R. W. Zellmer**

**Approved by: R. L. CORSBIE
Director, Program 39
Director, Civil Effects Test Group**

**School of Aviation Medicine, U. S. Air Force
Brooks Air Force Base, Texas
June 1969**

PARTICIPANTS

*School of Aviation Medicine
The Radiobiological Laboratory, USAF*

R. E. Benson (Maj., VC, USAF)	B. H. Noland, B.A.
W. L. Brown, Ph. D.	J. E. Pickering (Col., USAF)
J. C. Capehart, M.S.	R. M. Ritter, M.A.
G. L. Hekhuis (Col., MC, USAF)	H. N. Rose (Capt., MC, USAF)
A. Hernandez-Dias (S/Sgt., USAF)	W. T. Sallee (Maj., MC, USAF)
L. H. Jordan, B.A.	J. A. Stuart (A/IC, USAF)
T. P. Lettingwell, M.A.	J. E. Wicker
L. C. Logie (Capt., USAF)	D. B. Williams (Maj., USAF)
A. A. McDowell, Ph. D.	S. F. Wilson (Capt., MC, USAF)
A. C. McTee, B.A.	R. W. Zellmer (Maj., MC, USAF)
G. S. Melville, Jr. (Capt., USAF)	

ABSTRACT

Macaca mulatta monkeys were exposed to prompt neutron and gamma radiation from two nuclear detonations (Project 39.6). At a period roughly two years postirradiation, the survivors have been examined with respect to long-term effects. The present condition of the animals relative to clinical appearance, peripheral hematology, behavior, and cataractogenesis has been evaluated and compared with the acute effects that were noted and reported for the first 30 days following exposure.

Recovery of erythroid indices in shot Wilson survivors was (1) functionally complete by about 9 weeks postexposure, (2) effected by production of larger hyperchromic erythrocytes with a normal hemoglobin concentration, and (3) followed by a possible macrocytic hyperchromic anemia for the majority of the 63- to 840-day postexposure period. Similar phenomena were not observed in the lower-dose shot Fizeau survivors.

Lymphocytes of the myeloid series were the last to evidence recovery; the single animal that died exhibited a unique lymphocytic hypoplasia, which suggests a differential effect on the precursor tissue. By about 100 days, when the myeloid recovery was essentially complete, only a depressed total leukocyte count reflected any long-term effect; relative populations of the component cells were normal. Shot Fizeau animals evidenced the depression/response pattern observed in the shot Wilson animals, but no long-term differences were apparent.

The results with respect to behavior parameters include (1) differences on preliminary Wisconsin General Test Apparatus training which support the hypothesis of a radiation-induced elevation of response threshold values, (2) learning-performance differences in the male radiation dosage groups which are in accord with previous researches on other groups of monkeys, (3) observed differences between male and female monkeys on both learning performance and free-cage behavior parameters, and (4) a radiation-induced facilitation on difficult size discrimination problems.

ACKNOWLEDGMENTS

The authors wish to acknowledge the excellent cooperation and advice obtained from participants in Projects 39.1, 39.5, 39.7, and 39.7a; without this free exchange of data, equipment, and personnel, the original study could not have been accomplished. In this same regard, the over-all supervision and administrative support furnished by members of the Civil Effects Test Group staff, under the direction of R. L. Corbie, as well as Program 39, contributed immeasurably to the success of the work. During the early stages of the study, W. H. Langham, W. T. Ham, and K. Z. Morgan gave generously of their time.

In addition, the authors wish to acknowledge the cooperation and support of the Department of Radiobiology and the Department of Ophthalmology, School of Aviation Medicine, and the Radiobiological Laboratory of the University of Texas and the U. S. Air Force, Austin, Texas, in carrying out the long-term phases of the study.

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Chapter 1

INTRODUCTION

1.1 BACKGROUND

The primary objective of Project 39.6 was to correlate neutron and gamma measurements with biological response. The Project participated on two shots of the Operation Plumbbob series. These shots were optimal for animal exposures on the basis of yield, cab shielding, and geographical location. Station placement, field exposure sites, and classified parameters of the experiment are described in detail in Report WT-1505 (reference 1). All dosimetric measurements and pretest calibrations were made by Projects 39.1 (gamma dosimetry) and 39.5 (neutron dosimetry). The neutron measurements were made using the fission-foil system of Hurst,² and the gamma-ray measurements were made using the USAF chemical dosimeter system.³ The blast containers used in the biological experiments of Operation Greenhouse⁴ were modified for use in Operation Plumbbob, and they are documented in WT-1505.

1.2 OBJECTIVES

Three technologic objectives were advanced when participation in Operation Plumbbob was first designed: (1) determination of the LD_{50} and the survival time vs. dose relation; (2) examination of acute clinical signs and their approximate thresholds; and (3) the study of long-term effects, such as cataract production, life-span shortening, bone-marrow changes, and carcinogenesis. The first two objectives have been fulfilled and reported.¹ This report begins the accomplishment of the third objective by documenting the results of an analysis and comparison of findings in the surviving animals 21 to 24 months postirradiation.

REFERENCES

1. J. E. Pickering et al., Operation Plumbbob Report, WT-1505, December 1958.
2. G. S. Hurst et al., Operation Plumbbob Report, WT-1504, March 1958.
3. S. C. Sigoloff et al., Operation Plumbbob Report, WT-1500, November 1958.
4. R. H. Draeger et al., Operation Greenhouse Report, WT-15, Annex 2.3, August 1951.

Chapter 2

CLINICAL OBSERVATIONS

2.1 MORTALITY

2.1.1 Wilson Shot

Through the 30th day postirradiation, 63 of 72 animals were dead. Of the 9 survivors, 3 have since died: 3 animals in group H, 410 rads (1 on the 102d day and the other on the 708th day postirradiation) and the other in group I, 366 rads (on the 651st day postirradiation). As evidence of a past history of irradiation, the animals that died were generally emaciated with some epilation; there usually was atrophy of some of the seminiferous tubules. On the other hand, the lymphoid tissues and bone-marrow cellularity seemed to be in a condition consistent with the age of the animals.

2.1.2 Fizeau Shot

Through the 30th day postirradiation, 21 of 72 animals were dead. On the 46th day, 1 animal from group B (496 rads) died. There were practically no effects of the radiation still visible in the tissues of this animal. The lymphoid tissue was in fair condition. The gastrointestinal tract was free of lesions, and the bone marrow appeared to be of normal cellularity. The spleen was an exception; some germinal centers were missing.

2.1.3 Discussion

It is probable that none of the 30-day postirradiation deaths should be considered as typical of any special type of radiation death; however, there is no doubt that the exposure to radiation was indirectly causative of many of the facets of the clinical picture which culminated in death.

A summary of mortality on both shots is given in Table 2.1.

2.2 WEIGHT

The long-term picture of body weight is summarized in Fig. 2.1. For Wilson shot, control mean weights have been plotted against those two animals that lived 651 and 708 days postirradiation. For Fizeau shot, the control mean weights have been plotted against group C mean weights (this group received the highest rad dose in which there have been no deaths since the first 30 days).

There was definite recovery from the weight loss during the first 30 days in both groups. The Wilson animals that ultimately died showed a decline near death. The irradiated animals, in general, increased in weight at the same rate as the controls; but, of course, they started at a lower level.

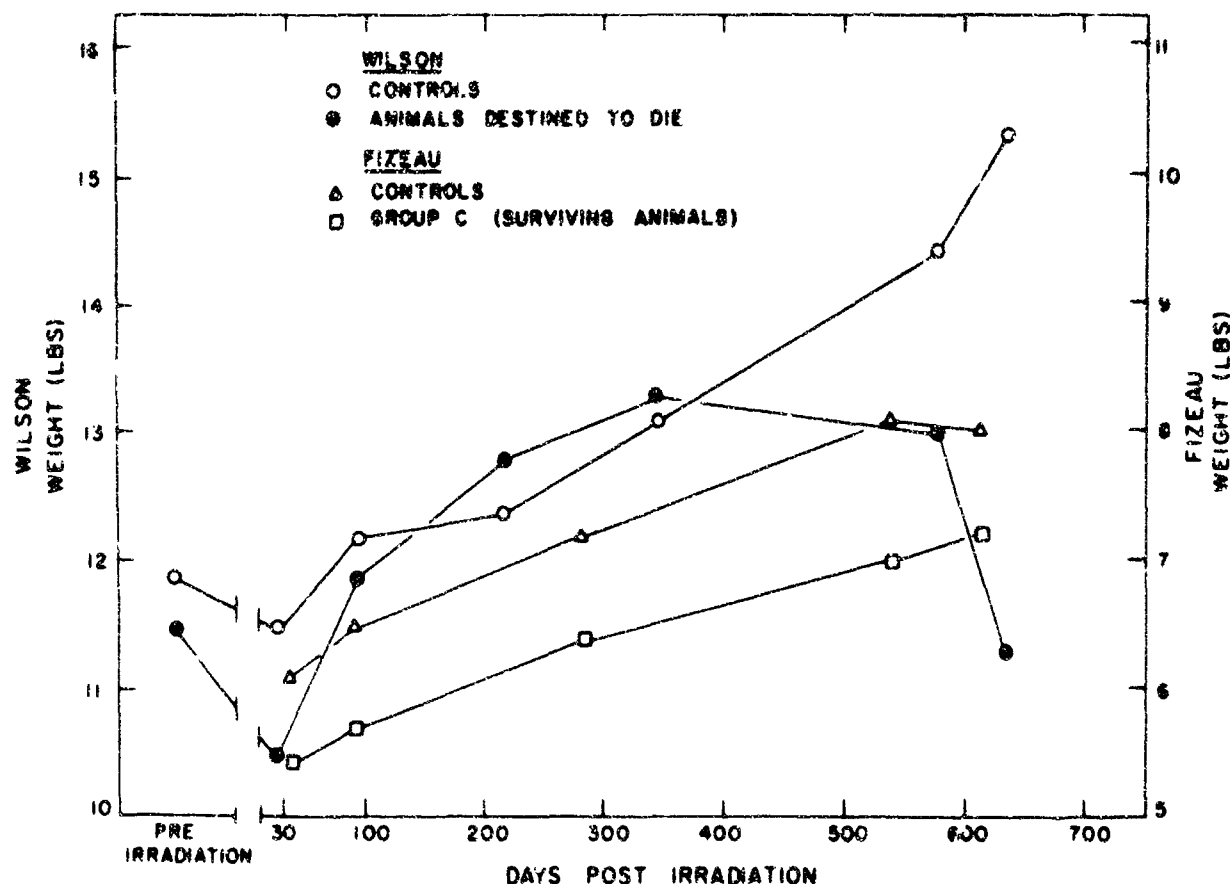


Fig. 2.1—Body weight changes in monkeys exposed to nuclear radiation.

2.3 OPTHALMOLOGY

2.3.1 Introduction

During the course of Operation Plumbbob, ophthalmologic studies were made on 97 monkeys: 17 animals from Wilson shot (3 in group H, 6 in group I, and 8 controls) and 80 animals from Fizeau shot (nine groups of 8 and 8 controls). For Wilson five examinations over a period of approximately 669 days were performed. For Fizeau only three examinations are available over a period of 580 days; no preirradiation examinations were made. No early lens changes were observed; however, cataractogenesis has taken place with time, and at the present time significant lens damage has been observed and appears to be increasing in severity.

2.3.2 Results

(a) *Wilson Shot.* The preirradiation examination, using the slit lamp, showed all lenses to be clear. For a period up to 165 days postirradiation, there was no lens damage; in some animals a transitory iridocyclitis characterized by flare and cells in the anterior chamber, cells deposited on the anterior lens capsule, and increased numbers of cells in the retroretinal space was noticed. By 365 days postirradiation, the iridocyclitis had disappeared, and the lenses were clear. At approximately 670 days postirradiation, the first really significant findings began to appear. Table 2.2 summarizes the information available. In general, for Wilson animals these changes consist of vacuole formation, formation of discrete moderate-size opacities located chiefly in the anterior cortex, and the very early formation of posterior subcapsular cataract.

(b) *Fizeau Shot.* There were no preirradiation examinations performed; at 97 and 232 days postirradiation there were no lens changes. Transitory iridocyclitis was present and

TABLE 2.1—MORTALITY AS OF MAY 31, 1959

Group*	Dose, rads		Mortality	
	Wilson	Fizeau	Wilson	Fizeau
A	977	583	8	8
B	860	496	8	7
C	758	440	8	2
D	668	386	8	3
E	591	341	8	0
F	520	301	8	1
G	462	266	8	0
H	410	235	7	0
I	366	206	3	0
J		183		1
Control	0	0	1	0

* Eight animals in each group.

TABLE 2.2—SUMMARY OF OPHTHALMOLOGIC FINDINGS

Cataract category	Wilson		Fizeau		Clinical observations
	Group	Dose, rads	Group	Dose, rads	
I			J	183	No significant deviation from normal
			I	206	
			H	235	
			G	266	
			F	301	
II	H	410	E	341	Discrete opacities in anterior cortex; early stages of posterior subcapsular cataract
	I	366			
IV			D	386	Some complicated cataract; also vacuoles and anterior cortical opacities.
III			C	440	Complicated cataract; granular, polychromatic, posterior subcapsular cupuliform cataracts
			B	496	

was of the type described previously for the Wilson animals. At approximately 580 days after irradiation, definite changes were noted; they are summarized in Table 2.2. Groups B and C are in category III (complicated cataract); group D lies between categories II and III, showing both types of syndrome; groups E and F are in category II; and groups G, H, I, and J are in category I.

2.3.3 Discussion

Fizeau group D, at a dose of 386 rads, may prove to be the group that represents the transition point or threshold indicator. At the present time, the appearance of complicated cataract in category III animals is considered to be a nonspecific finding (a complication of the iridocyclitis, a nonspecific result of neutron damage, synergism between neutron and gamma radiations, or simple responses of young lens to irradiation damage).

The most fertile area for study would appear to be those animals in category II from both Wilson and Fizeau. The changes seen are minimal, early, and nonspecific; however, the progression of the lesions which will apparently take place should be carefully documented.

2.4 OTHER PARAMETERS

Immediately postirradiation, five other clinical signs were observed and reported: (1) vomiting, (2) anorexia, (3) diarrhea, (4) purpura, and (5) epilation. At this time (some 21 months after Fizeau shot and 24 months after Wilson shot), none of these symptoms are to be found in these surviving animals as a result of radiation.

Chapter 3

HEMATOLOGY

3.1 WILSON SHOT

3.1.1 Introduction

Changes that occurred in the peripheral blood picture of groups G, H, and I during the first 30 days postirradiation have been discussed in Report WT-1505. Of the 10 animals originally exposed and studied, 3 survived at least 30 days: 1 animal from group H (462 rads) and 2 animals from group I (410 rads).

Some 14 other animals had received simultaneous exposure to nuclear radiations at sites identical with those employed for the hematology animals. These completely analogous survivors were used to supplement the depleted hematology groups. The supplemental groups and concurrent controls (3 animals per group) were reinjected with $Fe^{59}Cl_3$ on day 34 after exposure; seven hematologic samplings were effected between days 34 and 51.

Because the animals were subjected to other experimental procedures that might have affected the peripheral hematology after day 51, statistical treatment of the data has been limited to the postexposure period from day 34 to day 51. A semiquantitative evaluation has been made for the period 63 to 840 days postexposure, during which time sampling was done at intervals of approximately six weeks.

3.1.2 Results

(a) *Fe⁵⁹ Incorporation.* The incorporation of radioiron into erythrocyte hemoglobin indicated considerable repair of erythrogenic tissues in the surviving irradiated animals. Both supplemented groups exhibited greater average incorporation than the controls. However, on approximating an asymptote, all values were within the range determined for *Macaca mulatta* at the Radiobiological Laboratory. Figure 3.1 shows the incorporation curves that were obtained prior to exposure and at two intervals after exposure.

(b) *Erythroid Parameters.* Days 34 to 51: Time-course plots for peripheral erythroid parameters are shown in Fig. 3.2. Data are expressed as percentages of concurrent control animal values. Figure 3.3 reflects the integrated picture for hemoglobin-containing blood elements in terms of mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCHB) for the same time period. Table 3.1 summarizes the results of a type I analysis of variance (Lindquist) of the raw data for the 10 peripheral hematologic parameters that were followed.

Days 63 to 840: Figure 3.4 shows time-course plots for erythrocyte, hemoglobin, and hematocrit values for the supplemented groups from days 34 to 840 postexposure. Nucleated red blood cells and reticulocytes approximated control values for this segment of the plot and are not shown. Table 3.2 summarizes the average values obtained for the entire observation period.

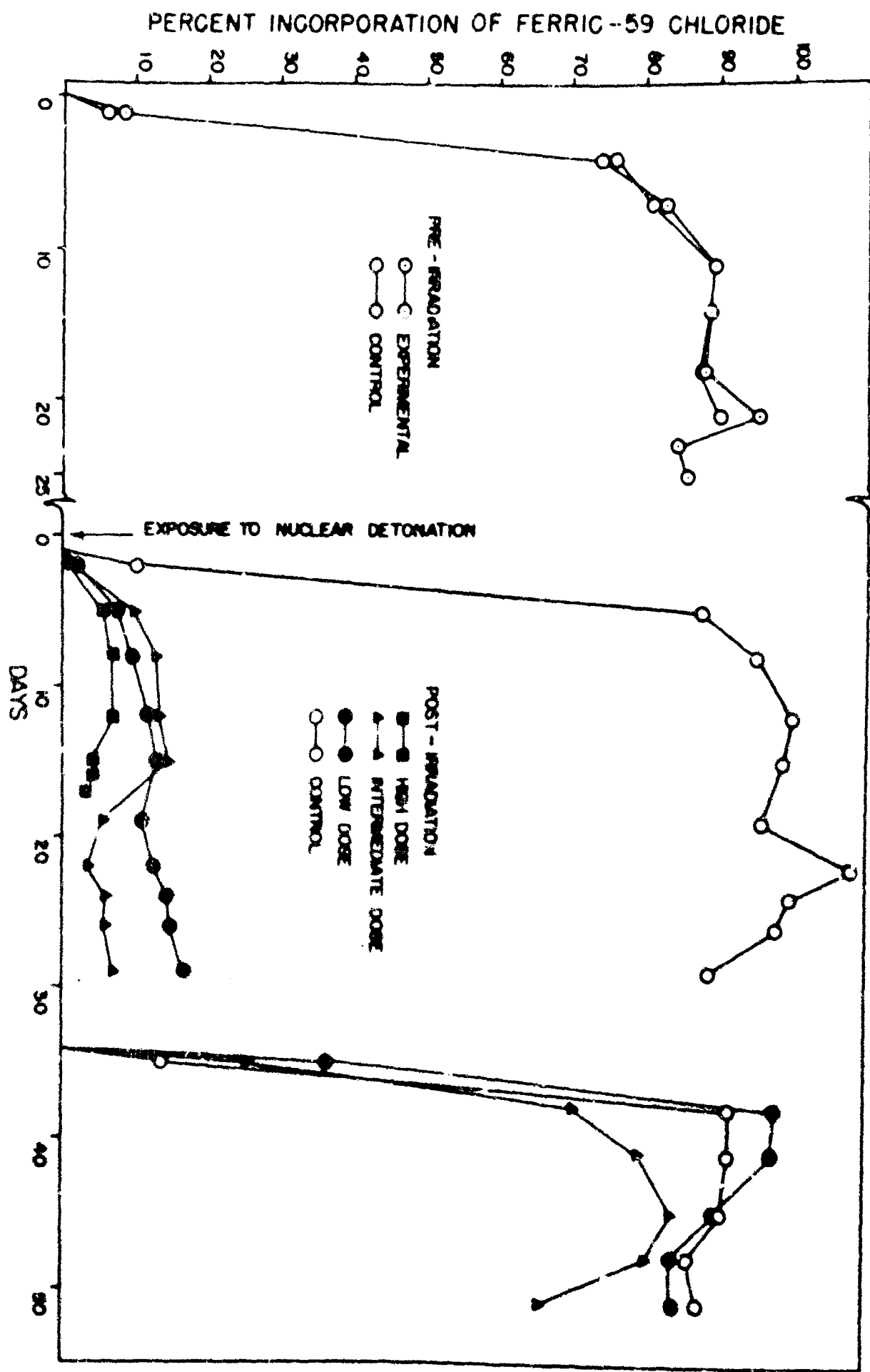


Fig. 3.1— Fe^{59} uptake in red blood cells.

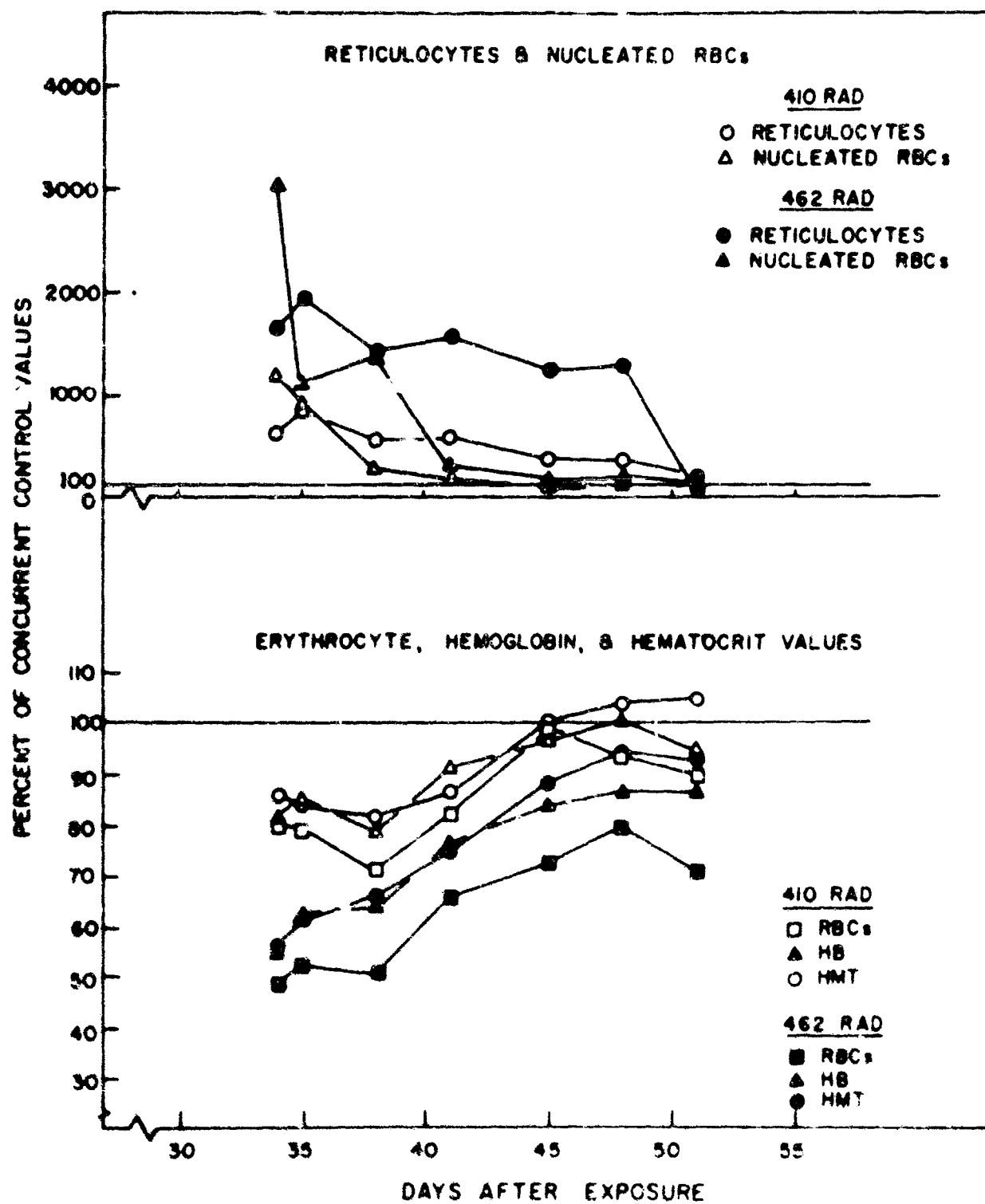


Fig. 3.2—Temporal changes in peripheral erythroid elements.

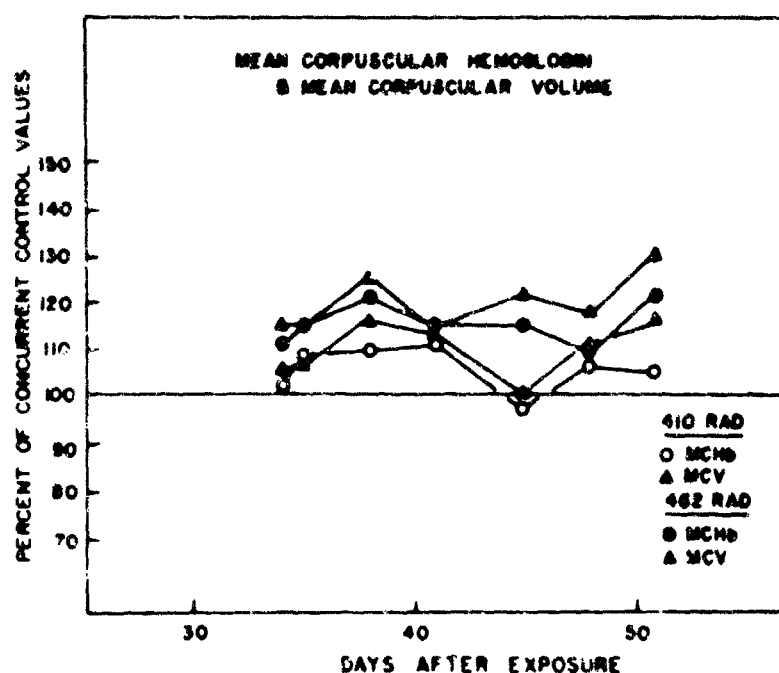


Fig. 3.3—Temporal changes in mean corpuscular volume and mean corpuscular hemoglobin.

TABLE 3.1—SUMMARY OF TYPE I ANALYSIS OF VARIANCE

Parameter	p value		
	A*	B†	AB‡
Erythrocytes	0.01	0.01	0.01
Hematocrit	0.01	0.01	0.01
Hemoglobin	0.01	0.01	0.01
Reticulocytes	0.01	0.01	0.01
Platelets	0.01	0.05	0.01
White blood cells	0.01	<0.05	0.01
Lymphocytes	0.01	0.01	0.01
Polymorphonuclear neutrophils	0.01	<0.05	0.05
Monocytes	0.01	0.01	0.01
Eosinophils	0.01	0.01	0.01

*A (time effect): changes that occurred with time when compared with the concurrent control animals.

†B (group effect): resolution of the animals into groups as a function of radiation dose when compared with the concurrent control animals.

‡AB (interaction): test of the differences between irradiated and control groups for the entire testing period.

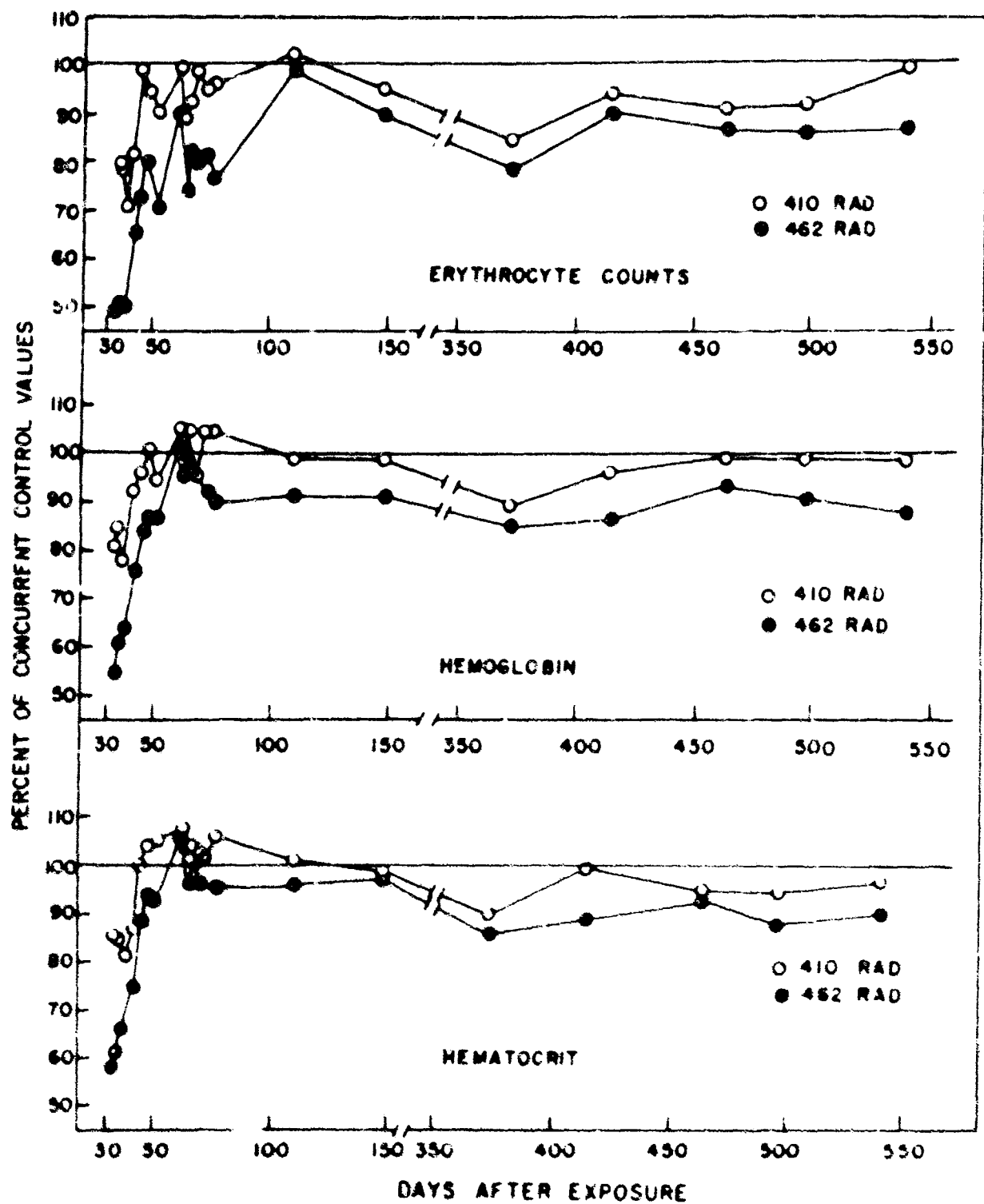


Fig. 3.4—Changes in peripheral erythroid elements from 34 to 540 days postexposure.

TABLE 3.2.—MEAN VALUES FOR PERIPHERAL HEMATOLOGIC PARAMETERS

Parameter	Group			Approximate percentage of control values	
	Controls	410 rads	492 rads	410 rads	492 rads
Days 34 to 51					
Erythroid:					
Erythrocytes, $10^6/\text{mm}^3$	5.26	4.46	3.36	85	64
Hematocrit, %	38.3	35.6	29.2	93	76
Hemoglobin, g %	10.1	9.0	7.4	89	73
Mean corpuscular volume, μ^3	74	79	86	110	119
Mean corpuscular hemoglobin, μg	19.2	20.3	22.2	106	114
Mean corpuscular hemoglobin concentration, g/100 ml red cells	26.3	25.3	25.3	96	96
Myeloid:					
Total white blood cells, $10^3/\text{mm}^3$	12.7	11.0	10.3	87	81
Lymphocytes, cells/100	48	33	20	69	41
Polymorphonuclear neutrophils, cells/100	46	37	56	80	121
Platelets ($\times 10^4$)	35.5	26.6	19.0	75	53
Days 62 to 504					
Erythroid:					
Erythrocytes, $10^6/\text{mm}^3$	6.28	5.0	5.4	80	86
Hematocrit, %	45.4	43.0	40.6	95	89
Hemoglobin, g %	11.0	11.8	11.0	99	92
Mean corpuscular volume, μ^3	72	72	87	100	107
Mean corpuscular hemoglobin, μg	19.1	19.7	20.4	103	107
Mean corpuscular hemoglobin concentration, g/100 ml red cells	26.2	27.4	27.0	104	103
Myeloid:					
Total white blood cells, $10^3/\text{mm}^3$	13.8	11.0	8.9	84	64
Lymphocytes, cells/100	23	55	48	100	94
Polymorphonuclear neutrophils, cells/100	42	26	42	83	100
Platelets ($\times 10^4$)	25.2	20.2	22.2	111	90

(c) *Myeloid Parameters.* Days 34 to 51: Figure 3.5 expresses the total white blood cell counts determined for the supplemented irradiated groups as percentages of concurrent control values. Amplitude of the bar denotes the relative total leukocyte count. The stippled, striped, and open segments reflect the proportion of the total population which was contributed by polymorphonuclear neutrophils, lymphocytes, and the aggregate of monocytes and eosinophils. Figure 3.6 shows the relation of the monocytes and eosinophils which comprised this aggregate population. Stab cells were rarely found in any of the animals and are not shown. The results of the statistical testing of the raw data are summarized in Table 3.1.

Days 63 to 540: Figures 3.7 and 3.8 are time-course plots for total leukocyte, lymphocyte, and polymorphonuclear neutrophil counts. Figure 3.9 shows the average platelet count for the same period. All data are expressed as percentages of concurrent control animal values. Table 3.3 summarizes the mean values found for the myeloid series constituents for two sub-periods after the exposure.

3.1.3 Discussion of Recovery and Long-term Effects

(a) *Erythroid Series.* Bone-marrow aplasia, with recovery becoming apparent in those animals destined to survive for at least 30 days, was the finding for the Wilson animals. In other animals which had also survived the exposure for at least 30 days and which were used to supplement the depleted groups, the peripheral blood pictures coincided well with those of the original survivors. Statistical analysis of the data showed the apparent changes were significant to the 0.01 confidence level in almost all parameters.

A reticulocytosis was apparent as early as 15 days after exposure to 410 rads and on day 12 for the 462-rad survivor. The reticulocytosis was accompanied by large numbers of nucleated red blood cells; both these recovery indexes were at the maximum observed values on postexposure days 34 and 35, but separation into dose groups remained apparent. It appears that the recovery in the 462-rad animals was slightly delayed with respect to the recovery in the 410-rad survivors.

Erythrocyte counts and hemoglobin and hematocrit values were inclining toward normal values throughout the period from day 34 to day 51. Separation as a function of radiation dose was uniformly apparent in all three parameters. Erythrocyte counts remained depressed below concurrent control animal values. On the basis of mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration calculations, it appears that a stem-cell proliferation rate phenomenon may have been limiting. To compensate for such a deficiency, cells attained volumes and hemoglobin contents in excess of control values; however, the concentration of hemoglobin in these megaloblasts was essentially the same (or slightly depressed) as the cells of the control animals. If erythropoiesis, cell volume, and hemoglobin content are assumed to be primarily a function of pO_2 in the blood, then such findings become more understandable.

Corollary to such a postulate is that the collective differences in erythrocyte number and hemoglobin and hematocrit values for the 62- to 540-day period are depressed by an average 3.3 and 11 per cent for the 410- and 462-rad animals, respectively. For the corresponding differences in MCV and MCHb, the average elevation above control values is 2.5 and 5.6 per cent for the 410- and 462-rad survivors, respectively. Therefore it appears that a long-term effect of exposure may be manifested in the red cells; either a stem-cell proliferative rate or a genetically modified precursor cell could be involved.

(b) *Myeloid Series.* Beginning platelet, monocyte, and eosinophil recovery in the 410-rad survivors was observed on postexposure day 19 and in the 462-rad survivor by days 22 to 24 for the first two parameters. Increased total leukocyte counts were observed in all survivors by day 24. Peak monocyte production was apparent from days 34 to 38; eosinophils attained maximum values from days 41 to 48. The polymorphonuclear neutrophil portion of the white-cell population appears to have increased almost linearly from days 22 to 35 in the 410-rad animals and had attained maximum values by day 41 in the 462-rad animals. Lymphocytes, which had comprised almost the entire leukocyte population during the period of marrow aplasia, still had not attained normal numbers through the 51st postexposure day. About 63 days after exposure, the 410-rad animals had a "normal" lymphocyte count; two of the 462 rad ani-

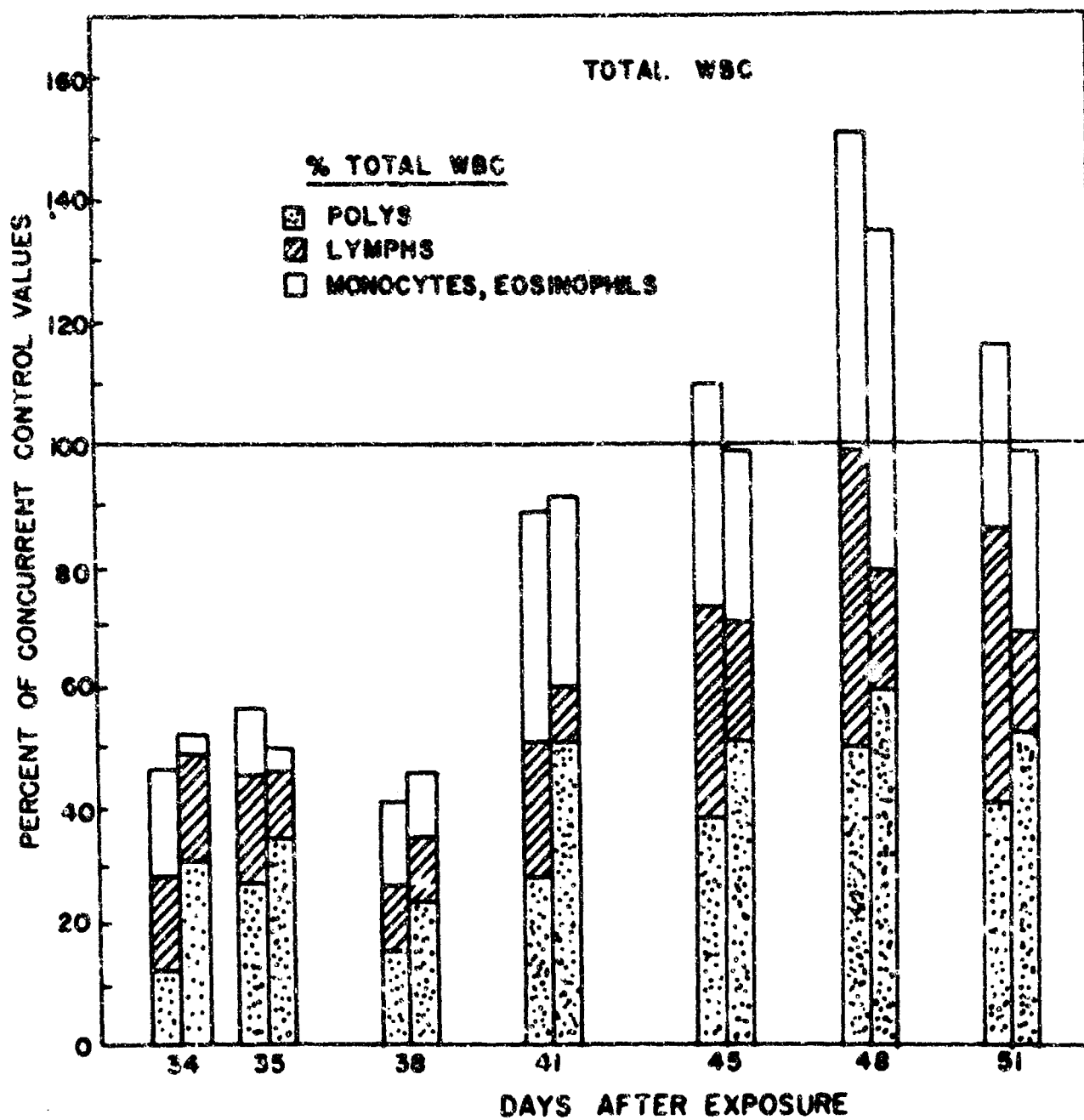


Fig. 3.5—Temporal change in leukocytic cell types expressed as percentage of control values.

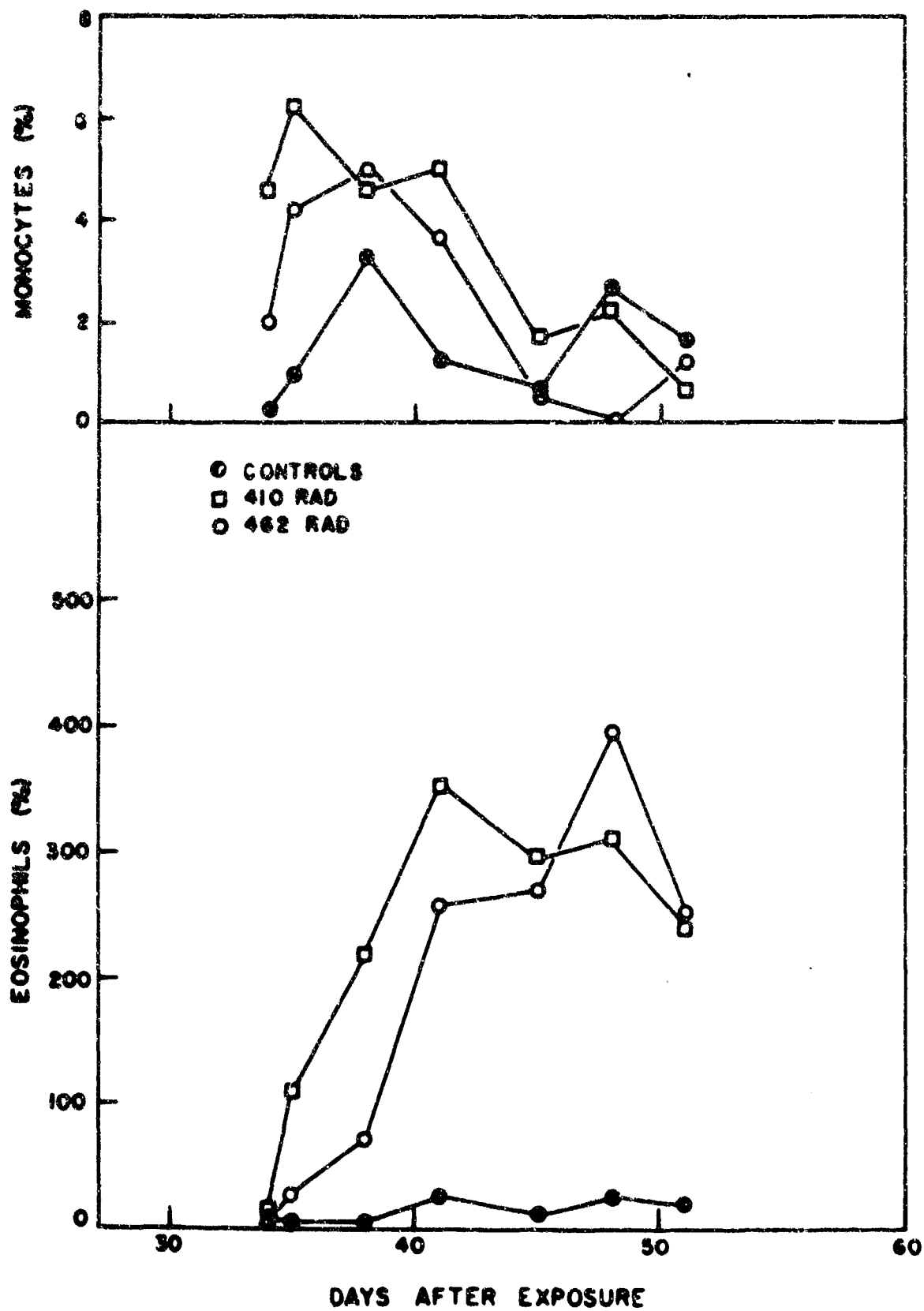


Fig. 3.8—Percentage of monocyte and eosinophil values from 34 to 51 days postirradiation.

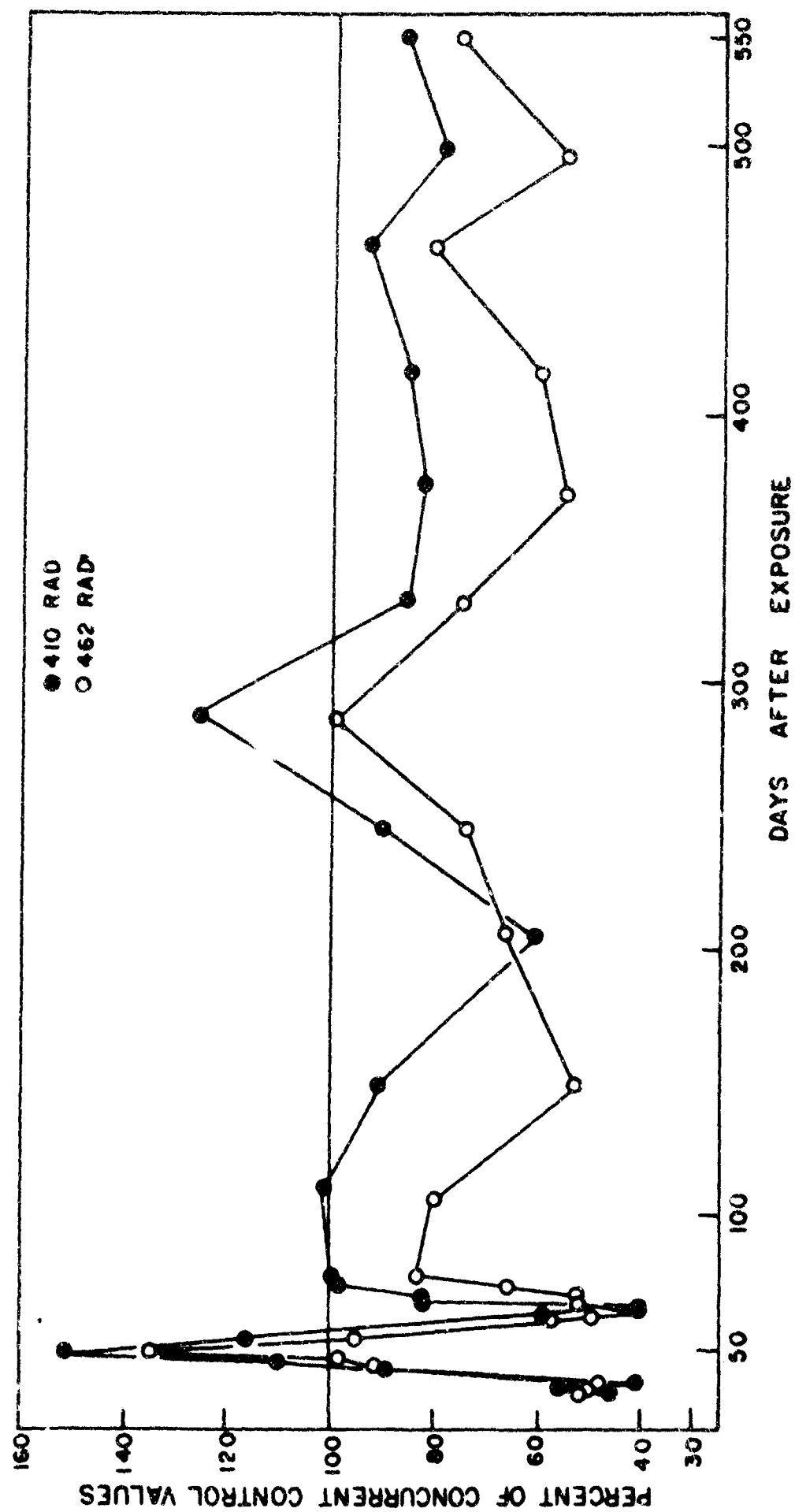


Fig. 3.7—Changes of total lymphocyte cells from 34 to 540 days postirradiation.

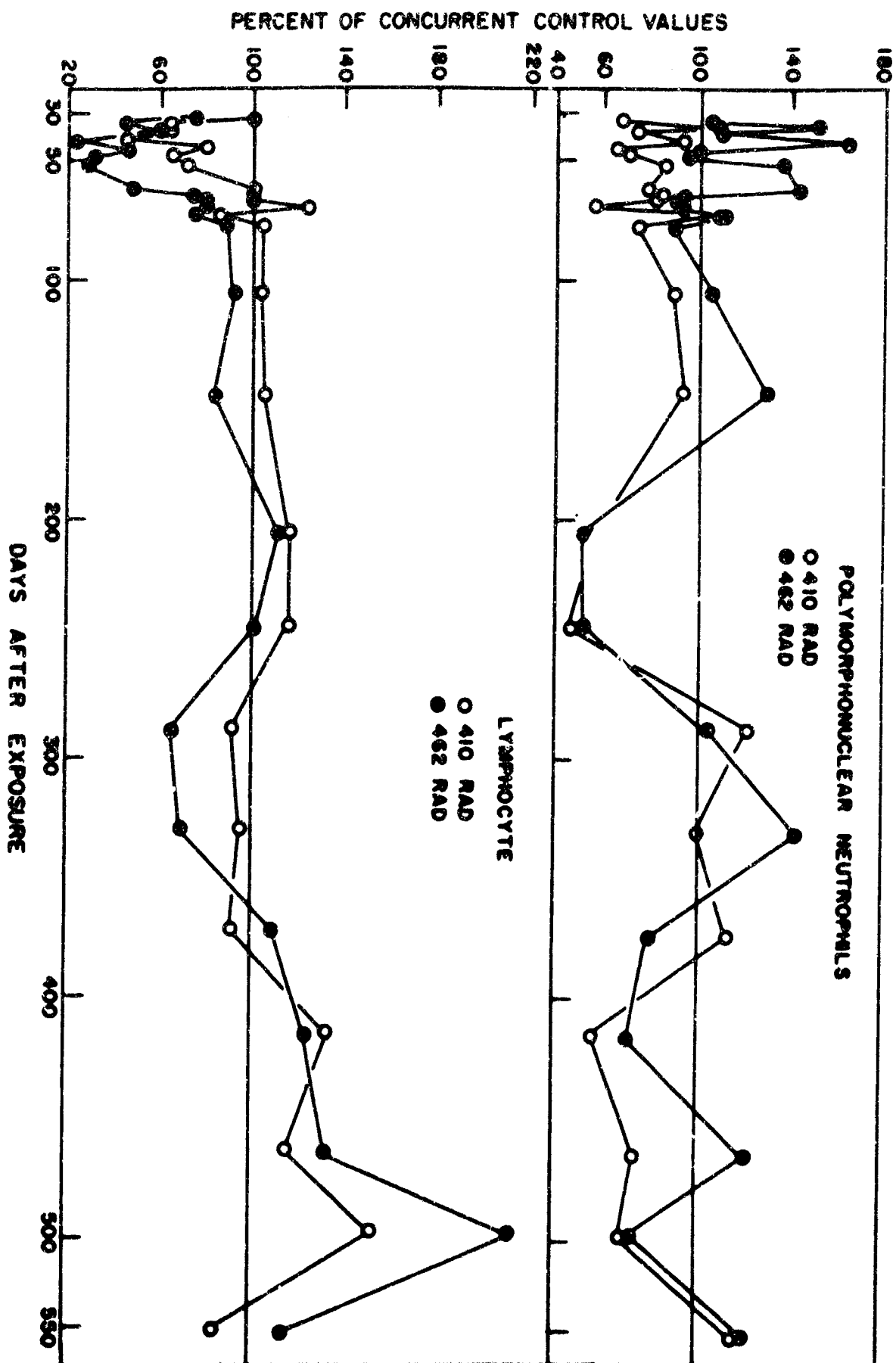


Fig. 3.8—Changes of lymphocytes and polymorphonuclear neutrophils from 34 to 560 days postirradiation.

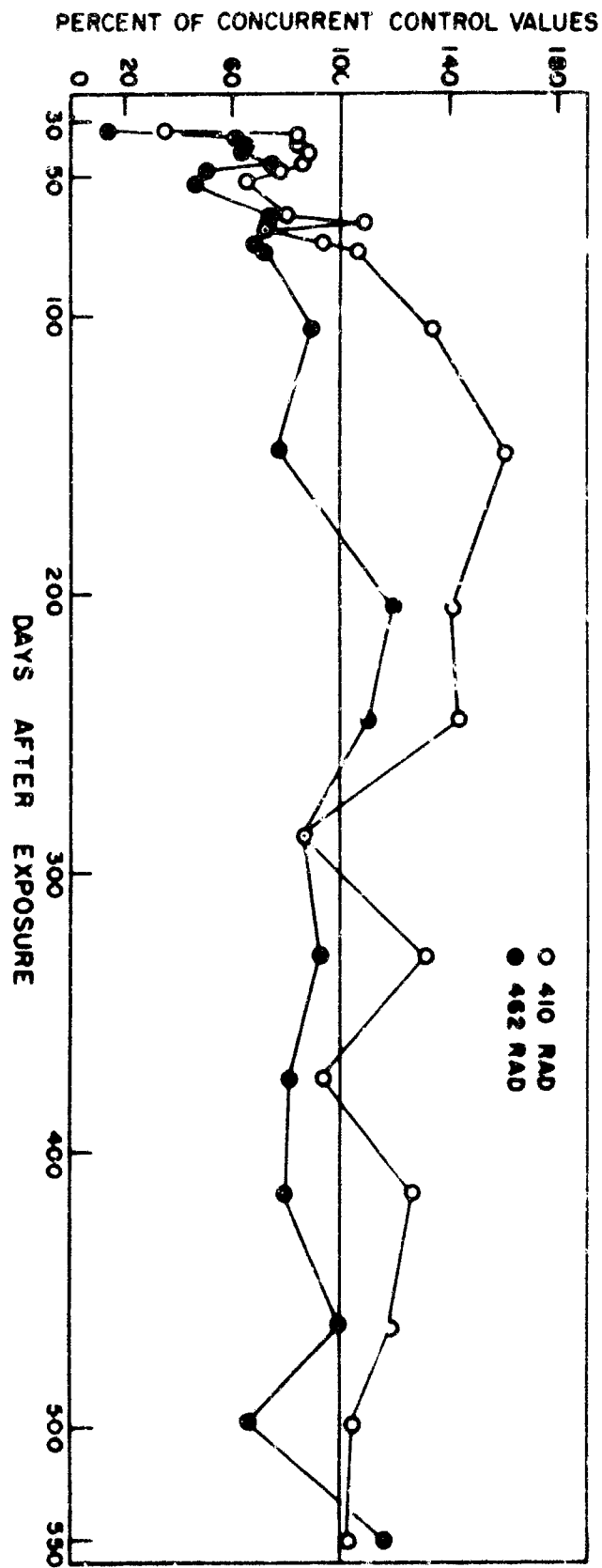


Fig. 3.9—Platelet count values from 34 to 540 days postirradiation.

imals approximated control values at this time, but the third animal remained markedly depressed.

This animal was the sole survivor of the original hematology 462-rad exposure group. He died 102 days after exposure. All myeloid elements in the blood had returned to essentially normal values in phase with the animals used to supplement his group. However, after neutrophil recovery had established the true relation concerning the lymphocyte and neutrophil populations, it became possible to determine that no appreciable lymphocyte production occurred in this animal. The maximum value observed after the neutrophil recovery was "complete" was 13 lymphocytes per 100 cells; on that day the controls averaged 42 lymphocytes per 100 cells, and his two exposure groupmates averaged 44 cells per 100 leukocytes. His lymphocyte count at the last predeath sampling was 6 per cent. This would appear to be a differential type of sensitivity in which a single tissue failed to reestablish its functionality.

In general, other peripheral leukocyte elements had an average depression below control values for the 62- to 540-day postexposure period. Exceptions were lymphocyte and platelet counts in the 410-rad survivors; these parameters averaged 105 and 111 per cent above control values for the entire period.

3.1.4 Summary

In animals exposed to 410 and 462 rads of mixed neutron-gamma radiation, marrow aplasia is in evidence for at least two weeks. Reticulocytosis and nucleated red blood cells attain maximum values at about five weeks postexposure; hemoglobin and hematocrit values are at control levels from seven to nine weeks postexposure, but erythrocyte counts lag. Megaloblastic cells were formed, apparently in a compensatory mechanism. A possibility exists that megaloblastic cells remain in the animals through 540 days after exposure.

Leukocyte production was apparent as early as 19 days after exposure. Polymorphonuclear neutrophil production appears to have attained a maximum five weeks after exposure; monocytes attained a maximum at about the same time. Eosinophils attained a maximum at about six weeks postexposure. Lymphocytes, which comprised almost the entire white-cell population while counts were less than $1000/\text{mm}^3$, were the last component to recover. The animal that died during the 540-day period failed to recover in only one way, lymphocytes were essentially absent from his white-cell population eleven weeks after the exposure. For the 62- to 540-day postexposure period, most of the other leukocyte parameters averaged a depression below concurrent control animal values. The decrease in variability of white blood cell counts noted in chronic irradiations of monkeys was not seen in the shot Wilson animals.

3.2 FIZEAU SHOT

3.2.1 Introduction

Peripheral hematology on the young animals comprising shot Fizeau was not reported during the first 30-day postirradiation period since it was desired to place no stress whatsoever on these animals which might influence mortality.

Immediately after this period, a series of complete blood counts was performed during a period of 90 days. In April 1960, over a period of about 40 days, another series of data was taken on a selected group of these monkeys. These two sets of data have been compared by statistical means, and the results and conclusions are reported below.

3.2.2 Materials and Methods

Standard clinical laboratory procedures such as utilized in USAF hospital laboratories have been used for all hematologic measurements.

For purposes of analysis, four animals were selected from each group in which there were values both for the period 30 to 120 days (T_1) and the period 360 to 600 days (T_2) postirradiation. Nine parameters were available: red blood cell counts, hemoglobin, hematocrit, platelets, white blood cell counts, percentage of lymphocytes, percentage of neutrophils, percentage of monocytes, and percentage of eosinophils. These nine sets were then treated by an

analysis of variance for all scores in T_1 . The parameters that were significant at the 5 per cent level were then tested at T_2 in the same manner. Additionally, the mean value for each parameter at T_2 was compared to a similar mean for T_1 by an analysis of variance.

3.2.3 Results

(a) *Time Period 1 (T_1), 30 to 120 Days Postirradiation.* Red Blood Cells: There is a slight trend upward in the higher dose group, indicating recovery from the radiation. However, there are no significant time differences, and the groups cannot be distinguished from the controls.

Hemoglobin: There is a distinct difference between irradiated animals and controls which is attributable to the effect of radiation and is statistically significant at the 5 per cent confidence level. Figure 3.10 shows the mean values of five selected groups plotted against days postirradiation; the over-all mean for T_1 is shown also for each group.

Hematocrit: There is a recovery trend present here which actually tends to overshoot the controls and then decrease somewhat. There are no significant differences between groups, but the time differences are significant at the 5 per cent confidence level. Figure 3.11 shows the mean values of five selected groups plotted against days postirradiation; the over-all mean for T_1 is also shown for each group.

Platelets: These values during this period recovered to the point where the trends became somewhat less distinct; there are, however, significant differences between groups attributable to radiation. These effects, at this point, are probably contributed largely by group C (the highest dose group). Figure 3.12 shows the mean values for five selected groups plotted against days postirradiation; the over-all mean for T_1 is also shown for each group.

White Blood Cells: There are no trends or differences between groups which are significant. Some recovery is evident in the early stages (30 to 60 days postirradiation).

Percentage of Lymphocytes: Figure 3.13 shows the mean values for five selected groups plotted against days postirradiation; the over-all mean for T_1 is also shown for each group. There is definitely a recovery pattern which occurs from the 60th to 120th day postirradiation. The apparent anomaly during the first two periods results from the inability of the lymphocytic cells to appear in their proper perspective until the neutrophils, which recover sooner, reach normal levels. The trends depicted are significant at the 5 per cent confidence level; however, there are no significant differences between the groups.

Percentage of Neutrophils (Polymorphonuclear Leukocytes): These cells had almost completely returned to normal by the time these blood counts were taken, and there are no significant differences or trends to discuss.

Percentage of Monocytes: These results are presented in Fig. 3.14. The data have been normalized with respect to the concurrent control values; the percentage of monocytes as percentage of control values has been shown for each group for the five samples in T_1 , as well as the five samples in T_2 . These data demonstrate forcefully the tremendous increase in this type cell in the period 30 to 60 days postirradiation and the subsequent decline to, and continuance at, normal levels. The depicted changes are significant at the 5 per cent confidence level and must be attributed to irradiation.

Percentage of Eosinophils: The results are presented in Fig. 3.15. The data, which have been normalized with respect to the control values, are given for each group for the five samples taken in each time period (T_1 and T_2). There is a highly significant ($p = 0.01$) increase that takes place 45 to 90 days postirradiation. Normal levels are reached at very nearly 100 days, and they have continued until the present time.

(b) *Time Period 2 (T_2), 360 to 600 Days Postirradiation.* For all parameters tested there were no differences at all between any irradiated animals and the controls which could be a direct result of the irradiations received in 1967. The recovery noticed in the formed elements of the peripheral blood up to 100 days was essentially complete at that time, and no further changes have occurred.

(Text continues on page 26.)

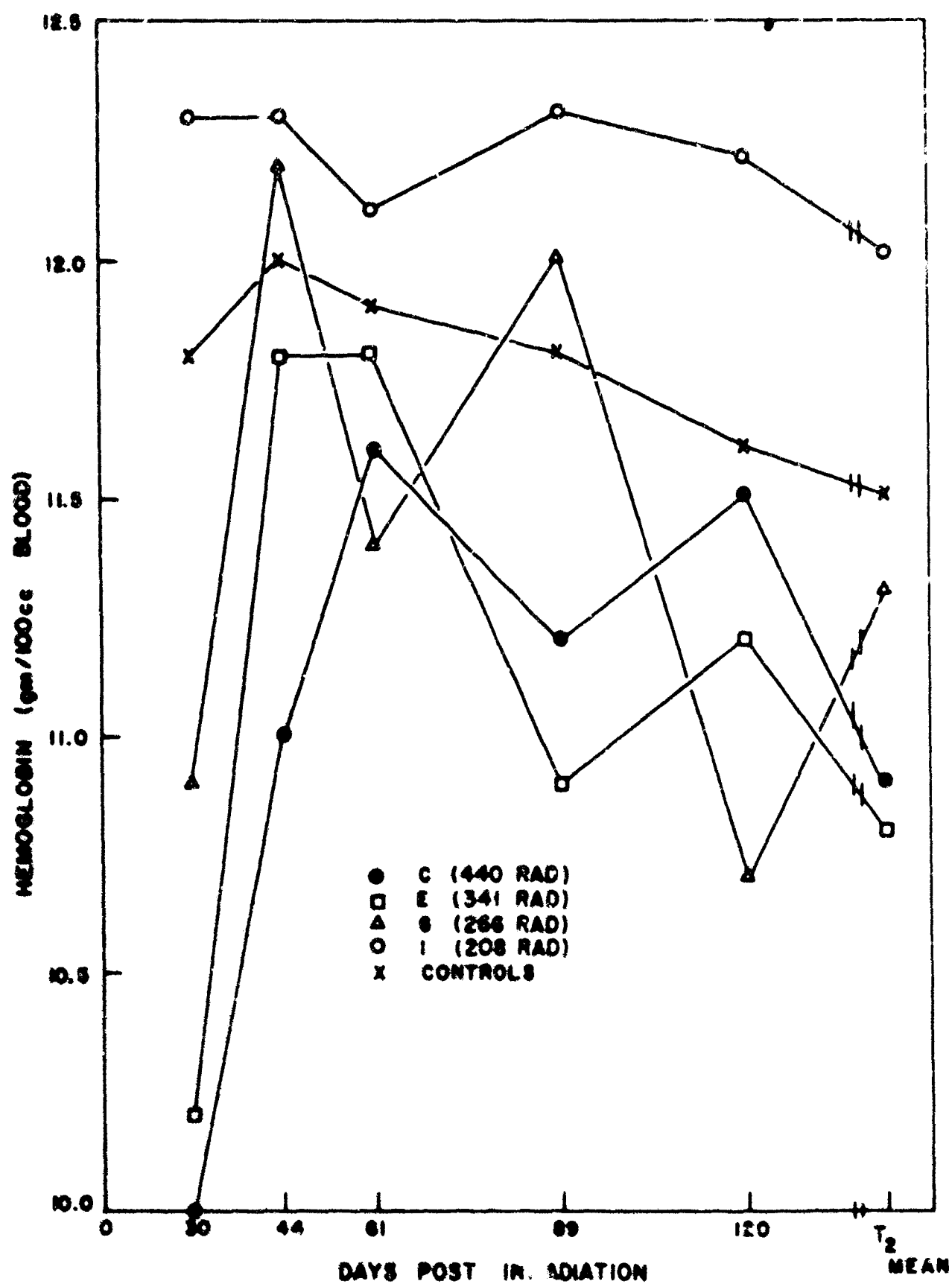


Fig. 3.10—Temporal changes in hemoglobin in selected groups of animals from Finnan shot.

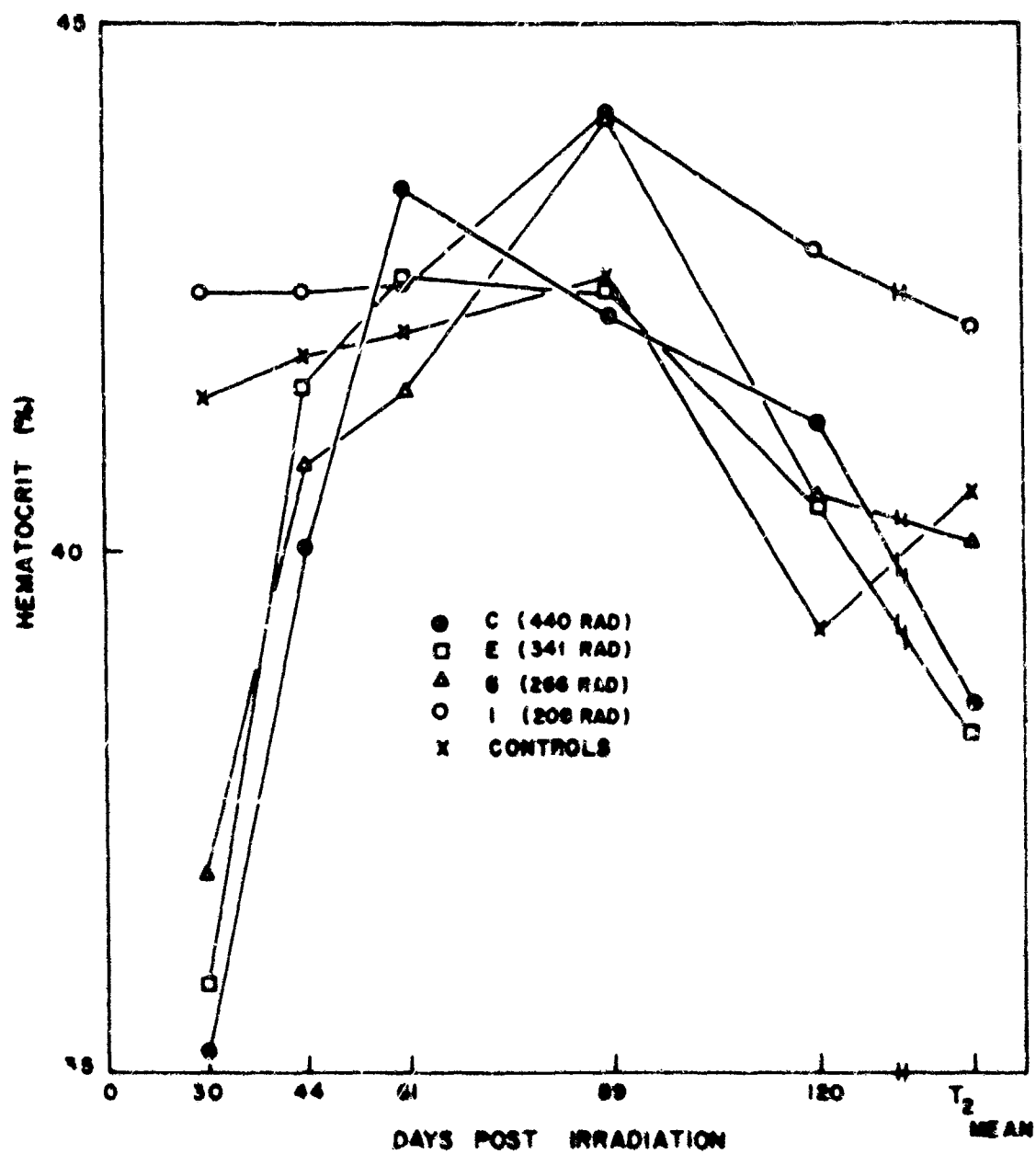


Fig. 2.11—Temporal changes in hematocrit in selected groups of animals.

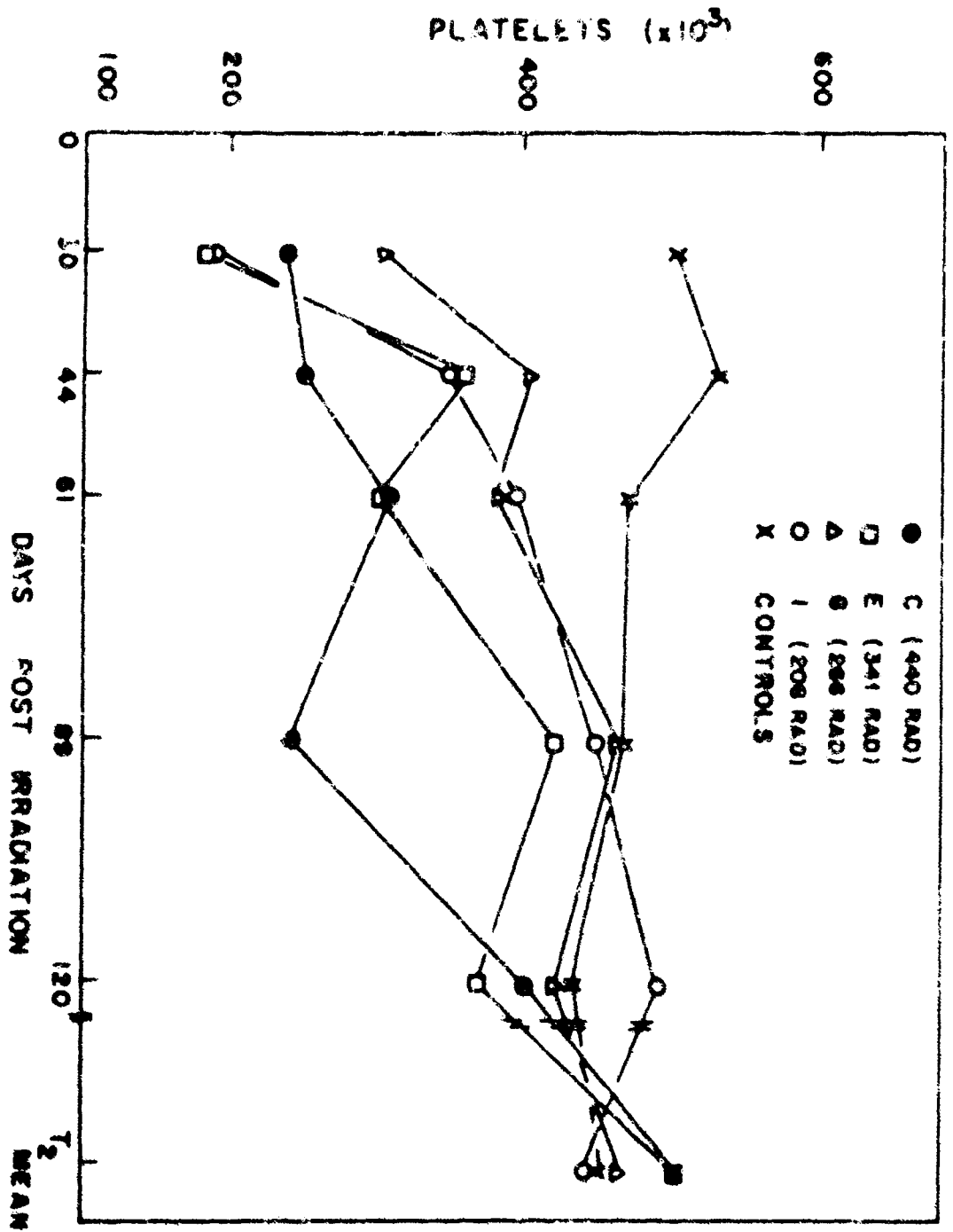


Fig. 13.—Temporal changes in platelet counts in selected groups of mice.

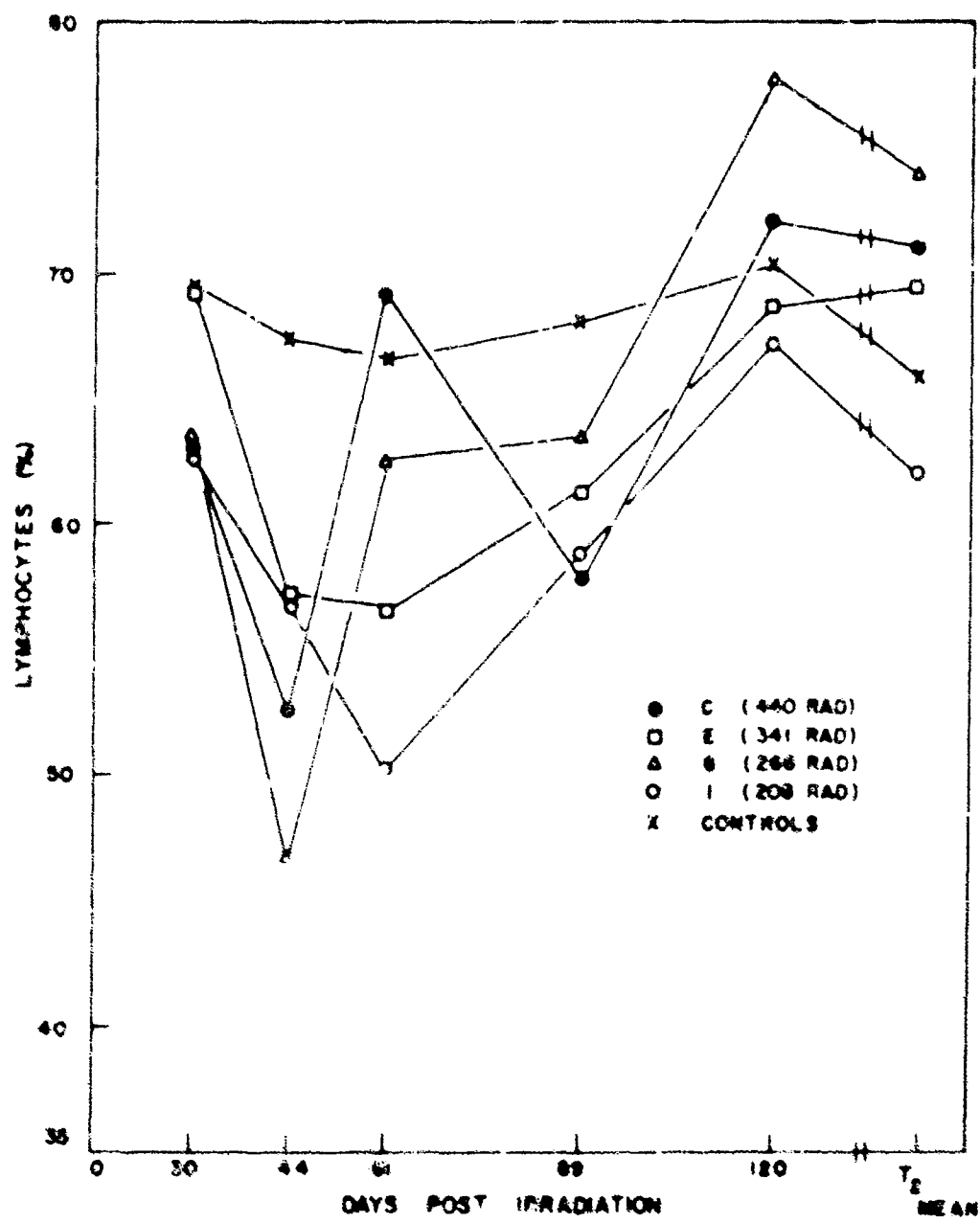


Fig. 2.13—Temporal changes in lymphocyte counts in selected groups of animals.

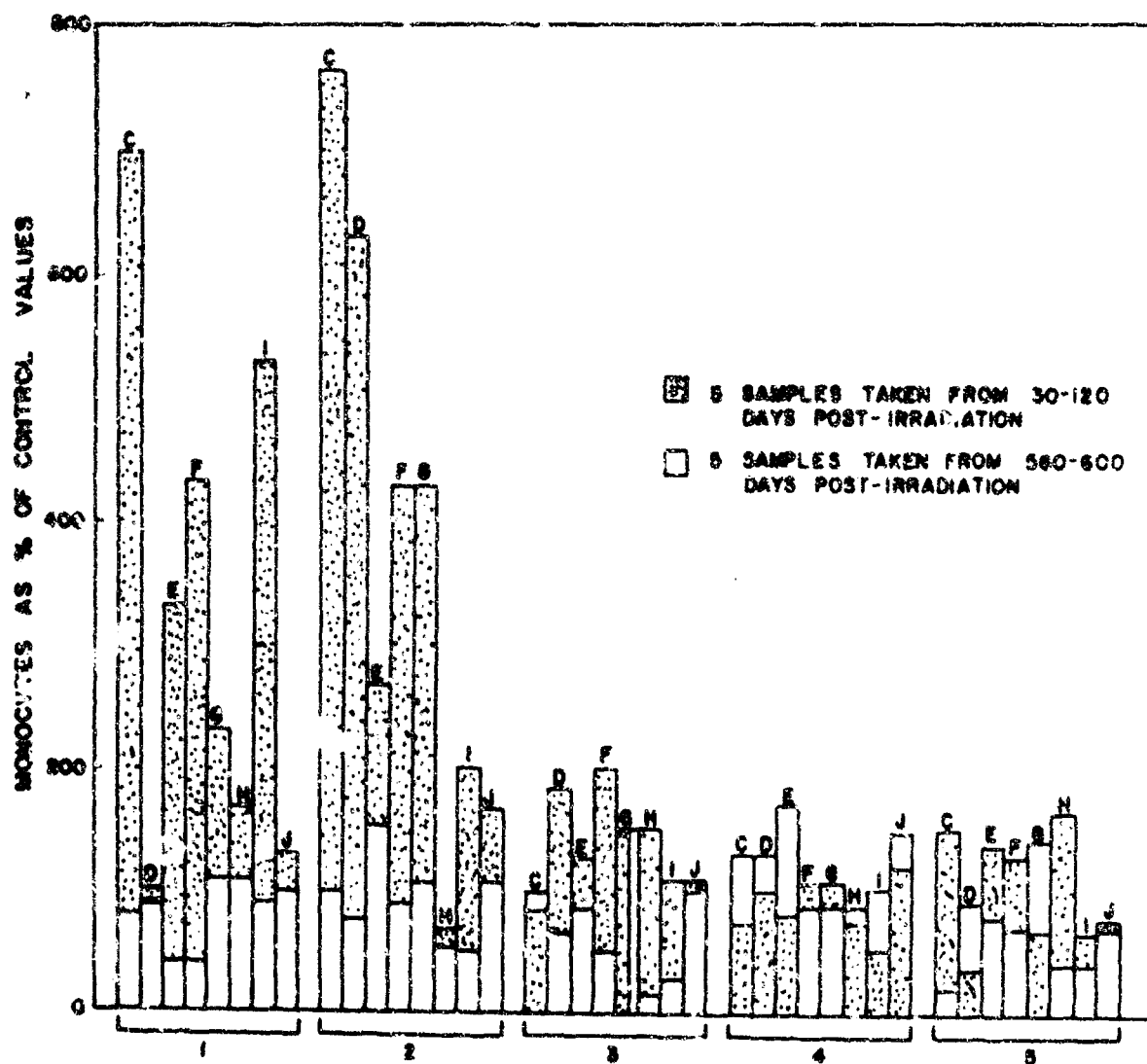


Fig. 3.14—Temporal changes in monocytes in all groups of animals expressed as percentage of control values.

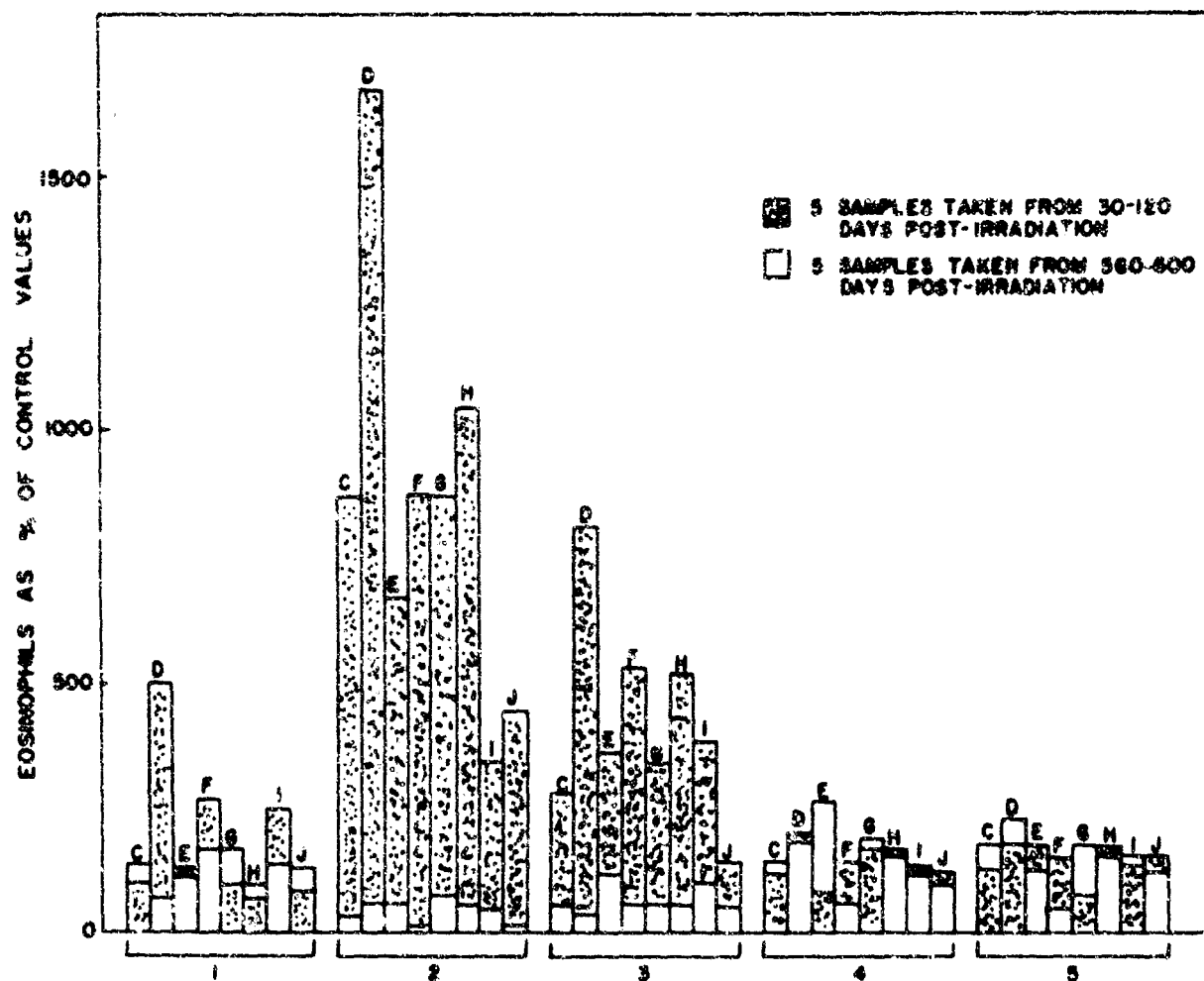


Fig. 3.15— Temporal changes in eosinophils in all groups of animals expressed as percentage of control values.

3.2.4 Discussion

Of the six parameters in which significant changes were found, only three showed any lasting effects, i.e., hemoglobin, platelets, and eosinophilia. This is not to say that they are late effects but rather that complete recovery was not effected in 120 days but at some later date. This recovery is proportional to total dose, and probably the threshold lies between 200 and 250 rads under the irradiation conditions of this shot.

The eosinophilia noted is most probably an "overshoot" phenomenon resulting from two factors: (1) the general tendency of the marrow to produce more cells after the losses due to radiation and (2) the serious "stress" on the animals imposed by the irradiation caused a marked eosinopenia during the period 7 to 30 days postirradiation.

In general, the response and results represent the classical picture of the results of sub-lethal to midlethal doses of ionizing radiation; the response is identical with, but of a lesser degree, the response in the monkeys in shot Wilson which received much higher doses. Therefore at 600 days postirradiation, there are few or no residual effects on peripheral hematology in the shot Fizeau animals that survived the first 30 days.

It must be noted that the animals of shot Fizeau comprise a mixed group of males and females. Of the nine groups of 4 animals each analyzed without regard to sex, 22 were males and 14 were females; five groups contained 2 females, and the remaining four groups each had 1 female. Further discussion of effects in relation to sex differences will be covered in Chap. 4.

Chapter 4

BEHAVIOR

4.1 INTRODUCTION

Past research at the Radiobiological Laboratory, conducted with male rhesus monkeys previously exposed in the Laboratory to a mixed source of gamma and neutron radiation, found that the effects of such radiation exposure include changes in cage behavior,¹ decreased distractibility,¹ facilitated performance on discrimination problems with reduced stimulus cues,² facilitated delayed-response performance,³ and some deficit in visual acuity performance.^{4,5}

The present series of studies was undertaken to determine the effects of the field exposure of the monkeys of the Fizeau shot on performance on the same and similar tasks.

4.2 METHODS

4.2.1 Subjects

Sixty-four rhesus (*Macaca mulatta*) monkeys of the Fizeau shot were used as subjects, 40 males and 24 females. For this study the 23 animals of the control group and of radiation subgroups I and J constituted radiation dosage group 1, the 32 animals of radiation subgroups F, G, and H constituted radiation dosage group 2, and the 19 animals of radiation subgroups C, D, and E constituted radiation dosage group 3. Grouping in this manner was necessary, in the initial study to be reported here, to meet the requirements of the chi-square test with respect to expected frequencies in each cell. The same groupings were maintained in subsequent tests to render the appraisal of radiation dosage effects comparable from test to test.

4.2.2 Procedure

(a) *Preliminary Wisconsin General Test Apparatus (WGTA) Training.* This training was conducted from June 9, 1958, to Aug. 4, 1958. Its purpose was to train the subjects (1) to take food from the test tray of the WGTA, (2) to associate object blocks with food, (3) to respond to object blocks only as such response is instrumental in procuring food, (4) to continue response to object blocks in spite of the distraction of the sliding screens of the WGTA, and (5) to continue response when only 0.50 of responses to object blocks are rewarded with food. A schematic drawing of the WGTA is shown in Fig. 4.1. The program involved five successive criteria, which were tested in the following order:

1. Criterion 0: If an animal on the initial day of testing failed to respond immediately to three pieces of food placed on the front-center surface of the test tray, he was tested to the criterion of 24 successive procurements of food from the surface of the test tray per day for two successive days before being tested on criterion 1. However, if an animal on the initial day of testing responded immediately to food on the open test tray, his testing on criterion 1 was begun. Both screens of the WGTA remained up during all testing on criterion 0.

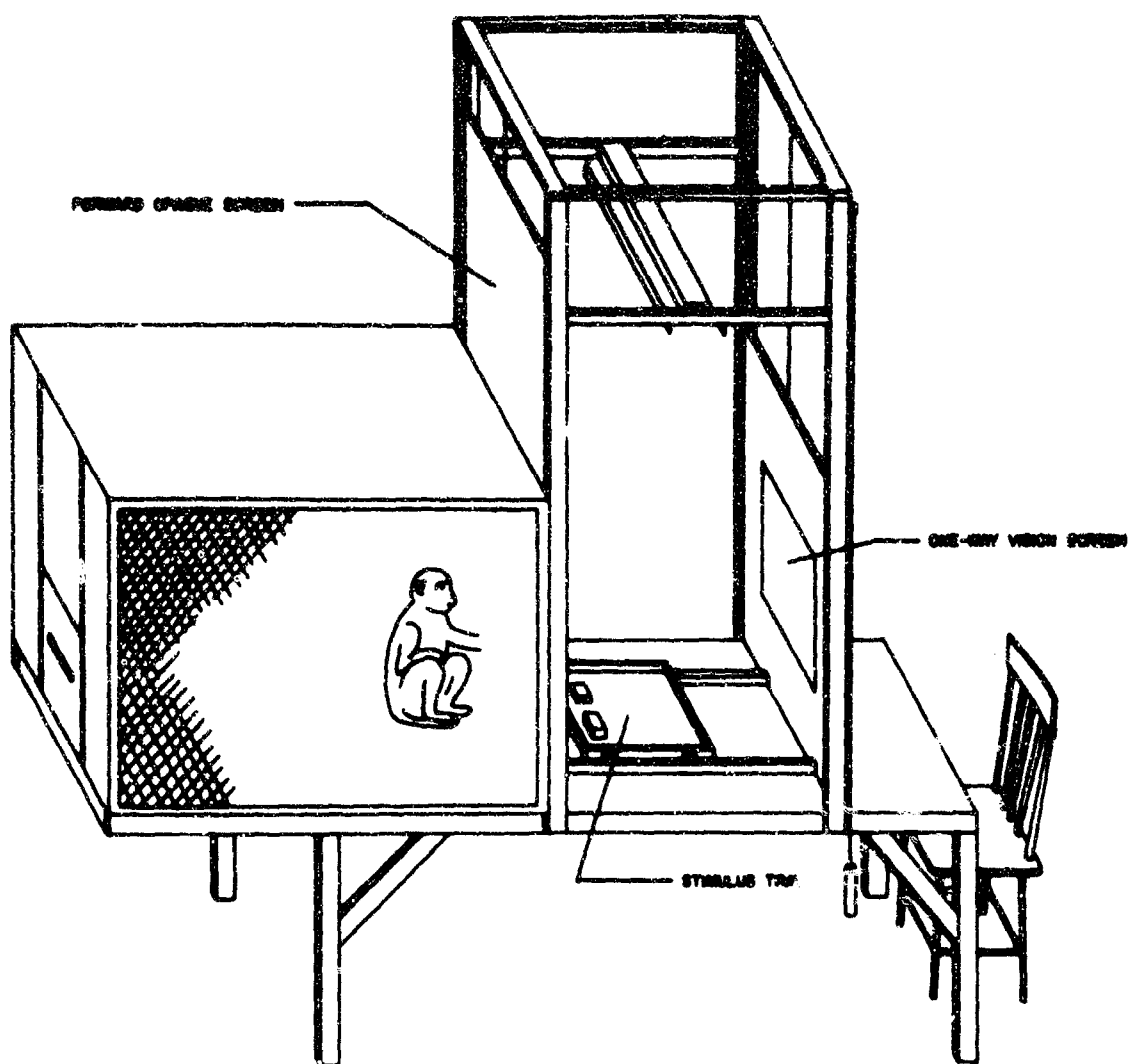


Fig. 4.1—Wisconsin General Test Apparatus.

2. Criterion I: A red-painted square wooden block measuring $3\frac{1}{2}$ by $3\frac{1}{2}$ by $1\frac{1}{2}$ in. was used in this test as well as in all subsequent testing. The block was chained to the test tray to prevent the animal from pulling it to him in the test cage. The animal, on each trial, saw a piece of food placed in the center food well of a tray having three food wells, saw the chained block placed over the baited food well, and was then given an opportunity to push away the block and procure the food reward. Each animal under this condition was tested to the criterion of 24 successive procurements of food reward per day for two successive days.

3. Criterion II: Testing on criterion II was the same as on criterion I, except that the forward screen was dropped during the baiting procedure. Twenty-four successive responses per day for two successive days were again required.

4. Criterion III: Testing on criterion III was the same as on criterion II, except that the block was no longer chained to the test tray.

5. Criterion IV: Testing on criterion IV was the same as on criterion III, except that manual response to the block was randomly reinforced with food only half the time.

If an animal failed to respond within 3 min in the appropriate manner at any stage of the day's training on each criterion, his testing was terminated for the day. Pieces of diced apple were used as the food reward.

After completion of the above training procedure for all animals, testing was initiated on a single two-object discrimination problem. The positive of the two objects was a yellow-painted square wooden block, measuring 3 by 3 by $\frac{3}{4}$ in., with a circular red-painted wooden block, measuring 2 in. in diameter and $\frac{3}{4}$ in. in depth, superimposed. The negative stimulus object was a yellow-painted square wooden block with the same dimensions as the base of the positive stimulus object. Each animal was tested 24 trials per day on this discrimination problem to a criterion of two successive days with three errors, or fewer, per day.

(b) *Discrimination Problems with Reduced Stimulus Cues*. This training was conducted from Sept. 12 to Nov. 20, 1958. The stimulus objects for this training were identical to those used on the two-object discrimination problem. Each problem on this task consisted of two trials. On the learning trial the animal was rewarded for responding as he had learned to do in the discrimination training. On the test trial, with only the two identical yellow wooden blocks being present, he was rewarded for response to the position that was rewarded on the learning trial. Position of reward was, of course, randomly varied from problem to problem. Each animal was tested on 24 problems per day for 32 days, a total of 768 reduced-cue discrimination problems.

(c) *Spatial Delayed Response*. This training was conducted from Dec. 2, 1958, to Jan. 15, 1959. The stimulus objects were the two identical yellow wooden blocks that have been used in both the single discrimination training and the training on discrimination problems with reduced stimulus cues. Standard direct-method spatial delayed-response techniques were used. The length of each delay was 10 sec, and the opaque screen of the WGTA was raised during each delay. Each animal was tested 24 trials per day for 24 days, a total of 576 spatial delayed-response problems.

(d) *Visual Acuity Testing*. This training was conducted from Jan. 19 to Mar. 5, 1959. The training was intended to evaluate the minimum-size figure that an animal can perceive. The problems required the animals to choose between blank cards and cards containing black dots of various sizes. A card with a dot measuring 2 in. in diameter was used in the preliminary training; and, in the visual acuity testing, five cards containing dots varying in diameter from 1 to $\frac{1}{16}$ in. were used. In the preliminary training each animal was tested to the criterion of 21 correct responses (24 trials each day) for two successive days. In the visual acuity testing each animal was tested 24 trials per day for five days on each of the five remaining cards given in order of increasing difficulty. Response to the card containing the black dot was reinforced.

(e) *Systematic Observations of Cage Behavior*. This testing included three sampling periods. The first set of observations was made from May 12 to May 23, 1958, the second set from Nov. 10 to Nov. 21, 1958, and the third set from May 26 to June 4, 1959. The methodology followed that of previous studies⁶⁻⁸ and consisted of systematic observations of the free-cage behavior of the monkey. During each observation the animal was placed in a special holding

cage. This cage measured 3 by 3 by 3 ft and was constructed of steel bars placed 3 in. apart center-to-center. A wooden cage bed was affixed to one side of the cage.

To record an observation, the experimenter sat 8 ft from the cage and recorded on a mimeographed category sheet what the animal's behavior was every 10 secs on the 10-sec mark. Since each observation was of 5-min duration, the total frequency count for each animal for each observation was 30. Each animal was observed five times during each of the three sets of observations.

The behavior categories discussed here include (1) nondirected locomotor activity; (2) object-directed activity, either by response to the wooden cage bed or to the metal cage parts; and (3) attention to auditory stimuli occurring outside the test room. Each of these categories had differentiated between the irradiated and the normal animals in previous work.¹

4.2 RESULTS

4.3.1 Preliminary WGTA Training

Figure 4.2 shows the proportion of animals in each radiation group that responded immediately to food on the surface of the test tray on the initial day of testing. Statistical treatment of this data yielded a chi-square value of 16.44, which, for 2 degrees of freedom, is beyond the 0.001 significance level. The probability of immediate response to food on initial exposure to the test situation increases directly with relative radiation dosage.

Figure 4.3 shows the median number of days to criterion for each group on each of the last four criteria. Only with respect to criterion I was a difference manifested. Statistical analysis of the data for criterion I, using the median test, yielded a chi-square value of 6.07, which, for 2 degrees of freedom, is beyond the 0.05 significance level. The median days to criterion were significantly greater for the animals of group 3 than for the animals of either groups 1 or 2, suggesting slower association of the object block with food reward for the animals of group 3.

Figure 4.4 compares the groups with respect to proportion of subjects in each group at or below the common median number of days to criterion on the single discrimination problem. Statistical analysis of these data, comparing proportions above the common median to proportions at or below the common median, yielded a chi-square value of 7.98, which, for 2 degrees of freedom, is beyond the 0.02 significance level.

4.3.2 Discrimination Problems with Reduced Stimulus Cues

The percentage of errors for successive four-day periods of testing on the discrimination problems with reduced stimulus cues is shown in Fig. 4.5. The upper portion of Fig. 4.5 shows the data for all the animals of each dosage group, the middle portion shows the data for the male animals only, and the lower portion shows the data for the female animals only.

Statistical analysis of the error data for all the animals of each radiation group, using a mixed type analysis of variance design, yielded no significant difference between radiation groups ($p = 0.20$),* a significant practice effect ($p = 0.001$), and no groups by practice interaction.

A similar analysis for the error data of the males yielded identical results. The results of the analysis for the females were the same, with the exception that the difference between radiation groups did not reach the 0.20 significance level.

4.3.3 Spatial Delayed Response

The percentage of errors for successive four-day periods of testing on the spatial delayed-response problems is shown in Fig. 4.6. The upper portion of Fig. 4.6 shows the data for all animals in each dosage group, the middle portion shows the data for the male animals only, and the lower portion shows the data for the female animals only.

* To permit a subjective evaluation of joint probabilities, all differences in this and subsequent analyses at or beyond the 0.02 significance level are presented.

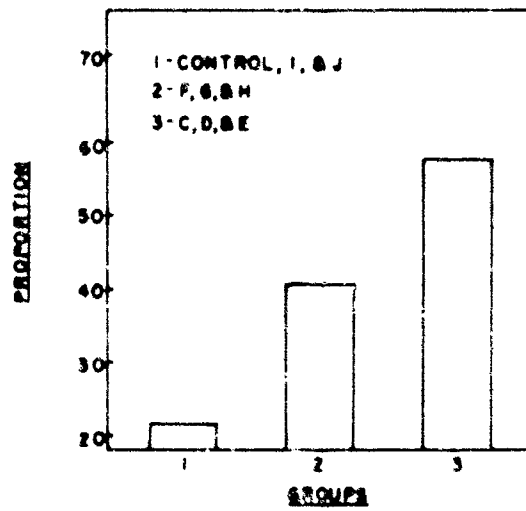


Fig. 4.2—Proportion of animals in each group that responded immediately to food on initial day of testing.

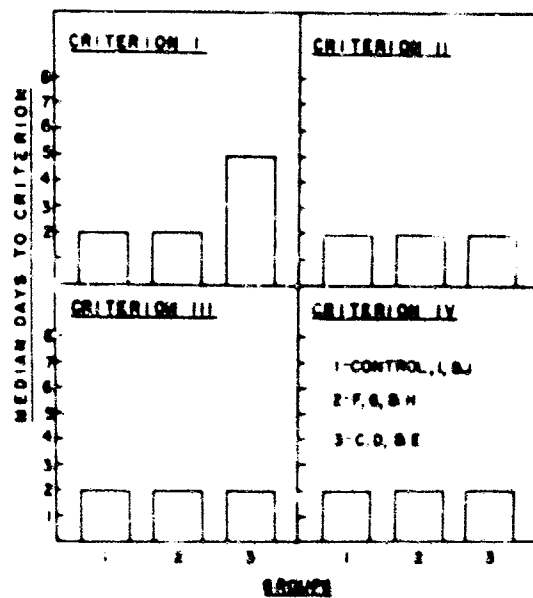


Fig. 4.3—Median number of days to criterion for each group on criteria I to IV.

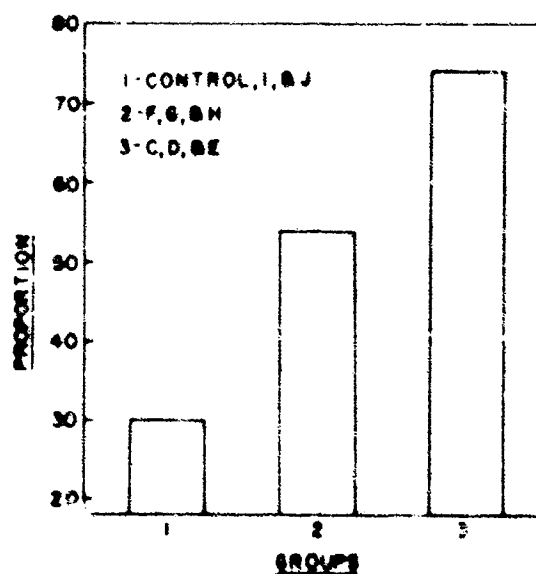


Fig. 4.4—Proportion of subjects in each group at or below the common median number of days to criterion on the single discrimination problem.

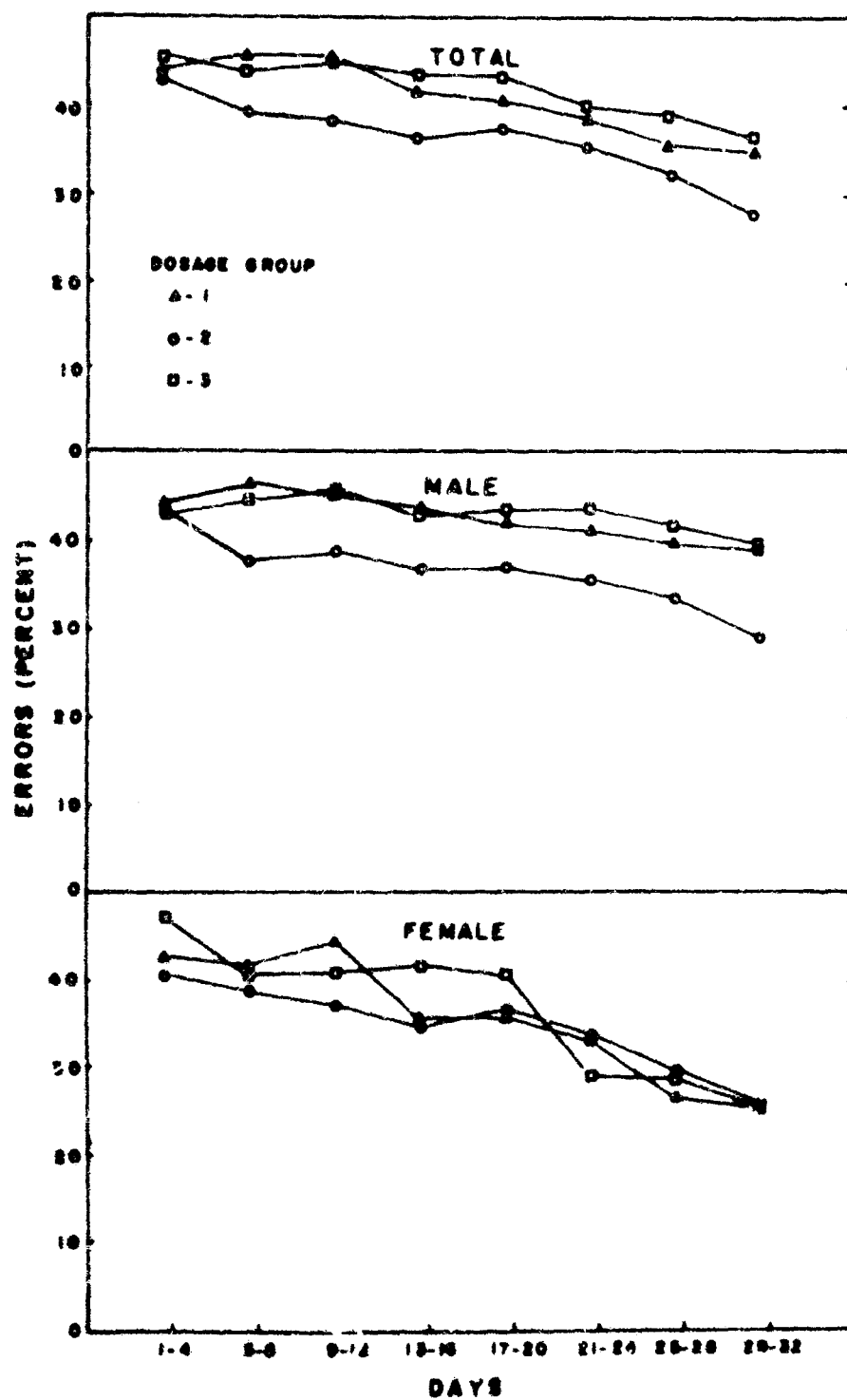


Fig. 4.5—Percentage of errors for successive four-day periods of testing on the discrimination problems with reduced stimulus cues.

Statistical analysis of the error data for all the animals of each radiation group yielded no significant difference between radiation groups, a significant practice effect ($p = 0.001$), and no groups by practice interaction.

The analysis based on the error data for the males yielded a significant difference between radiation groups ($p = 0.05$), a significant practice effect ($p = 0.001$), and a significant groups by practice interaction ($p = 0.05$). The results of the analysis for the females yielded a significant practice effect ($p = 0.001$), with the other effects not achieving the 0.20 significance level.

4.3.4 Visual Acuity Testing

The radiation groups did not differ significantly with respect to trials to criterion on the preliminary training of the visual acuity testing. The mean errors for each of the five problems of the visual acuity testing are shown in Fig. 4.7. The problems are arranged from left to right in order of decreasing size of the dot to be discriminated. The upper portion of Fig. 4.7 shows the data for all the animals of each dosage group, the middle portion shows the data for the male animals only, and the lower portion shows the data for the female animals only.

Statistical analysis of the error data for all the animals of each radiation group yielded no significant difference between radiation groups ($p = 0.20$), a significant difference between problems ($p = 0.001$), and a significant groups by problems interaction ($p = 0.05$).

The analysis of the error data for the males yielded only a significant difference between problems ($p = 0.001$). The results of the analysis for the females yielded similar results, with the exception that the groups by problems interaction reached the 0.20 significance level.

4.3.5 Systematic Observations of Cage Behavior

The mean frequency of attention to auditory stimuli occurring outside the test room for each of the three successive observation periods is shown in Fig. 4.8. The upper portion of Fig. 4.8 shows the data for all animals in each dosage group, the middle portion shows the data for the male animals only, and the lower portion shows the data for the female animals only.

Statistical analysis of the frequency data for all the animals of each radiation group yielded a significant difference between radiation groups ($p = 0.01$), a significant time effect ($p = 0.02$), and no groups by time interaction.

The analysis of the frequency data for the males yielded a significant difference between radiation groups ($p = 0.025$), no significant time effect ($p = 0.20$), and no groups by time interaction. The analysis for the females yielded no significant effects. The time effect for the females was, however, at the 0.10 significance level and the interaction effect at the 0.20 significance level.

The mean frequency of cage responses for each of the three observation periods is shown in Fig. 4.9. The upper portion of Fig. 4.9 shows the data for all animals in each dosage group, the middle portion shows the data for the male animals only, and the lower portion shows the data for the female animals only.

Statistical analysis of the frequency data for all the animals of each radiation group yielded no significant difference between radiation groups ($p = 0.20$), a significant time effect ($p = 0.001$), and no groups by time interaction.

Analysis of the frequency data for the male animals yielded no significant difference between radiation groups ($p = 0.20$), a significant time effect ($p = 0.005$), and no groups by time interaction. Analysis for the females yielded a significant difference between radiation groups ($p = 0.05$), no time effect ($p = 0.10$), and no interaction.

In the analysis of the frequency data concerned with locomotor activity, none of the effects reached the 0.05 significance level.

4.4 DISCUSSION

The data of the first of the series of studies reported here show that the higher the dose of previous whole-body irradiation (within the range of the dosages used), the greater the probability of immediate response to food by monkeys when first placed in the WOTA; the slower the association between an object block and food, and, once such an association has been formed, the faster the discrimination between a food-rewarded and a nonfood-rewarded object block.

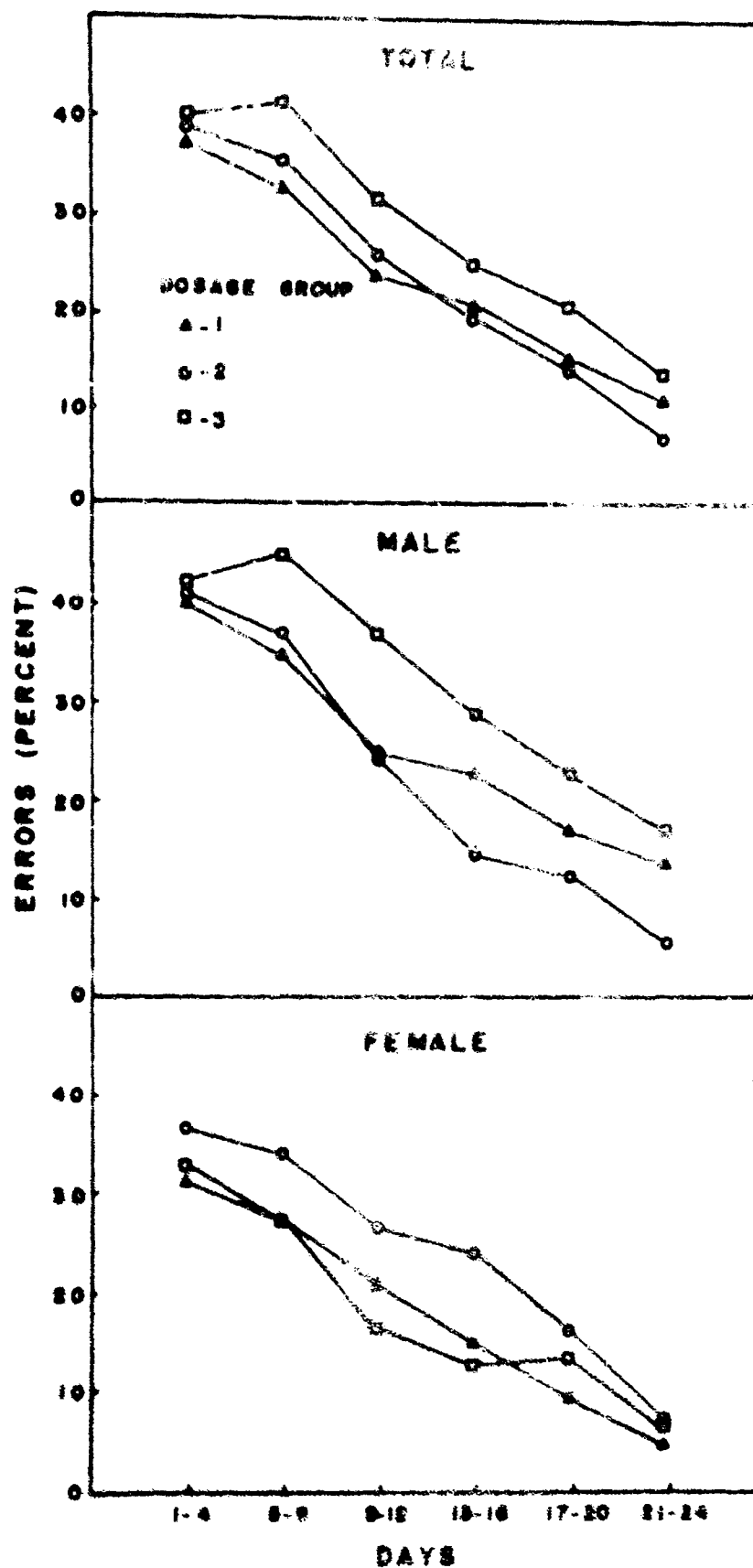


Fig. 4.6—Percentage of errors for successive four-day periods of testing on the spatial delayed-response problems.

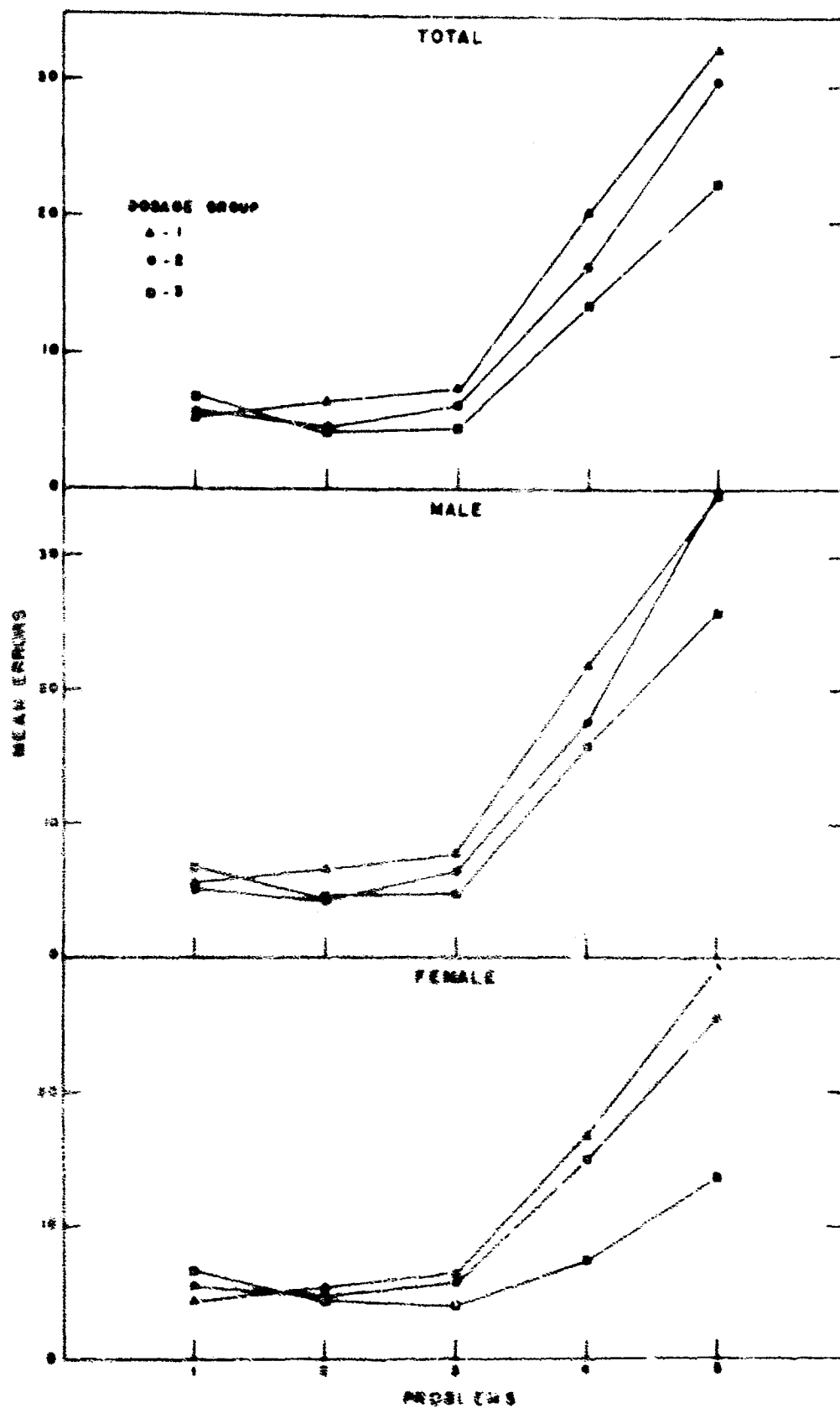


Fig. 4.7—Mean scores for each of the five problems of the visual acuity testing

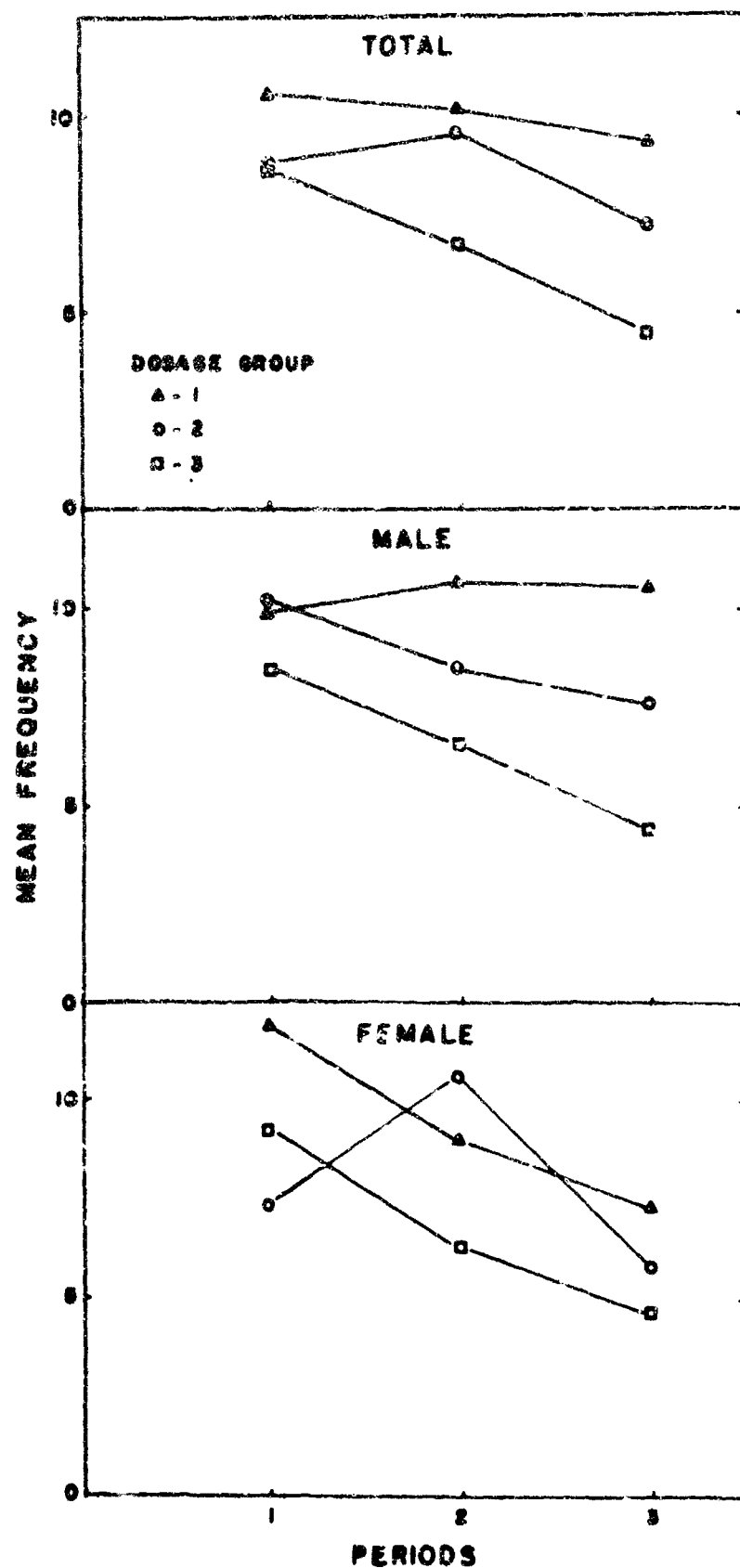


Fig. 4.3—Mean frequency of attention to auditory stimuli occurring outside the test room for each of the three observation periods.

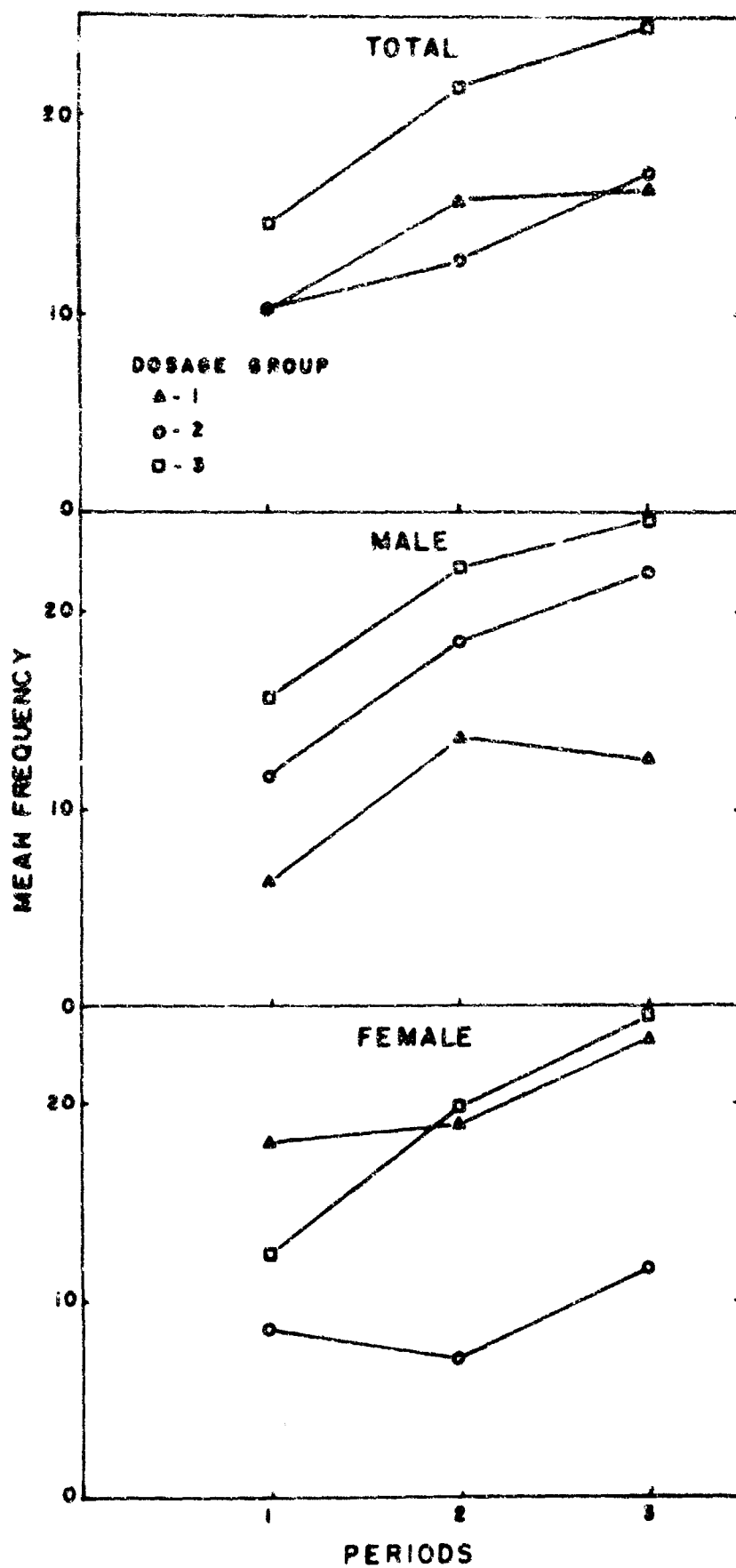


Fig. 4.9—Mean frequency of cage responses for each of the three observation periods.

These findings, based on an independent group of animals subjected to field-administered radiation rather than to laboratory-administered radiation, provide confirmation of an hypothesis previously advanced by McDowell and Brown.¹

These investigators hypothesized, to explain facilitative effects of irradiation on the performance of monkeys on discrimination problems with reduced stimulus cues, that previous irradiation elevates thresholds for all responses to the stimuli in the animal's environs to the same degree. Consequently, the response-provoking potentialities of the weaker stimuli are reduced or lost, and an increased percentage of total responses are directed to the stronger stimuli. In the first of the present series of studies in line with this hypothesis, the higher the previous dosage, the faster the response to food (which is a relatively strong stimulus), the slower the response to a wooden object block (which is a relatively weak stimulus), and the faster the discrimination of a food-rewarded object block, after object blocks had acquired the stimulus value of food.

The significant findings for the male radiation dosage groups of the present series of studies on spatial delayed-response performance and on attention to auditory stimuli occurring outside the test room are in accordance with previous findings by McDowell^{1,2} and Brown.³ In addition, the trends suggested in the analyses of the data for the male radiation dosage group animals on discrimination problems with reduced stimulus cues and on responses to cage parts are in the direction of agreement, although the differences do not reach the conventional levels of significance, with previous researches.^{1,2}

The observed differences between males and females relative to the radiation dimension on the four above-mentioned variables suggest the need for investigations of the sex variable as it relates to performance and radiation.* These findings render questionable generalization from any of the behavioral analyses which are based on all the animals of each radiation dosage group.

The findings on the visual acuity testing of the present series of studies show no deficit in minimum-size discrimination as the relative radiation dosage increases. On the contrary, a facilitation seems suggested on the more difficult discriminations. The contrast between these findings and those of Davis et al.⁴ and Brown and McDowell⁵ must await further research for resolution. Some of the possible sources of difference may be differential radiation sources, differential dosage rates, age of the animals at time of exposure, or the calendar time between testing and exposure. The last of these possible sources of difference appears to be the most probable to the authors.

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*Such investigations are projected and are currently awaiting an appropriate statistical design from the Department of Biometrics, School of Aviation Medicine.

7. A. A. McDowell and W. Lynn Brown, Some Effects of Nuclear Radiation Exposure on the Behavior of the Rhesus Monkey, School of Aviation Medicine, USAF, Report No. 58, 1958.
8. A. A. McDowell and W. Lynn Brown, Some Persisting Effects of Nuclear Radiation Exposure on the Behavior of the Rhesus Monkey, School of Aviation Medicine, USAF, Report No. 66, 1958.

Chapter 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 CONCLUSIONS

5.1.1 Clinical Observations

(a) *Lethality.* The 13 animals currently alive from Wilson shot and the 66 animals currently alive from Fixeau shot show no clinical symptoms that would allow any specific prognosis of death.

(b) *Weight.* Weight losses due to irradiation have been recovered in all survivors, and further changes should be very similar to those seen in the normal control monkeys.

(c) *Ophthalmology.* Definite cataractogenesis has been observed at the end of the second year postirradiation; this damage is generally proportional to the rad dose received, with a threshold near 303 to 332 rads.

(d) *Other Parameters.* At the date of this report, the animals that suffered from vomiting, anorexia, diarrhea, purpura, and epilation resulting from the exposure to nuclear emanations have recovered. Of all these parameters, lens damage appears to be the only late effect with clinical manifestations.

5.1.2 Hematology

(a) *Wilson Shot.* Erythroid elements of the peripheral blood recovered by 540 days; larger numbers of megaloblastic cells appear to be present right up to the time of writing. For the 63- to 540-day postexposure period, most leukocytic cells show a depression below concurrent control values; an animal that died during this period showed practically no lymphocytes in the circulation. The decrease in variability of white blood cell counts noted in chronically irradiated monkeys was not seen in shot Wilson animals.

(b) *Fixeau Shot.* The radiation damage resulting from exposure to the nuclear detonation (which appeared during the first 30 days postexposure) has now (about 21 months postirradiation) been repaired.

5.1.3 Behavior

It must be concluded that, with regard to preliminary WQTA training, discrimination problems with reduced stimulus cues, spatial delayed response, and systematic observations of cage behavior, the previous laboratory findings have been confirmed under the conditions of irradiation in the field.

The facilitation of visual acuity as the relative radiation dosages increase may prove to be of great interest.

5.2 RECOMMENDATIONS

5.2.1 Clinical Observations

(a) *Lethality.* All the surviving animals should, if possible, be maintained indefinitely to observe mortality and determine the cause of death and any changes in life span or gerontology.

(b) *Weight.* Since these data are always maintained in the practice of good animal husbandry, they should be analyzed and interpreted at frequent intervals.

(c) *Ophthalmology.* It is felt that the category I animals should be studied at intervals of six months to one year in a continuing search for the least-detectable result of the type of radiation employed. Examination of the category II animals should now be done at more frequent intervals, perhaps every 90 days, to watch for progression of the changes already present and to detect the appearance of new changes should these occur.

5.2.2 Hematology

Sampling for all surviving Operation Plumbbob animals should continue on a semiannual basis. Approximately 24 months from the time of this report, it would probably be of considerable interest to sample the peripheral circulations weekly for five weeks and once again to analyze and interpret the results.

5.2.3 Behavior

The value of further observations to confirm the long-term effects on behavior, to demonstrate or disprove the apparent facilitation of visual acuity, and to amplify the differential sex response indicated cannot be overestimated.