

AD629723

THE KINETICS OF RECUPERATION FOLLOWING 55 MEV PROTON IRRADIATION

GLENN V. DALRYMPLE, Captain, MC, USAF, et al.

Volanti Subvenimus

CLEARINGHOUSE FOR FEDERAL SCIENTIFIC AND TECHNICAL INFORMATION			
Hardcopy	Microfiche		
\$1.60	\$0.50	11 pp	as
ARCHIVE COPY			

Code 1

February 1966

USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas

Qualified requesters may obtain copies of this report from DDC. Orders will be expedited if placed through the librarian or other person designated to request documents from DDC.

When U. S. Government drawings, specifications, or other data are used for any purpose other than a definitely related government procurement operation, the government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

Distribution of this document is unlimited.

**THE KINETICS OF RECUPERATION FOLLOWING 55 MEV
PROTON IRRADIATION**

GLENN V. DALRYMPLE, Captain, MC, USAF*

IAN R. LINDSAY, Wing Commander, RAF, Exchange Officer*

JOHN C. MITCHELL, B.S.*

JAMES D. HALL, Ph.D.†

IRA L. MORGAN, Ph.D.†

***USAF School of Aerospace Medicine, Brooks Air Force Base, Texas**
†Texas Nuclear Corporation, Austin, Texas

FOREWORD

This report was prepared in the Radiobiology Branch under contract No. AF 41(609)-2418 and task No. 775704. The work was initiated on 28 April 1965 and completed on 30 June 1965.

The authors are grateful for the technical assistance of A. Hernandez-Diaz, M. J. Diemer, and D. B. Shupe.

The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

This report has been reviewed and is approved.

Harold V. Ellingson
HAROLD V. ELLINGSON
Colonel, MC, USAF
Commander

ABSTRACT

The kinetics of recuperation following initial doses of 470 rads of 55 Mev protons and 350 rads of Co^{60} γ radiation were investigated by means of the paired-dose method. By using semilog plots, recovery half-times of $4.85 \pm .85$ days and $2.02 \pm .45$ days were found after initial doses of the protons and Co^{60} γ radiation, respectively.

THE KINETICS OF RECUPERATION FOLLOWING 55 MEV PROTON IRRADIATION

I. INTRODUCTION

Since space travel will place man in a position to be irradiated with protons, a most important consideration concerns the characteristics of recovery from the injury produced by the protons. This communication gives the results of experiments in which the kinetics of recuperation after 55 Mev protons and Co^{60} γ irradiation were studied by the paired-dose method. Throughout the literature, the terms "repair" and "recovery" are given specialized meanings. The term "recuperation" (after Kallman and Silini (1)) will be used to indicate the improvement of the radiation-induced injury with time.

II. EXPERIMENTAL METHODS AND MATERIALS

Protons

The Oak Ridge Isochronous Cyclotron (ORIC) was used as a source of the protons. Mice were irradiated in groups of 3 with doses of 470 rads of 55 Mev protons delivered at 470 rads/min.; they were held in aluminum mesh cylinders and rotated at a rate of 10 r.p.m. during exposure. The experimental arrangement and the beam characteristics have already been described (2, 3).

Co^{60} γ irradiations

The USAF School of Aerospace Medicine Cobalt Irradiation Facility was used for the exposures. The mice were irradiated in groups of 12; the beam characteristics and the dosimetry have already been described (4).

Animals and experimental design

A total of 1,352 adult, female, white Swiss Webster mice was used; they were obtained in a single shipment from a single supplier (Simonson Laboratories, White Bear Lake, Minn.) when they were approximately 8 weeks old. Immediately after arrival, the mice were assigned to plastic cages (6 mice to each cage) by a random number table and subsequently maintained in the animal quarters until time for exposure. The details of the animal care have already been described (4).

Just prior to irradiation the mice were divided into four basic groups by use of a random number table. Groups I and II were made up of 576 mice each. Those of group I were given single doses of 350 rads of Co^{60} γ radiation delivered at 350 rads/min. while the mice of group II received 470 rads of 55 Mev protons given at 470 rads/min. The original plan was to deliver initial doses of 350 rads of the 55 Mev protons to parallel the Co^{60} exposures. After the irradiations (both protons and Co^{60}) had been completed, however, an error in proton dosimetry was detected. The gas pressure within the ion chamber was found to be excessively low. This meant that a larger dose was required to produce a unit amount of ionization (as determined during the first calibration at the correct gas pressure) (2). Recalibration at the correct gas pressure indicated that the dose delivered during a 1-minute exposure was 470 rads. Although there had been an error in absolute dosimetry, the relative dosimetry was not affected; the cyclotron beam current remained very stable during all of the irradiations. After irradiation, these large groups were further subdivided by a random number table into groups

TABLE I
Experimental results

Days after irradiation	350 rads Co^{60} γ radiation (initial dose)			450 rads 55 Mev protons (initial dose)		
	Number of animals	LD _{50/30} on day	Injury (rads)	Number of animals	LD _{50/30} on day	Injury* (rads)
0†	144	735 $\pm$ 18‡	—	—	—	—
1	144	555 $\pm$ 19	180 $\pm$ 26	144	308 $\pm$ 18	427 $\pm$ 25
2	144	582 $\pm$ 20	153 $\pm$ 27	144	256 $\pm$ 26	479 $\pm$ 32
4	144	607 $\pm$ 18	128 $\pm$ 25	144	358 $\pm$ 28	377 $\pm$ 33
8	144	753 $\pm$ 31	-18 $\pm$ 36	144	565 $\pm$ 16	155 $\pm$ 24

*In this context, injury is the difference between the single dose LD_{50/30} for Co^{60} γ radiation, 735 rads, and the LD_{50/30} on a given day after the initial exposure.

†Only single doses of Co^{60} were given to the mice to determine the LD_{50/30} of the normal population.

‡S.E.

of 144 mice each which were given challenging doses of Co^{60} γ radiation on 1, 2, 4, or 8 days after the initial dose. The specific time at which a given group would receive the challenging doses was decided by a random number table.

Each group of 144 animals was divided by a random number table into six subgroups of 24 mice each which were given single-spaced doses of Co^{60} γ radiation delivered at 350 rads/min. for estimation of LD_{50/30}'s. Therefore, at each time period after the initial doses, LD_{50/30}'s were estimated from 144 exposed mice (6 doses $\times$ 24 mice/dose). It should be noted that the animals of both group I and group II were given challenging doses of Co^{60} γ radiation; the only proton doses were the initial doses to group II.

The 144 mice of group III were subdivided by a random number table into six groups of 24 mice each and given spaced single doses of Co^{60} γ radiation; these mice served as irradiated controls. The 200 mice of group IV were nonirradiated controls. Of these, 120 were sham-irradiated while the others were left undisturbed in the animal quarters.

During the 60-day postirradiation period, the animals were observed daily (including Sundays and holidays) for dead animals.

III. RESULTS AND DISCUSSION

The LD_{50/30}'s were calculated from the 30-day cumulative mortality data by probit analysis (5); these values are given in table I. After the initial exposure with either the Co^{60} γ radiation or the 55 Mev protons, there was a progressive increase in the LD_{50/30} during the 8-day recuperation period. While a rising LD_{50/30} indicates a lessening of the injury induced by the initial dose, the kinetics of the recuperation process are more satisfactorily studied by considering the differences between the irradiated control group and the group which received the initial exposures. The rationale behind this method has been described in detail by Sacher (6) and by Kallman and Silini (1).

With this convention, the difference between the LD_{50/30}'s may be considered to represent the amount of residual injury remaining at the time that the challenging exposures were given; the injury would be in units of rads of the challenging radiation. The amounts of residual injury calculated by this means are given in table I.

Figure 1 shows these results plotted on a semilog coordinate system. The curves were fitted by the method of least squares. The

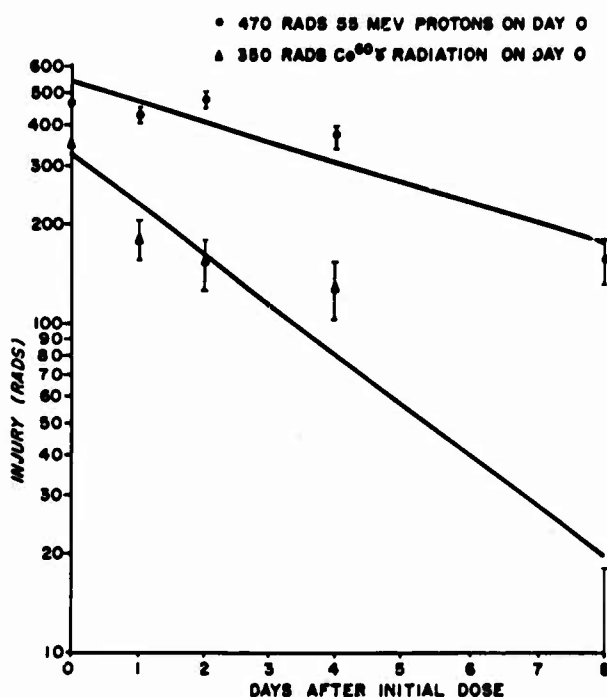


FIGURE 1

Semilog plot of injury as a function of time after the initial dose. Since logarithms are not defined for negative numbers, the -18 rads remaining at 8 days after 350 rads of Co^{60} γ radiation could not be plotted. The vertical bars indicate standard errors. The initial dose is plotted as the "zero-time" injury.

curve for the animals given an initial exposure of 470 rads of 55 Mev protons is given by:

$$Y_p = 548 (\pm 206) \exp (-.1430 \pm (.0288)) \quad (1)$$

where Y_p is the amount of residual injury (in rads) remaining at t days after the initial dose; the intercept and slope standard errors are enclosed in the parentheses. The correlation coefficient is $-.944$. Therefore, the recuperation half-time given by this curve is $4.85 \pm .85$ (S.E.) days.

The curve for the mice given an initial dose of 350 rads of Co^{60} γ radiation is given by:

$$Y_c = 327 (\pm 179) \exp (-.3422 \pm (.0490)) \quad (2)$$

The correlation coefficient is $-.9707$. The recuperation half-time given by this curve is

$2.02 \pm .45$ (S.E.) days. Comparison of the slopes of these curves by means of Student's t -test indicates a significant ($P < .01$) difference.

A great deal has been written about the value (and limitation) of the paired-dose technic for studying the kinetics of recuperation after irradiation (1, 6-11). While this technic represents at best a gross view of the recuperative process, it has been widely applied over the last two decades. The purpose of the present study was neither to add new dimensions to the paired-dose technic nor to broaden the controversy. Rather, the primary goal has been simply to compare the recuperation curves after proton and Co^{60} γ irradiation.

The use of Co^{60} γ radiation challenging exposures to evaluate the effects of another type of radiation, such as 55 Mev protons, has been used, in principle, by other workers for several years. The basic concept is that the amount of injury remaining after proton irradiation will manifest itself by a lowering of the $\text{LD}_{50/30}$ in proportion to an amount equivalent to a given number of rads of the challenging (Co^{60} γ) radiation.

The semilog plots shown in figure 1 indicate that although the recuperation half-times are significantly different (on statistical grounds) after 55 Mev protons and Co^{60} γ radiation, the results are comparable with the findings of a number of other studies (7). This interpretation assumes that recuperation following irradiation progresses in an exponential manner (5). Since a 40% larger initial dose of protons was used, this change may be a consequence of this larger dose. The results, therefore, would suggest that there does not appear to be any gross difference in the manner in which injury after 55 Mev proton irradiation is repaired as compared with the Co^{60} γ radiation.

REFERENCES

1. Kallman, R. F., and G. Silini. Recuperation from lethal injury by whole body irradiation. *Radiat. Res.* 22:622-642 (1964).
2. Williams, G. H., J. D. Hall, and I. L. Morgan. Irradiation of primates with protons. *Radiat. Res.* (In press)
3. Mitchell, J. C., G. V. Dalrymple, G. H. Williams, J. D. Hall, and I. L. Morgan. Proton depth dose dosimetry. *Radiat. Res.* (In press)
4. Dalrymple, G. V., I. R. Lindsay, J. D. Hall, J. C. Mitchell, J. J. Ghidoni, H. L. Kundel, and I. L. Morgan. The relative biological effectiveness of 138 Mev protons as compared to Co⁶⁰ gamma radiation. *Radiat. Res.* (In press)
5. Finney, J. D. Probit analysis, p. 318. Cambridge, Eng.: Cambridge University Press, 1952.
6. Sacher, G. A. Repairable and irreparable injury: A survey of the position in experiment and theory. In Clause, W. (ed.). *Radiation Biology and Medicine*, ch. 12. Boston, Mass.: Addison-Wesley, 1952.
7. Spalding, J. F., T. T. Trujillo, and W. L. Le-Stourgeon. Dependence of rate of recovery from acute gamma-ray exposure on size of the conditioning dose. *Radiat. Res.* 15:378-389 (1961).
8. Hagen, C. W., and E. L. Simmons. Effects of total body x-irradiation on rats. I. Lethal action of single, paired, and periodic exposures. Manhattan District Report (Univ. of Chicago Metallurgical Laboratory Report) CH-3815, Chicago, 1947.
9. Kohn, H. I., and R. F. Kallman. The influence of strain on acute x-ray lethality in the mouse. II. Recovery rate studies. *Radiat. Res.* 6:329-338 (1957).
10. Storer, J. B. Rate of recovery from radiation damage and its possible relationship to life shortening in mice. *Radiat. Res.* 10:180-196 (1959).
11. Blair, H. A. The constancy of repair rate and of irreparability during protracted exposure to ionizing radiation. University of Rochester Report UR-621, 1963.
12. Bradley, F. J., J. A. Watson, D. P. Doolittle, A. Brodsky, and R. B. Sutton. RBE of 440 Mev proton radiation compared to 125 kvp x-rays for LD_{50/30} of mice. *Health Phys.* 10:71-74 (1964).
13. Wang, C. C., J. Lyman, and C. A. Tobias. Relative biologic effectiveness of 730 Mev proton particles for acute lethality in mice. University of California Lawrence Radiation Laboratory Report UCRL-10211, pp. 43-49 (1962).

Unclassified

Security Classification

DOCUMENT CONTROL DATA - R&D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1 ORIGINATING ACTIVITY (Corporate author) USAF School of Aerospace Medicine Aerospace Medical Division (AFSC) Brooks Air Force Base, Texas		2a. REPORT SECURITY CLASSIFICATION Unclassified	
2b. GROUP			
3 REPORT TITLE THE KINETICS OF RECUPERATION FOLLOWING 55 MEV PROTON IRRADIATION			
4 DESCRIPTIVE NOTES (Type of report and inclusive dates) 28 Apr.-30 June 1965			
5 AUTHOR(S) (Last name, first name, initial) Dalrymple, Glenn V., Captain, MC, USAF Lindsay, Ian R., Wing Commander, RAF Mitchell, John C. Hall, James D. Morgan, Ira L.			
6. REPORT DATE Feb. 1966		7a. TOTAL NO. OF PAGES 4	7b. NO. OF REFS 13
8a. CONTRACT OR GRANT NO. AF 41(609)-2418		8a. ORIGINATOR'S REPORT NUMBER(S) SAM-TR-66-5	
b. PROJECT NO.		8b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)	
c. Task No. 775704			
d			
10. AVAILABILITY/LIMITATION NOTICES Distribution of this document is unlimited.			
11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY USAF School of Aerospace Medicine Aerospace Medical Division (AFSC) Brooks Air Force Base, Texas	
13. ABSTRACT The kinetics of recuperation following initial doses of 470 rads of 55 Mev protons and 350 rads of Co ⁶⁰ γ radiation were investigated by means of the paired-dose method. By using semilog plots, recovery half-times of $4.85 \pm .85$ days and $2.02 \pm .45$ days were found after initial doses of the protons and Co ⁶⁰ γ radiation, respectively.			

14 KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Radiobiology						
Irradiation, proton						
Protons						
Mice, irradiation						

INSTRUCTIONS

1. **ORIGINATING ACTIVITY:** Enter the name and address of the contractor, subcontractor, grantee, Department of Defense activity or other organization (*corporate author*) issuing the report.

2a. **REPORT SECURITY CLASSIFICATION:** Enter the overall security classification of the report. Indicate whether "Restricted Data" is included. Marking is to be in accordance with appropriate security regulations.

2b. **GROUP:** Automatic downgrading is specified in DoD Directive 5200.10 and Armed Forces Industrial Manual. Enter the group number. Also, when applicable, show that optional markings have been used for Group 3 and Group 4 as authorized.

3. **REPORT TITLE:** Enter the complete report title in all capital letters. Titles in all cases should be unclassified. If a meaningful title cannot be selected without classification, show title classification in all capitals in parenthesis immediately following the title.

4. **DESCRIPTIVE NOTES:** If appropriate, enter the type of report, e.g., interim, progress, summary, annual, or final. Give the inclusive dates when a specific reporting period is covered.

5. **AUTHOR(S):** Enter the name(s) of author(s) as shown on or in the report. Enter last name, first name, middle initial. If military, show rank and branch of service. The name of the principal author is an absolute minimum requirement.

6. **REPORT DATE:** Enter the date of the report as day, month, year, or month, year. If more than one date appears on the report, use date of publication.

7a. **TOTAL NUMBER OF PAGES:** The total page count should follow normal pagination procedures, i.e., enter the number of pages containing information.

7b. **NUMBER OF REFERENCES:** Enter the total number of references cited in the report.

8a. **CONTRACT OR GRANT NUMBER:** If appropriate, enter the applicable number of the contract or grant under which the report was written.

8b, 8c, & 8d. **PROJECT NUMBER:** Enter the appropriate military department identification, such as project number, subproject number, system numbers, task number, etc.

9a. **ORIGINATOR'S REPORT NUMBER(S):** Enter the official report number by which the document will be identified and controlled by the originating activity. This number must be unique to this report.

9b. **OTHER REPORT NUMBER(S):** If the report has been assigned any other report numbers (either by the originator or by the sponsor), also enter this number(s).

10. **AVAILABILITY/LIMITATION NOTICES:** Enter any limitations on further dissemination of the report, other than those

imposed by security classification, using standard statements such as:

- (1) "Qualified requesters may obtain copies of this report from DDC."
- (2) "Foreign announcement and dissemination of this report by DDC is not authorized."
- (3) "U. S. Government agencies may obtain copies of this report directly from DDC. Other qualified DDC users shall request through _____."
- (4) "U. S. military agencies may obtain copies of this report directly from DDC. Other qualified users shall request through _____."
- (5) "All distribution of this report is controlled. Qualified DDC users shall request through _____."

If the report has been furnished to the Office of Technical Services, Department of Commerce, for sale to the public, indicate this fact and enter the price, if known.

11. **SUPPLEMENTARY NOTES:** Use for additional explanatory notes.

12. **SPONSORING MILITARY ACTIVITY:** Enter the name of the Departmental project office or laboratory sponsoring (paying for) the research and development. Include address.

13. **ABSTRACT:** Enter an abstract giving a brief and factual summary of the document indicative of the report, even though it may also appear elsewhere in the body of the technical report. If additional space is required, a continuation sheet shall be attached.

It is highly desirable that the abstract of classified reports be unclassified. Each paragraph of the abstract shall end with an indication of the military security classification of the information in the paragraph, represented as (TS), (S), (C), or (U).

There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

14. **KEY WORDS:** Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context. The assignment of links, rules, and weights is optional.