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**THE EFFECT OF ORAL NEOMYCIN THERAPY
FOLLOWING WHOLE-BODY
X-IRRADIATION OF RATS**

J. B. Webster

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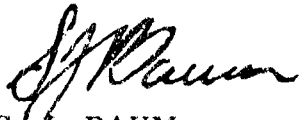
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THE EFFECT OF ORAL NEOMYCIN THERAPY FOLLOWING
WHOLE-BODY X-IRRADIATION OF RATS

J. B. WEBSTER



S. J. BAUM
Chairman
Experimental Pathology Department



J. S. BURKLE
Captain, MC, USN
Director

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
Bethesda, Maryland

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ABSTRACT

This study was designed to examine the beneficial effects of oral antibiotic treatment with neomycin following total-body X-irradiation of Sprague-Dawley rats. Survival times of irradiated, neomycin treated male rats were compared with those of irradiated, untreated controls. Eleven selected radiation exposures, beginning at 700 R and extending in increments to 2500 R, were used. Thirty-day lethality was also evaluated at and below exposures of 1100 R.

Neomycin treatment resulted in a significant prolongation of the mean survival times of irradiated animals at exposures between 800 R and 1500 R. At exposures between 1500 R and 2500 R, a small but consistent prolongation of mean survival time resulted. For exposures between 700 R and 1100 R, the 30-day lethality was consistently lower for the neomycin treated rats.

It is suggested that postradiation treatment with oral neomycin, administered every 12 hours, can effect an increase in the mean survival time of whole-body X-irradiated rats.

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I. INTRODUCTION

Much effort has been directed toward understanding the relationship between infection and radiation injury.¹ Apparently it is important to learn the effect that normally commensal, endogenous bacteria, harbored principally in the gastrointestinal system, have on the physiologically altered, irradiated animal. Work has been done on mice² to evaluate the role of bacteria in radiation sickness. This includes studies utilizing antibiotics³⁻⁷ or germfree animals.^{8,9} The effect of antibiotics on radiation sickness in rats has also been studied.^{10,11}

Although the response of germfree mice to radiation injury has been studied over large dose ranges, the effect of antibiotic therapy on response to radiation injury of conventional rodents has been generally observed over rather short dose ranges. The present study was designed to evaluate the effect of oral neomycin administered to groups of rats after exposure to lethal (LD 50/30 - LD 100/30) or supralethal (LD 100/6) doses of X-radiation. The particular antibiotic used in this study, neomycin, was chosen because of its ability to "sterilize" the enteric canal after sufficient oral administration,¹² thus placing the test rat's bacteriologic status somewhere between germfree and conventional. It was felt that a comparison of survival times of neomycin treated irradiated rats with similarly irradiated nontreated controls, over a large exposure range (starting with 700 R and extending in increments to 2500 R) would provide some additional information on the role of gastrointestinal bacteria in the postirradiation course of rats.

II. MATERIALS AND METHODS

Male Sprague-Dawley rats from the Charles River Breeding Laboratory, Inc., weighing 180-220 grams, were housed singly in wire mesh bottom cages. They were allowed food (D. N. G. Rat Food, Frederick, Maryland) and water ad libitum and were kept under these conditions for 1 or 2 weeks prior to experimental use. Five dozen unirradiated rats were used to evaluate antibiotic toxicity, and a total of 65 dozen rats were exposed to 11 selected doses of whole-body X-irradiation between 700 R and 2500 R (Table I, columns 1-3). On the day of exposure each of 20 rats was placed in a ventilated plastic box (2-3/4 x 2-3/4 x 6-1/2 inches), and transported to the radiation facility. Twenty animals were exposed simultaneously. Ten were then set aside for observation, and 10 were started on the antibiotic regimen of neomycin (described below) within 30 minutes after exposure. The latter group was considered the "treated" irradiated group as compared with the "untreated" irradiated control group.

Radiation was delivered by a 250 KVP X-ray generator (Maxitron). The physical factors of the X-ray unit during exposure were as follows: 250 KVP, 30 ma, with inherent filtration of 0.95 mm copper and 1.2 mm beryllium, HVL 1.9 mm copper, equivalent to 106 KVE. The dose rate as measured by a Victoreen dosimeter was 70.8 R/min \pm 3 percent in air. The exposure geometry was a circular slant array, 60 cm from the tube, with a field width of 12 cm and limited to \pm 4 percent variation throughout the 360° arc (Figure 1).

A neomycin solution was administered into the buccal pouch of test rats by way of a 15-gauge cannula with a blunt end. A 0.5 cc disposable syringe was used to

Table I. Survival Time Following Whole-Body X-irradiation of Neomycin Treated and Untreated Rats

Dose (R)	Group	Number of animals*	Mean survival time (hrs) Mean \pm S. D.	Standard error of mean (hrs)	Actual difference of means $\bar{X}_E - \bar{X}_C$	Percent change of control mean	p*
2500	Treated	30	95.39 \pm 12.60	\pm 2.30	+ 3.58	+ 3.90	N.S. ‡
	Untreated	30	91.81 \pm 7.42	\pm 1.35			
2300	Treated	30	98.32 \pm 11.80	\pm 2.15	+ 4.72	+ 5.04	> .05 †
	Untreated	30	93.60 \pm 8.75	\pm 1.60			
2100	Treated	30	98.52 \pm 10.20	\pm 1.86	+ 7.71	+ 8.49	< .05
	Untreated	30	90.81 \pm 6.77	\pm 1.24			
1900	Treated	30	103.00 \pm 13.94	\pm 2.54	+ 7.80	+ 8.19	< .05
	Untreated	30	95.20 \pm 8.42	\pm 1.54			
1700	Treated	30	100.40 \pm 20.94	\pm 3.82	+ 4.97	+ 5.21	N.S. ‡
	Untreated	30	95.43 \pm 8.92	\pm 1.63			
1500	Treated	30	104.05 \pm 24.57	\pm 4.48	+ 8.32	+ 8.70	> .05 †
	Untreated	30	95.72 \pm 11.02	\pm 2.01			
1300	Treated	30	139.91 \pm 55.52	\pm 10.13	+ 38.02	+ 37.31	< .001
	Untreated	30	101.89 \pm 12.13	\pm 2.21			
1100	Treated	29	203.9 \pm 74.8	\pm 13.9	+ 89.5	+ 78.26	< .001
	Untreated	27	114.4 \pm 29.1	\pm 5.6			
900	Treated	58	274.0 \pm 96.9	\pm 12.7	+ 98.3	+ 55.95	< .001
	Untreated	64	175.7 \pm 73.3	\pm 9.2			
800	Treated	24	302 \pm 124	\pm 25	+ 106	+ 54.08	< .001
	Untreated	27	196 \pm 46	\pm 9			
700	Treated	13	355 \pm 116	\pm 32	+ 55	+ 18.33	N.S. ‡
	Untreated	18	300 \pm 144	\pm 34			

* Only animals surviving <30 days are included.

† Probability by use of Student's "t" test, treated and untreated compared at each dose indicated.

‡ P = .25 - .20

§ P = .10 - .05

measure the dose. Between 0.10 and 0.15 cc of neomycin solution, containing 87 to 130 mg of neomycin sulfate, constituted a single dose. The animals readily accepted the material, which was prepared by dissolving 100 gm of micronized, unsterile, neomycin sulfate, U.S.P. (assayed 643 mg of neomycin base per gm of neomycin sulfate) in 100 cc of distilled water. Treated rats, fed the neomycin solution within 30 minutes after exposure, received a second dose in 10 ± 1 hours, and twice daily, about every 12 hours, thereafter. This regimen was continued until the demise of the animals or for a maximum of 14 days. The 60 unirradiated rats were randomly separated into two groups of 30 each, one group of which was fed the neomycin solution (described above) twice daily for 10 days. Both groups were allowed food

and water ad libitum. These 60 rats were weighed daily and observed for the appearance of diarrhea, and any other adverse response to the antibiotic.

In order to establish accurate postirradiation survival, all rats which received between 1100 R and 2500 R were observed at hourly intervals beginning on the 4th day after exposure. Rats exposed to lower doses were observed every 6 hours for 14 days, and thereafter every 12 hours through 30 days postirradiation.

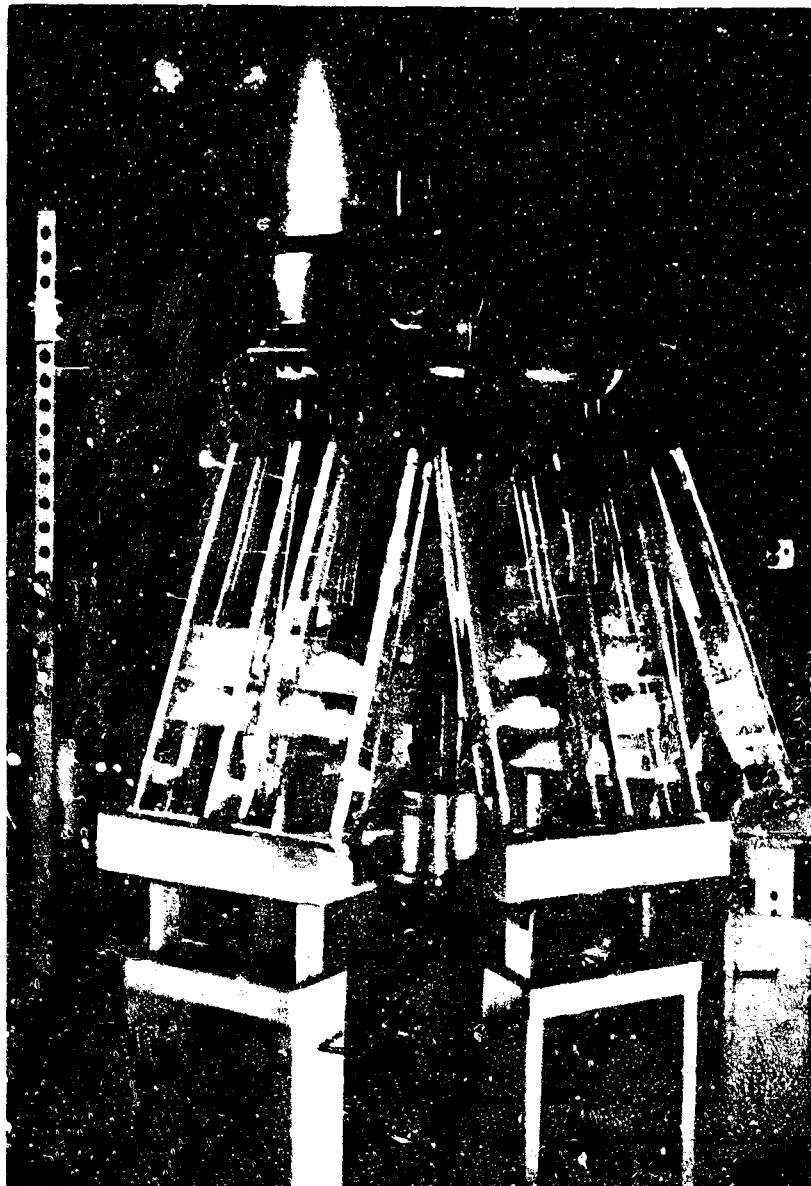


Figure 1. Maxitron exposure array

III. RESULTS

The 30 unirradiated, neomycin treated rats developed no diarrhea and the mean daily weight gain for the 10 days of treatment paralleled that of the untreated rats. Treated rats had a mean daily weight gain of 4.31 gm/rat, compared to 4.16 gm/rat for untreated rats.

Survival times of all X-irradiated, untreated rats surviving less than 30 days after exposure were tabulated and the usual acute death mean survival time versus exposure dose curve was obtained. Similar data were then tabulated for the neomycin treated rats (Table I). At exposures of 1500 R and greater, there was always an increase in the mean survival time of the treated rats when compared to the untreated rats. However, in only two of the six selected exposures in this dose range, specifically 1900 R and 2100 R, was the difference between the means of the two groups statistically significant when evaluated by Student's "t" test. Probabilities from the statistical tests are listed in Table I, column 8. Between 1300 R and 800 R the difference in mean survival times of the two groups at each exposure was much greater than at the higher doses, and at these lower doses, the differences between the means are highly significant. The difference in the mean survival times of the two groups decreased abruptly at 700 R, where this difference was again not statistically significant. In all cases, however, the mean survival time of the neomycin treated rats was longer than the mean survival time of the untreated rats (Table I, column 6). The largest increase of rat mean survival time (Table I, column 7) occurred with neomycin treatment after whole-body X-irradiation of 1100 R. Figure 2 demonstrates graphically the comparison of mean survival times of the

treated and untreated rats as a function of exposure dose of whole-body irradiation. The ranges plotted vertically are plus and minus one standard error of the mean (Table I, column 5).

Below 1100 R, acute death mean survival time was only one parameter of injury which changed. Another change occurred in the 30-day lethality (Table II) and consistently less mortality was noted among the neomycin treated rats when compared to equivalently irradiated untreated rats.

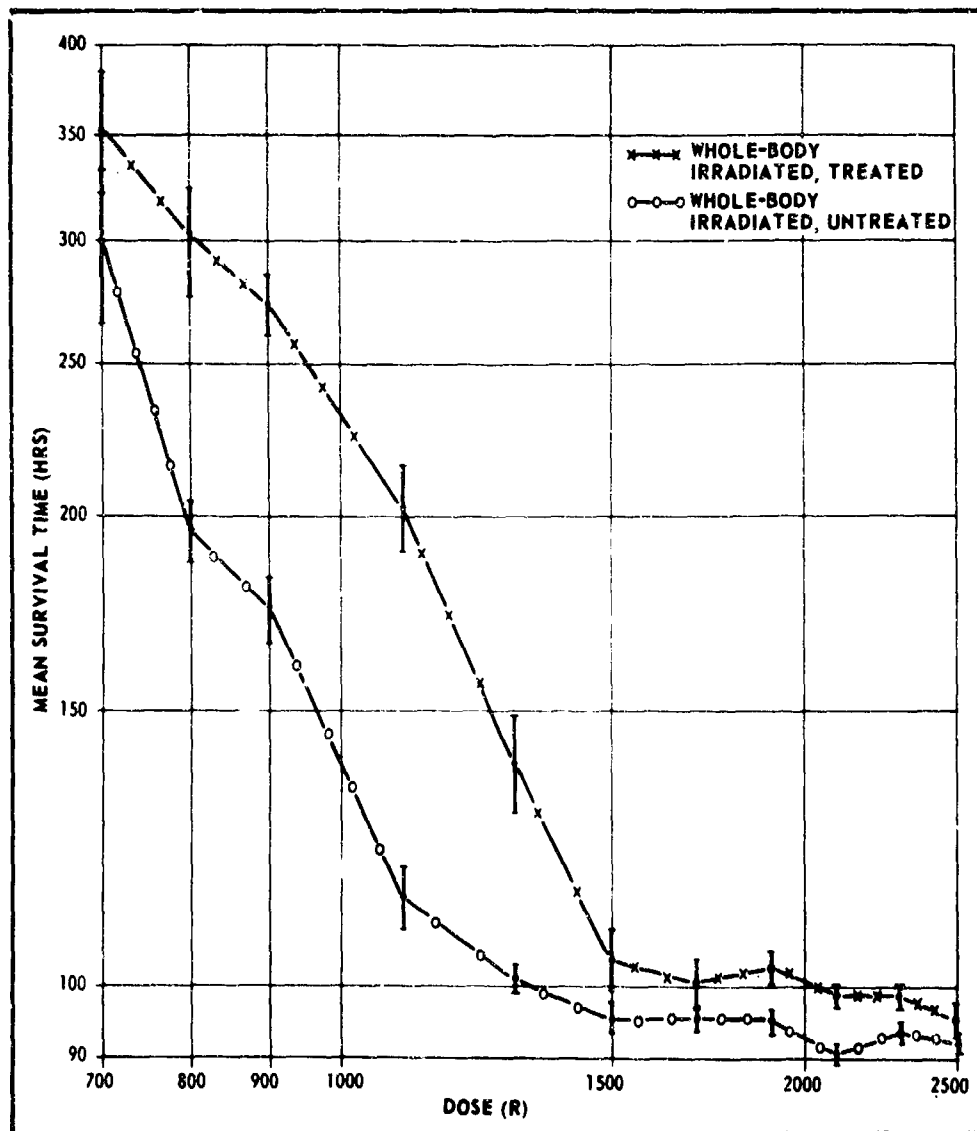


Figure 2. Comparison between mean survival time of whole-body irradiated, untreated rats and whole-body irradiated, neomycin treated rats

Table II. Lethality Following Whole-Body X-irradiation of Neomycin Treated and Untreated Rats

Dose (R)	Group	Number of animals	Number of 30-day survivors	Lethality
2500	Treated	30	0	LD 100/5
	Untreated	30	0	LD 100/5
2300	Treated	30	0	LD 100/6
	Untreated	30	0	LD 100/5
2100	Treated	30	0	LD 100/5
	Untreated	30	0	LD 100/5
1900	Treated	30	0	LD 100/6
	Untreated	30	0	LD 100/5
1700	Treated	30	0	LD 100/8
	Untreated	30	0	LD 100/5
1500	Treated	30	0	LD 100/9
	Untreated	30	0	LD 100/5
1300	Treated	30	0	LD 100/12
	Untreated	30	0	LD 100/6
1100	Treated	30	1	LD 97/30
	Untreated	27*	0	LD 100/30
900	Treated	70	11	LD 84/30
	Untreated	70	5	LD 93/30
800	Treated	40	16	LD 60/30
	Untreated	40	13	LD 68/30
700	Treated	40	27	LD 33/30
	Untreated	40	22	LD 45/30

* Records for hours of deaths were misplaced for 3 animals.

IV. DISCUSSION

The present study, planned to evaluate the effect of neomycin treatment on survival time, over a wide range of whole-body exposures, indicated prolongation of survival over this whole range. As seen in Table I, however, at the larger doses (1500 R through 2500 R) the prolongation of survival times of treated rats compared to untreated rats was quite small. Although this prolongation of survival time was not statistically significant, its constancy over a wide dose range indicates an apparent beneficial effect. Strikingly significant prolongation of mean survival times occurred for treated rats exposed in the dose range from 1100 R to 1500 R, at which doses there is known to be severe hematopoietic and significant gastrointestinal

damage. This beneficial effect of neomycin treatment, as measured by mean survival time, becomes much less significant as the exposure dose is further lowered from 1100 R to 700 R (Figure 2), but the effectiveness is reflected in the 30-day mortality. Between 1100 R and 700 R, consistently more treated rats survived 30 days than did untreated ones (Table II).

Although these findings are not in complete agreement with those of Quastler,¹³ they do support work reported by Taketa.¹¹ Early work by Quastler¹³ described the "intestinal radiation death" and laid emphasis on the role of the intestinal mucosa in this form of radiation death by accentuating the role of water and electrolyte loss, suggesting the possible role of proteolytic enzymes and other toxins, but minimizing the role of the intestinal bacteria. However, a subsequent study by Taketa¹¹ indicated that microorganisms play a prominent role in the genesis of acute intestinal death in the rat.

Further evidence for definite influence of gastrointestinal bacteria on the response to radiation injury includes the finding of a significant prolongation of mean survival time for X-irradiated germfree mice when compared to conventional controls,⁸ a prolongation of survival time when rats,^{10,11} mice,^{5,6} or dogs¹⁴⁻¹⁶ are treated with antibiotics, and rather dramatic survival of whole-body irradiated rats¹¹ and dogs¹⁷ after combined treatment including antibiotics and fluid replacement therapy or blood transfusion. For mice, well documented relationships exist between gastrointestinal epithelial cell villus transit time and the presence or absence of gastrointestinal bacteria,¹⁸ suggesting the possibility that bacteria might have a direct effect on radiation-induced intestinal injury and repair. Bacterial agents that

exist commonly in the enteric canal are frequently isolated from the blood, spleen, or lymph nodes of whole-body irradiated animals in the moribund state,^{2,7} implying a relationship between gastrointestinal bacteria and radiation limited hematopoietic defense mechanisms. Antibiotics which affect the intestinal flora may then exert an eventual beneficial effect on either or both of these radiation-injured systems.

Neomycin will, when administered orally, essentially sterilize the gastrointestinal tract,¹² yet is minimally absorbed from this route making large doses desirable. Orally administered after irradiation it theoretically removes only enteric bacteria and, therefore, appeared to be ideally suited to study the effect that the presence of enteric bacteria has on the irradiated, conventional rat. An encouraging study had been done using neomycin by gavage therapeutically for whole-body X-irradiated Wistar rats over a radiation exposure range from 325 R to 675 R.¹⁰ The study evaluated the effect of administering 10-15 mg of neomycin daily for 10-21 days and indicated that survival could occur after whole-body irradiation at levels lethal for controls, and that if survival occurred, it was related to the absence of coliform organisms in the rats' stools. The present study reinforces the evidence suggesting that microorganisms play a prominent role in the genesis of acute intestinal death in the rat.

As pointed out by Bond et al.,¹⁹ the "radiation gastrointestinal syndrome" is the generalized response to whole-body irradiation and includes the result of a combination of injury to both the hematopoietic system and the gastrointestinal system. For animals exhibiting the radiation gastrointestinal syndrome, the postirradiation survival time may well be determined by the result of the combined injury, rather

than by the gastrointestinal injury alone. In the present study, because there are two parameters changing (i. e., the 30-day lethality and the acute death mean survival time), it is difficult to interpret the overall beneficial effect of treatment with oral neomycin after radiation exposures which do not result in 100 percent lethality within 30 days. Although the beneficial effect of oral neomycin is small for exposures at and above 1500 R, postirradiation treatment with this agent at lower exposures appears to cause an increase in survival time of whole-body irradiated rats, perhaps by delaying bacterial overgrowth during a time of severe hematopoietic depression.

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International Atomic Energy Agency, Kaernstrasse 11, Vienna I. 1010, Austria (1)

Dr. L. G. Lajtha, Paterson Laboratories, Christie Hospital and Holt Radium Inst., Manchester, England (1)

Dr. L. F. Lamerton, Biophysics Department, Institute of Cancer Research, Surrey Branch, Belmont, Sutton, Surrey, England (1)

Dr. Helmut Mitschrich, Akademie des Sanitaets-und Gesundheits, Wessau BW, Spezialstau ATTN: 8 Muenchen, Schwere-Reiterstr. 4, Germany (2)

Puerto Rico Nuclear Center, ATTN: Reading Room, College Station, Mayaguez, Puerto Rico 00708 (2)

Directorate of Medical and Health Services, FAF (Federal Armed Forces), Bonn, Ermekeilstr. 27, West Germany (1)

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13 ABSTRACT <p>This study was designed to examine the beneficial effects of oral antibiotic treatment with neomycin following total-body X-irradiation of Sprague-Dawley rats. Survival times of irradiated, neomycin treated male rats were compared with those of irradiated, untreated controls. Eleven selected radiation exposures, beginning at 700 R and extending in increments to 2500 R, were used. Thirty-day lethality was so evaluated at and below exposures of 1100 R. Neomycin treatment resulted in a significant prolongation of the mean survival times of irradiated animals at exposures between 800 R and 1500 R. At exposures between 1500 R and 2500 R, a small but consistent prolongation of mean survival time resulted. For exposures between 700 R and 1100 R, the 30-day lethality was consistently lower for the neomycin treated rats. It is suggested that postradiation treatment with oral neomycin, administered every 12 hours, can effect an increase in the mean survival time of whole-body X-irradiated rats.</p>		

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