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DISCLAIMER

Sublethal damage repair: Is it independent of radiation quality?†

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Running head: Repair after fast neutrons

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1. Introduction

The high relative biological effectiveness (RBE) for single-dose cell killing offered by fast neutrons in comparison with x- or γ-rays is one important consideration in particle radiotherapy for cancer treatment. Sublethal radiation damage and repair are important factors that could significantly affect the overall RBE when dose fractionation is used.

Repair of sublethal damage after x-rays (Elkind and Sutton, 1959, 1960) has been repeatedly demonstrated (Elkind and Whitmore, 1967) and is generally expected to be associated with low linear energy transfer (LET) radiations. This is not the case with fast neutrons. The survival curve for cells exposed to fast neutrons exhibits a shoulder, whose absolute size, while dependent on neutron energy, is always smaller than that due to low-LET radiations (Broerse et al., 1967; Hall et al., 1975a and b; Ngo et al., 1977). This observation may indicate that, in general, cell killing due to accumulation of sublethal damage is less after neutron radiation than after low-LET radiation, although the degree to which this view should be qualified because of LET-dependent changes in age-response patterns has not been worked out. Nonetheless, the presence of a shoulder on a survival curve due to neutron irradiation does not always mean that a two-dose survival increase will be observed. Using split-dose, or fractionated dose techniques, some experiments have shown positive evidence of fractionation survival increases (Hornsey and Silini, 1962; Broerse and Barendsen, 1969; Bewley et al., 1965; Masuda, 1968; Hall et al., 1975b); others have shown insignificant or essentially no survival increases

(Schneider and Whitmore, 1963; Hornsey et al., 1965; Nias et al., 1971; Evans et al., 1971; Durand and Olive, 1977). The differences may be attributed to: (1) physical factors such as the neutron energy spectrum, the dose magnitude, and the temperature during the recovery periods; or (2) biological factors such as cell or tissue differences. At a molecular level, it is a possibility that the sublethal lesions caused by low- and high-LET radiations are not entirely the same. A combination of these factors, of course, cannot be ruled out.

In this paper we examine this problem by inquiring if differences in neutron energy spectra, and therefore differences in LET distribution, may affect the outcome of two-dose measurements.

2. Theory

A survival curve may be expressed as follows (e.g., Elkind, 1975)

$$S = e^{-aD} M(D); \qquad (1)$$

this is often referred to as modified single-hit, multitarget inactivation. Equation (1) indicates that the surviving fraction S is reduced as a result of two distinct inactivation processes. The first factor, e^{-aD}, where D is the dose and a is a constant, frequently referred to as the "single-hit" component, indicates that the survival decrement from each increment of dose is constant. The second factor, M(D), which stands for damage accumulation inactivation, indicates that each increment of dose becomes successively more effective in reducing survival. Analyses of survival curve shape by Hall (1974) and Chapman et al. (1977) suggested to them that in equation (1) a is LET dependent, increasing with LET for LET's less than a maximally effective value, and that the factor M(D) is LET independent.

according to Hall and Chapman,
Hence, the initial steepness of a survival curve increases with LET, but at
independent of LET
a given dose survival is further reduced by a constant factor due to damage accumulation. Consequently, other things remaining the same, for a given total dose, dose fractionation should result in the same relative survival increase, whereas at the same surviving fraction dose fractionation should increase net survival by a smaller factor for high-LET radiations than for low-LET radiations. This point was noted by Rossi (1976), who expressed M(D) in equation (1) by e^{-bD^2} where b was assumed to be independent of LET for LET's up to approximately a maximally effective value. Thus, in Rossi's analysis, a linear-quadratic dose-effect relationship (Sinclair, 1966; Kellerer and Rossi, 1972; Chadwick and Leenhouts, 1973) was used.

In this paper we analyze single and fractionation dose data to see whether the foregoing predictions are borne out.

3. Methods and materials

Cell culture procedure. V79-AL162 Chinese hamster cells, attached in polystyrene plastic flasks (25 cm^2), were exponentially grown at 37°C in a humid atmosphere of air containing 2% CO_2, for approximately 40 hours prior to radiation. A modified Eagle's Minimum Essential Medium, supplemented with 15% fetal calf serum (Stanners et al., 1971) was used for cell growth and survival assay. Under these conditions, the average cell generation time was ~9 hours.

About one hour before exposures, flasks containing attached cells were completely filled with growth medium and transported to the respective radiation facilities. The plating efficiency and radioresponse to

x-rays and neutrons were not affected by these handling procedures, as shown by appropriate control experiments (unpublished data). Incubation for repair between two fractionated doses was carried out by immersing the cooled flasks into a water bath preadjusted to 37°C. When the radiations were completed, samples were transported in ice to the cell culture laboratory at Argonne where the cells were trypsinized for the colony-forming assay with no further delay. The post-irradiation ice storage, the longest being one hour for the samples irradiated with neutrons at the Fermi Lab, was used to minimize any possible repair of potentially lethal damage (PLD), which might occur if room temperature had been used. A one-hour storage in ice did not cause significant expression of potentially lethal damage (Hall et al., 1976; Ngo, unpublished). Either repair or expression of PLD would complicate the interpretation of our data. Control samples were similarly treated. Usually three dishes were used for each dose point, and six for the controls.

Neutron sources. Neutrons at the Fermi National Accelerator Laboratory were produced by bombarding a thick beryllium target with 66 MeV protons extracted from the linear accelerator at the facility. The energy spectrum of this beam was broad with a mean value of 25 MeV. Fission-spectrum neutrons were produced at the JANUS Reactor at the Argonne National Laboratory and have a comparatively narrower energy distribution with a mean energy of 0.86 MeV. The LET distributions and other physical characteristics of the two neutron beams are available (Amols et al., 1977; Borak and Stinchcomb, 1978).

Irradiation procedure. At the JANUS Reactor, flasks were located vertically in air; cells were exposed to the direct neutron flux through the polystyrene surfaces to which they were attached and to scattered neutrons through the medium contained in the flask.

At the Fermi Lab, cells were irradiated with neutrons in a water phantom at 2-cm depth, which corresponds to the position of maximum dose rate (Amols et al., 1977).

Dosimetry was performed prior to each experiment with ionization chambers made with Shonka tissue-equivalent plastic walls placed at the position of the cell layer. This was done independently by the Physics Group at each facility. Neutron dosimetry at the Fermi Lab was cross checked with activation analysis of aluminim disks for each exposure. The disks were placed next to the polystyrene wall to which cells were attached during irradiation. The dose rate was 10 to 28 rad/min for the Fermi Lab neutrons and 37.8 rad/min for the JANUS neutrons.

For x-irradiation, flasks were placed on a horizontally rotating bakelite base. Cells were irradiated in flasks from above, with a GE Maxitron unit, through a polystyrene wall and the medium contained in the flasks. The unit was operated at 250 kVp, 30 mA with a half value layer equal to 1.10 mm Cu. The dose rate at the cell layer, measured with a Victoreen dosimeter, was approximately 118 rad/min.

4. Results

To facilitate a comparison of the repair of sublethal damage for the two neutron beams as well as for x-rays, we irradiated cells with single or equally-split doses. All the second doses were administered after 2.75 hrs during which interval the temperature was maintained at 37°C. The results are shown in Figure 1. The open symbols show the surviving fraction for cells exposed to single doses of a given radiation quality, and the corresponding closed symbols show the response to split doses.

For radiation qualities for which dose fractionation results in an increase in net survival, it is known that the magnitude of the survival increase depends upon the size of the individual doses for a given total dose (Elkind, 1967). Further, it can be shown that in general for a given total dose the ratio of two-dose survival is a maximum when equal first and second doses are used (Dienes, 1971). As a consequence, a split dose survival curve would be expected to be continuously curved (semilog coordinates) even if the single-dose curve has a straight line terminal region. Hence, to facilitate a quantitative comparison of single and split-dose survival curves, we adopt for this analysis the survival expression,

$$S = \exp(-aD - bD^2), \qquad (2)$$

in order that the coefficients a and b may be evaluated for both cases.

It is evident in Fig. 1, that split doses result in net increases in survival except for JANUS fission-spectrum neutrons. Further to document the absence of two-dose survival increases in the case of JANUS neutrons, in Fig. 2 we show the results of a more conventional dose fractionation experiment. For the fractionation data, even though the first dose surpasses the shoulder, after two hours the fractionation survival curve lies superimposed on the remainder of the single-dose curve. This is in accord with the implications of the split-dose results for JANUS neutrons in Fig. 1 and two-dose data already published (Ngo et al., 1977b) in which intervals up to 5 hrs were used.

The survival curves shown in Fig. 1 were obtained by a least-square fit of the data points to equation (2) (see Acknowledgments). The linear and quadratic coefficients, a and b, for the single and split-dose survival curves are given in Table 1. The relative magnitude of two-dose survival increases can be determined by taking the ratio of the surviving fraction after a split-dose exposure to that after an equal single dose. This ratio

is given by

$$S_2/S_1 = \exp\,[-\,(a_2 - a_1)D - (b_2 - b_1)D^2] \qquad (3)$$

where the subscripts 1 and 2 denote single and split doses, respectively. Thus, by inserting the appropriate coefficients for each radiation quality given in Table 1, we are able to obtain the ratio of surviving fractions for a given set of data.

Figure 3 shows the computed ratios, equation (3), as a function of the single-dose surviving fraction for x-rays, Fermi Lab neutrons, and JANUS neutrons. It is evident that two-dose survival increases are largest for x-rays, less for Fermilab neutrons, and essentially not detectable for JANUS neutrons. Figure 4 depicts these ratios, as a function of total dose for the three different radiations. These curves show that after x-rays and after Fermilab neutrons cells appear able to repair radiation damage to approximately the same degree. However, once again little if any survival increase is observed after JANUS neutrons.

5. Discussions and conclusions

The fractionation results for JANUS neutrons in Figs. 1 and 2 show no increase in survival for the dose-fractionation schemes applied in these experiments despite the evident, although small, shoulder associated with the single-dose survival curve. This is consistent with the results of our previous split-dose experiments (Ngo et al., 1977b). A qualitatively similar result with fractionated doses of JANUS neutrons was recently reported for the C3H mouse cell line designated 10T1/2 (Han and Elkind, 1979). Similarly, a lack of survival increase was reported when hybrid mice were exposed to fractionated

doses of JANUS neutrons and survival of femoral colony forming units or intestinal microcolonies was assayed (Grahn et al., 1972). Thus, for JANUS fission-spectrum neutrons, fairly generally, two-dose survival increases are not observed when relatively short time intervals are used.

It should be pointed out, however, that the lack of a two-dose increase in survival after a high LET radiation does not necessarily mean that no non-lethal lesions are produced in cells. Using either JANUS or Fermi Lab neutrons, followed by x-rays, we have demonstrated that a significant amount of neutron-induced damage, which acts like sublethal x-ray damage, is repaired within 2-3 hrs (Ngo, Han, and Elkind, 1977). Pertinent to this, it was recently reported that high-LET charged particles also produce a qualitatively similar type of damage (Ngo, Blakely, and Tobias, 1978). Hence, while it is possible that the rates of repair of sublethal damage may depend upon LET when the damage persisting from a first dose is assessed by using a second dose of the same radiation quality, the fact that neutron-induced sublethal damage with which x-ray damage interacts is rapidly repaired, and about equally as fast for both Fermi and JANUS neutrons suggests that repair processes as such are not differentially affected by the two neutron beams.

Two further points could compromise the interpretation of our results. Since these experiments were performed with asynchronous cells, we consider the possibility that the partial synchronization resulting from the first doses could have varied with radiation quality in such a way that the split-dose survival increases for JANUS neutrons, relative to Fermi neutrons or x-rays, would have been obscured. Although the age-response variations for

V79 cells have not been measured for Fermi neutrons, from the measurements of Sinclair (1966, 1969) we may compare JANUS neutron with x-ray survival variations through the cycle of V79 cells. Sinclair's results show that for equal doses, JANUS neutrons compared to x-rays produce larger fluctuations in survival; although at the same survival, the reverse is true. However, in both cases, late S cells are the most resistant. Since, as a consequence of partial synchronization, the low-LET fractionation response of V79 cells reflects primarily repair in late S (e.g., see Sinclair, 1966, 1969, and Elkind and Sinclair, 1965), we cannot attribute the results in Fig. 4 to partial synchronizations induced by the first doses which are qualitatively different for these radiations. In fact, for the same dose, the synchronization would be more complete after JANUS neutrons compared to x-rays.

The second point concerns possible LET-dependent effects on the rates of aging of cells surviving first doses. It is known that the fluctuations in 2-dose x-ray survival observed when asynchronous populations of V79 cells are exposed reflect the concomitant processes of repair of sublethal damage and the aging of cells which survive the first dose (Elkind and Sinclair, 1965). Further, the x-ray 2-dose survival variation of synchronized late S cells shows that a delay in aging, in addition to a delay in division, is induced by the first dose (e.g., Sinclair, 1969). In spite of this delay, survivors initially in late S become inherently more sensitive to a second dose as they leave S and enter the G_2 phase. Hence, the combined effect of partial synchronization, followed by sublethal damage repair accompanied by aging in the cell cycle, is that 2-dose survival rises to a maximum and then drops to a minimum.

Detailed studies along the foregoing lines have not as yet been performed with JANUS neutrons. Nevertheless, since we know that for these neutrons the RBE for division delay is larger than for survival (Ngo et al., 1977b), at the same dose we would expect the delay in aging for neutrons to be greater than it is for x-rays, other things being equal. Consequently, we would further expect that, after the same dose, the sensitization due to progression into G_2 to proceed more slowly for first-dose neutron survivors than for first-dose x-ray survivors. Hence, if anything, we would expect a differential effect on aging to increase the maximum in 2-dose survival and to shift it to later times, for JANUS neutrons compared to x-rays, if repair rates and extents are equal.

The data in Figs. 1 and 3 demonstrate differences between all three qualities of radiation. In contrast, Figs. 1 and 4 show that, while x-rays and Fermi neutrons do not appear to be significantly different, JANUS neutrons differ from them both. A common feature in the analyses of Hall (1974) and Chapman et al. (1977), and the inferences made by Rossi (1976), is that the damage accumulation factor in the single-dose survival equation--i.e., $M(D)$ in equation (1) or $\exp(-bD^2)$ in equation (2)--is independent of radiation quality. As the data in Table 1 indicate, we do not find this to be the case. Moreover, from the results of Sinclair (1969), for JANUS neutrons relative to x-rays, we would not expect this to be true at least for asynchronous cells. As we noted, Sinclair found that for the same dose of either radiation the age-response patterns of V79 cells, while of similar shapes, have survival fluctuations that are appreciably more pronounced for JANUS neutrons than for x-rays. Clearly, this implied that the damage accumulation term, as in equations (1) or (2), cannot be independent of radiation quality for all ages of cells since for these radiations at the same dose the decrement in survival

resulting from it does not vary with cell age in the same way. Although Gillespie et al. (1975) have concluded to the contrary, an alternate possibility is that the "single-hit" term could be age dependent from which the implications follow that, through the cycle, either the targets or their repair change as a function of LET. Evidence in support of the possibility that so-called "single-hit" killing can involve repair processes has already been presented (Ngo et al., 1978; Utsumi and Elkind, 1979).

Aside from the influence of LET on cell-age responses, our fractionation data do not support the notion that the dose dependence of damage accumulation is independent of radiation quality. Hence, in addition to the fact that both a and b in equation (2) increase with LET (Fig. 1 and Table 1), we find that V79 cells appear to be deficient in their ability to repair sublethal damage due to JANUS neutrons, or at least their rate of repair is much slower than for the other radiations. Consequently, it is possible that the repair of sublethal damage is independent of radiation quality but that only the rate (and possibly other factors such as radiation-induced differences in aging) is LET dependent. But even if this qualification should prove to be correct, at the least it would follow that survival relationships, such as equations (1) and (2), and inferences derived therefrom, are not adequate to predict the influence of LET on the manner in which net survival depends on dose fractionation.

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Table 1

Survival Curve Parameters* for the Data in Figure 1 Fitted by Equation (2).

RADIATION	EXPOSURES	$\frac{a_1 \cdot 10^3,\ rad^{-1}}{a_2 \cdot 10^3,\ rad^{-1}}$	a_2/a_1	$\frac{b_1 \cdot 10^6,\ rad^{-2}}{b_2 \cdot 10^6,\ rad^{-2}}$	b_2/b_1
250 kvp	Single dose	1.80 (0.98)**	1.06 (0.87)	2.61 (0.70)	0.49 (0.25)
X-rays	Split dose	1.92 (0.78)		1.29 (0.56)	
Fermilab	Single dose	3.51 (0.56)	1.02 (0.55)	4.08 (0.60)	0.70 (0.36)
Neutrons	Split dose	3.59 (1.50)		2.84 (1.44)	
JANUS	Single dose	6.13 (1.33)	1.01 (0.35)	14.3 (2.44)	0.98 (0.27)
Neutrons	Split dose	6.21 (1.69)		14.0 (3.08)	

*Subscript 1 refers to single dose survival curves; subscript 2 to split-dose survival curves. The ratios of the coefficients show that dose fractionation probably does not affect the initial slope of any of the curves nor the rate of curvature of the JANUS neutron survival curve.

**Numbers in parentheses are the ± 95% confidence limits.

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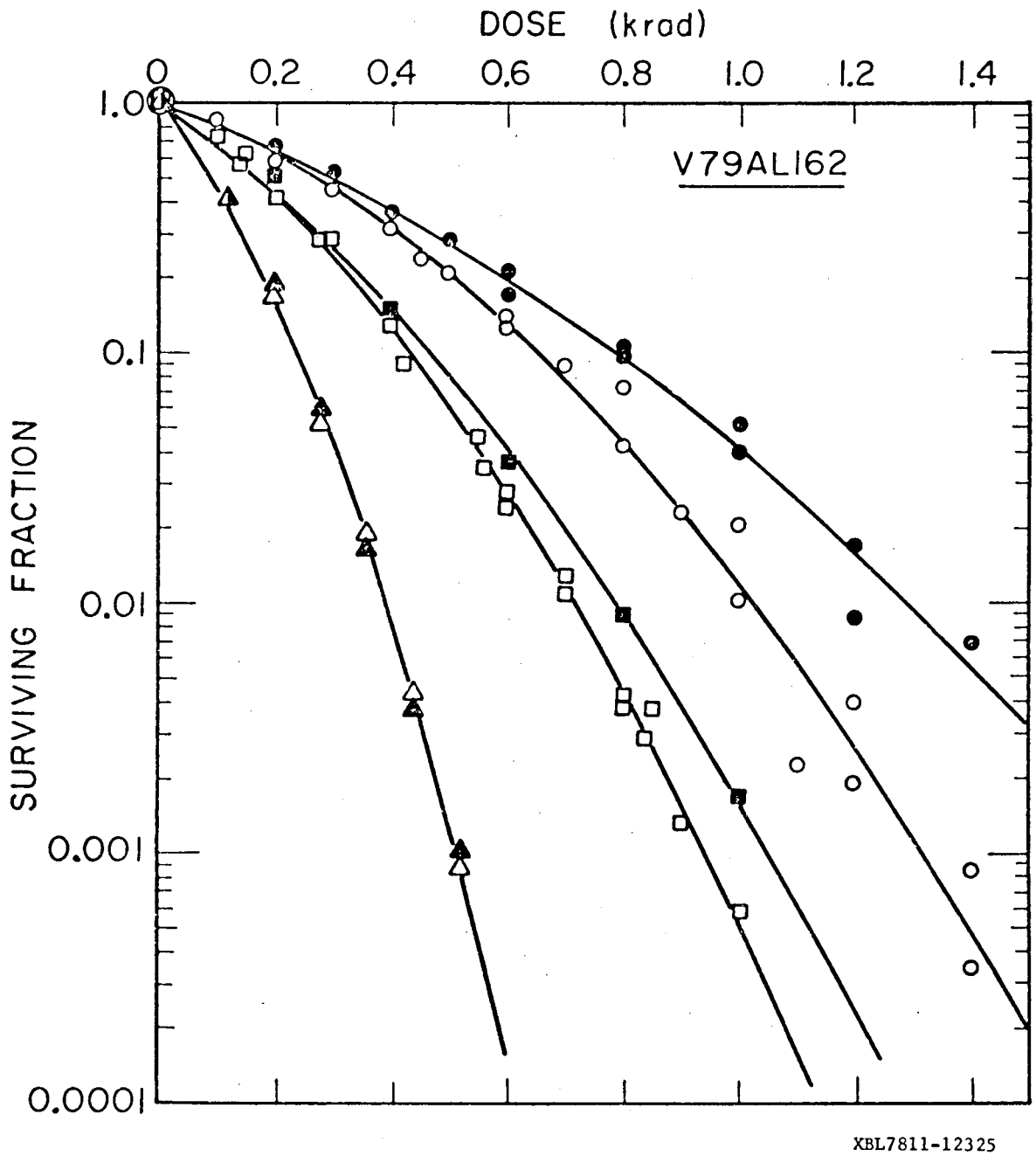
FIGURE LEGENDS

Figure 1 - Survival data of V79 Chinese hamster cells exposed to x-rays (O, ●), Fermilab neutrons (□ , ■), or JANUS neutrons (△ , ▲). Open symbols represent single doses, closed symbols equal-size split doses delivered at 2.75-hour intervals, during which the cells were kept at 37°C. The data for x-rays and single-dose Fermilab neutrons come from several experiments. The survival curves are least-square fits to the data points based upon equation (2).

Figure 2 - Survival data of Chinese hamster cells irradiated with single or fractionated doses of the JANUS fission-spectrum neutrons. P.E. denotes the plating efficiency; $\overline{N}$ is the average cell multiplicity when cells were plated for colony formation. Error bars, standard errors, are indicated where these are larger than the symbols used.

Figure 3 - Split-dose to single dose ratios of surviving fractions for the data in Fig. 1 determined by computation using equation (3) and the values for a and b in Table 1. The ratios are plotted as a function of surviving fraction.

Figure 4 - Plots of split-dose to single dose ratios of surviving fractions determined as for Fig. 3 except that the ratios are plotted as a function of total dose.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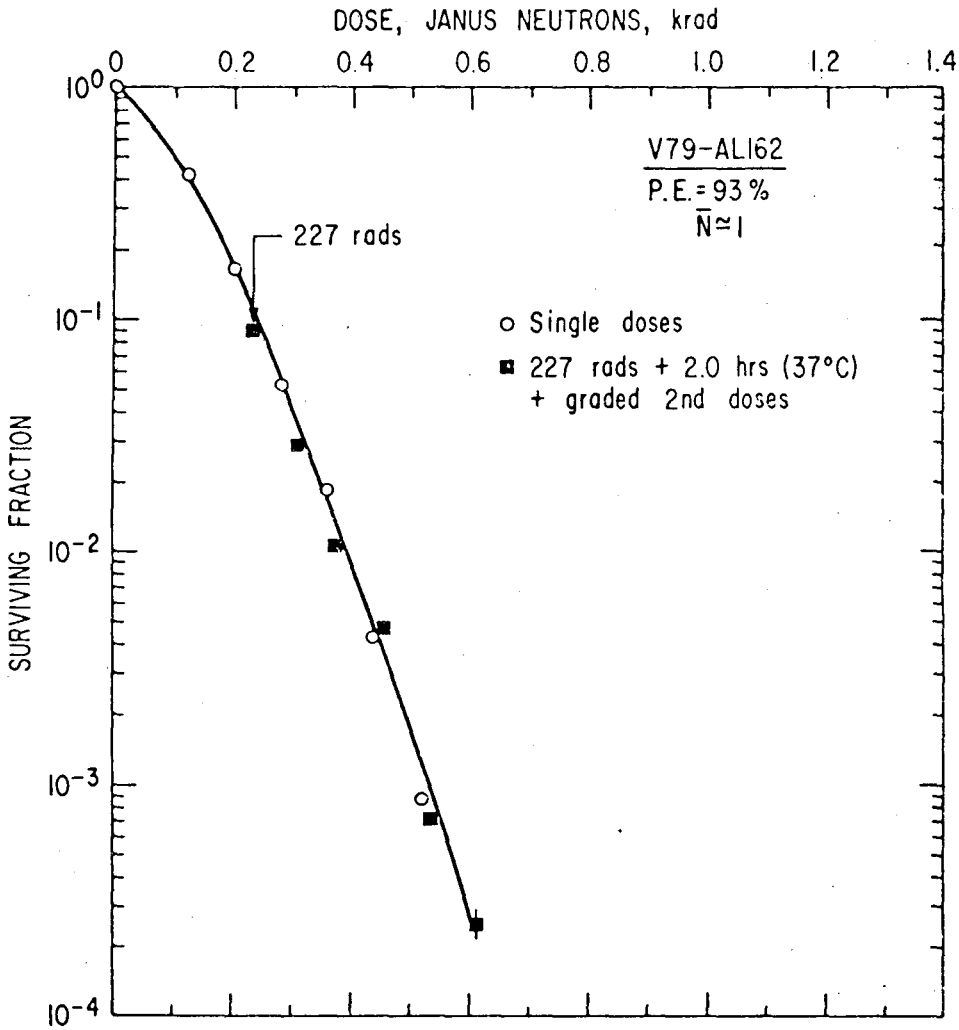
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SURVIVING FRACTION
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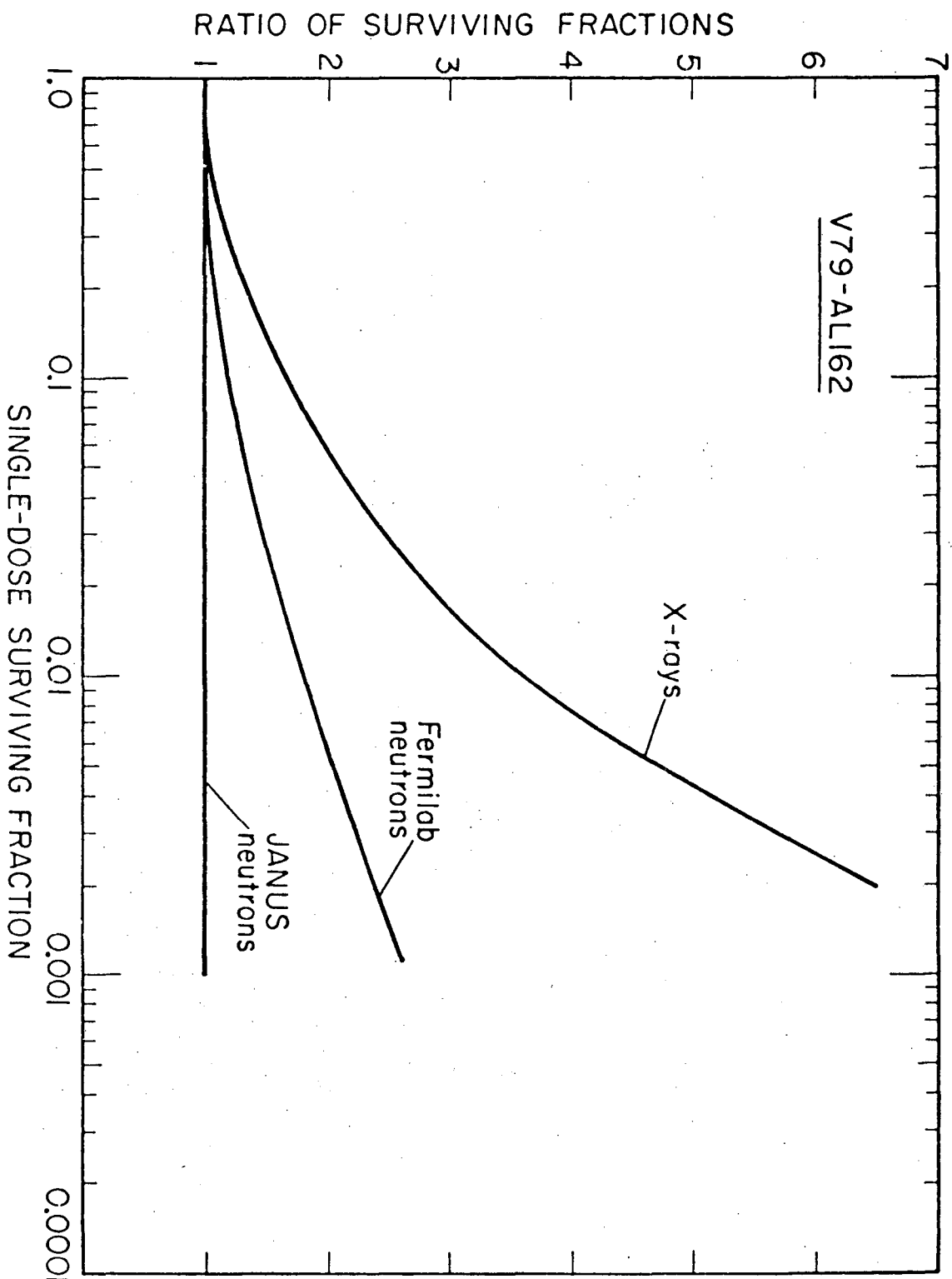
Single doses
227 rads + 2.0 hrs (37°C)
+ graded 2nd doses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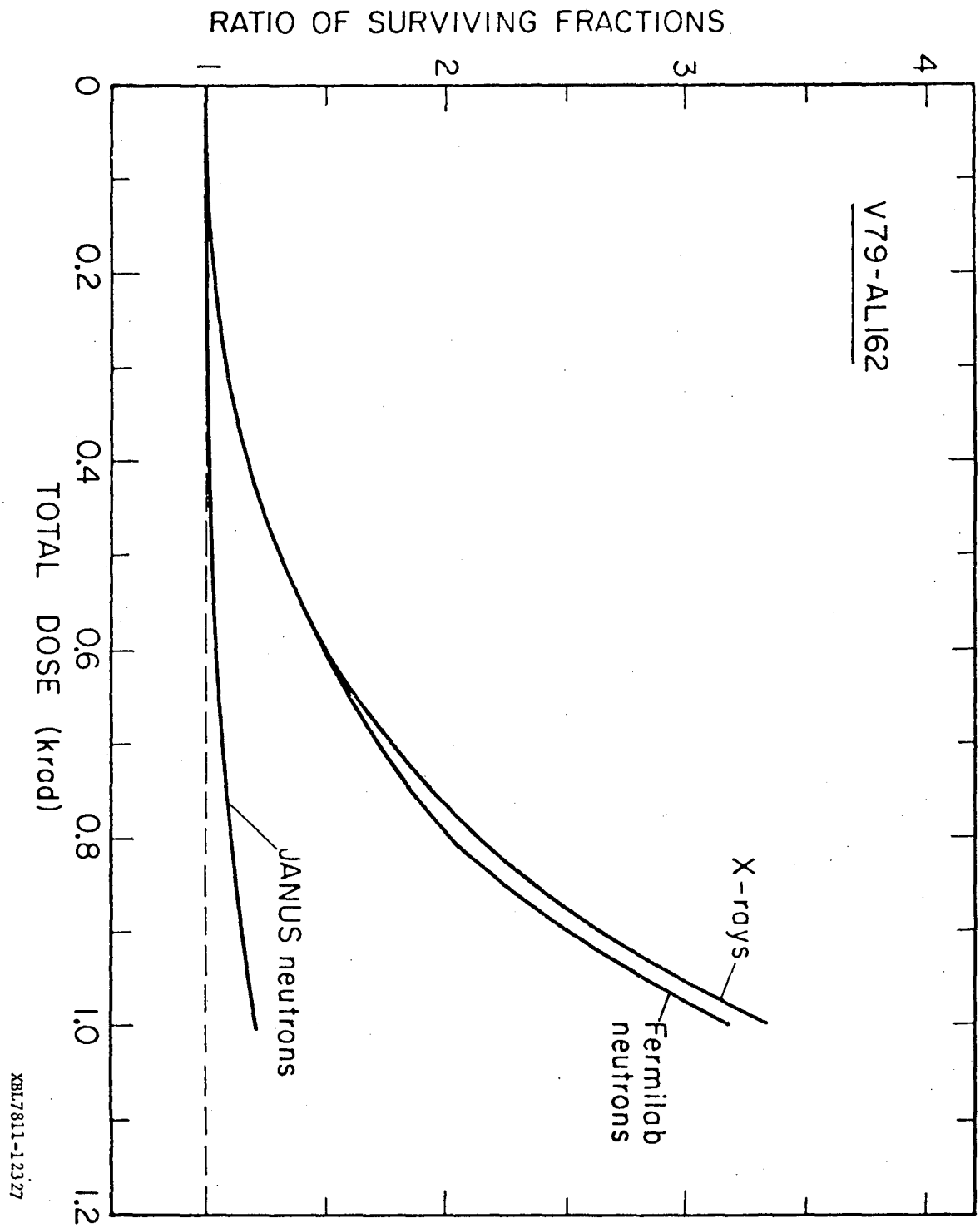
SINGLE-DOSE SURVIVING FRACTION
V79-AL162
X-rays
Fermilab neutrons
JANUS neutrons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0.6
0.8
1.0
1.2
TOTAL DOSE (krad)
JANUS neutrons
X-rays
Fermilab neutrons
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