LBL-31298

Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

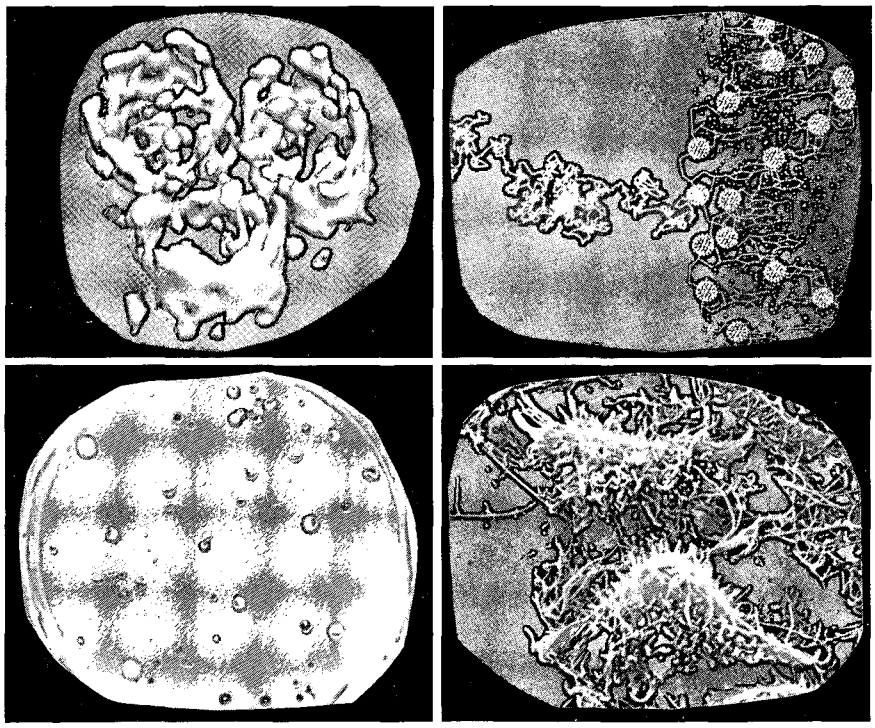
CELL & MOLECULAR BIOLOGY DIVISION

Presented at the Commission of the European Communities Workshop
on Biophysical Modelling of Radiation Effects, Padua, Italy,
September 2–5, 1991; and to be published in the Proceedings

Application of the LPL Model to Mixed Radiations

S.B. Curtis

September 1991



Prepared for the U.S. Department of Energy under Contract Number DE-AC03-76SF00098

DISCLAIMER

LBL-31298

APPLICATION OF THE LPL MODEL TO MIXED RADIATIONS

Stanley B. Curtis

Cell and Molecular Biology Division
Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720, USA

This work was supported by the Office of Health and Environmental Research of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

Application of the LPL Model to Mixed Radiations

Stanley B. Curtis

Lawrence Berkeley Laboratory, University of California, Berkeley,
California 94720 , U.S.A.

ABSTRACT: The LPL (Lethal, Potentially Lethal) formulation was used to analyze sets of cell survival data from mixes of (1) alpha particles and X rays and (2) neon ions and X rays. The hypothesis tested was whether survival after mixed radiation could be predicted by simply adding the total number of *lethal* and *potentially lethal* lesions from each radiation in the theoretical survival expression. Results show that all data appear to conform satisfactorily to the LPL hypothesis except for the mixed neon-ion and X-ray results with a large dose of X rays (8 Gy) given first.

1. INTRODUCTION

An important aspect of evaluating the hypotheses underlying a theoretical treatment of radiobiological action is to apply the theory to analyze experimental data sets obtained in conditions under which radiations of different qualities are mixed with each other in well-defined ways. One of the goals of the present Workshop was to test various models and theories by applying them to the analysis of such mixed radiation survival curves. This paper deals with the application of the Lethal, Potentially Lethal (LPL) theoretical formulation (Curtis 1986) to the analysis of survival curves after mixed high and low LET radiation. The data chosen were a mixed alpha-particle and X-ray set (Barendsen *et al.* 1960), another mixed alpha-particle and X-ray set which includes both aerobic and hypoxic survival data (Raju and Jett 1974), and a set of mixed neon-ion and X-ray survival data (Ngo *et al.* 1981).

2. THE HYPOTHESES OF LPL THEORY

LPL theory has been described in some detail in previous publications (Curtis 1986, 1987, 1988). The important hypotheses are presented here:

1. Two major types of lesions are formed by radiation: irreparable and repairable. These lesions could be DNA double-strand breaks of different severity. Irreparable lesions are formed in a manner proportional to absorbed dose, with proportionality constant η_L.

2. Repairable lesions are formed in (at least) two classes, distinguishable by their rates of repair: one slowly repairing (with mean repair rate ε_{PL}), one rapidly repairing

(with repair rate ε'_{PL}). Each is formed in a manner proportional to absorbed dose with proportionality constants η_{PL} for the slowly repairing lesions and η'_{PL} for the rapidly repairing lesions. One explicit suggestion for the differences in the repair rates is that the slowly repairing lesions occur in the linker DNA between nucleosomes and the rapidly repairing lesions occur in the DNA bound to the nucleosomes (Curtis 1988).

3. Rapidly repairing breaks are not usually expressed as they are normally repaired with high fidelity. They are expressed, however, if the cell is placed in hypertonic saline solution soon after irradiation before being repaired. Such lesions will not be considered further in the present treatment.

4. Slowly repairing breaks can undergo "binary misrepair", i.e., can rejoin with a "wrong" part of the DNA, thus leading to cell lethality. This process proceeds with a rate ε_{2PL}.

With the above hypotheses, the following two kinetic differential equations describe the time rate of change of the mean values per cell of the lethal lesions, n_L, and potentially lethal lesions, n_{PL}:

$$\frac{d\, n_{PL}(t)}{d\, t} = -\varepsilon_{PL} n_{PL}(t) - \varepsilon_{2PL} n_{PL}^2(t) \qquad (1)$$

$$\frac{d\, n_L(t)}{d\, t} = \varepsilon_{2PL} n_{PL}^2(t) \qquad (2)$$

with initial conditions:

$$n_L(0) = \eta_L D$$

$$n_{PL}(0) = \eta_{PL} D.$$

Assuming a Poisson distribution for the number of lethal lesions per cell:

$$S = \exp\,[-n_{TOT}(t_r)] = \exp\,[-n_L(t_r) - n_{PL}(t_r)] \qquad (3)$$

where t_r is the available repair time.

Substituting the solutions for $n_L(t_r)$ and $n_{PL}(t_r)$ (Curtis 1988), we obtain

$$S = \exp\left\{ -(\eta_L D + \eta_{PL} D) + \varepsilon \ln \left\{ 1 + \frac{\eta_{PL} D}{\varepsilon} \left[1 - \exp(-\varepsilon_{PL}\, t_r) \right] \right\} \right\} \qquad (4)$$

with $\varepsilon \equiv \dfrac{\varepsilon_{PL}}{\varepsilon_{2PL}}$.

3. MIXED RADIATIONS

For a mixture of radiation, the theory would predict that the number of both lethal and potentially lethal lesions from each type of radiation can be simply added as follows:

Table I

	Barendsen	Raju and Jett		Ngo *et al.*
		Aerobic	Hypoxic	
Particles	α	α	α	neon ions
LET (keV/μm)	170	210	210	183
z^{*2}/β^2	3052	3980	3980	1549
σ_0 (μm^2)	45	27	27	45
F_{PL}	0.1	0.1	0.1	0.1
n	12	12	12	12
k_0	2.5E-04	2.5E-04	1.7E-04	2.5E-04
		X ray Radiation		
η_L (Gy^{-1})	0.2531	0.0767	0.0402	0.1313
η_{PL} (Gy^{-1})	0.8792	1.0	0.4177	0.7711
ε	10	10	10	10

$$-\ln S = (\eta_{lo}D_{lo}+\eta_{hi}D_{hi}) - \varepsilon \ln \left[1 + \frac{\eta_{lo,PL}D_{lo}+\eta_{hi,PL}D_{hi}}{\varepsilon} T\right] \quad (5)$$

D_{lo} and D_{hi} are the doses from the low and high LET components, respectively.

Here $\eta_{lo} = \eta_L+\eta_{PL}$ for low LET radiation (6)

$$\eta_{hi} = \frac{k}{L}(\sigma_L+\sigma_{PL}) \quad (7)$$

$$\eta_{hi,PL} = \frac{k}{L}\sigma_{PL} \quad (8)$$

with L the LET of the high LET beam, and

$$\sigma_L = \sigma_0\left\{1 - \left[e^{-k_0 z^{*2}/\beta^2}(1 + k_0 z^{*2}/\beta^2)\right]^n\right\} \quad (9)$$

$$\sigma_{PL} = F_{PL}\sigma_0 n k_0 z^{*2}/\beta^2 e^{-k_0 z^{*2}/\beta^2} \quad (10)$$

$T = (1 - e^{-\varepsilon_{PL} t_r})$, and has been set equal to unity in this analysis.

3.1 ^{210}Po Alpha Particles and X rays (Barendsen *et al.* 1960)

The alpha particle source used in this experiment was ^{210}Po with the initial alpha energy of 3.4 MeV. The average LET within the cell nuclei was calculated by the authors to be 170 keV/μm. The values of the parameters used for the calculations are given in Table I. Values for σ_0, k_0, F_{PL} and n were taken from an analysis of alpha particle data in Barendsen *et al.* (1966), made in Curtis (1986). The values of η_L and η_{PL} used for the X-ray curve were obtained by setting ε equal to 10 and using the fitting program FIT vrs. 2.00 developed by Norman Albright. The results are shown in Fig. 1 for X-rays alone, alpha particles alone, and mixtures of 0.5 and 1 Gy of alpha

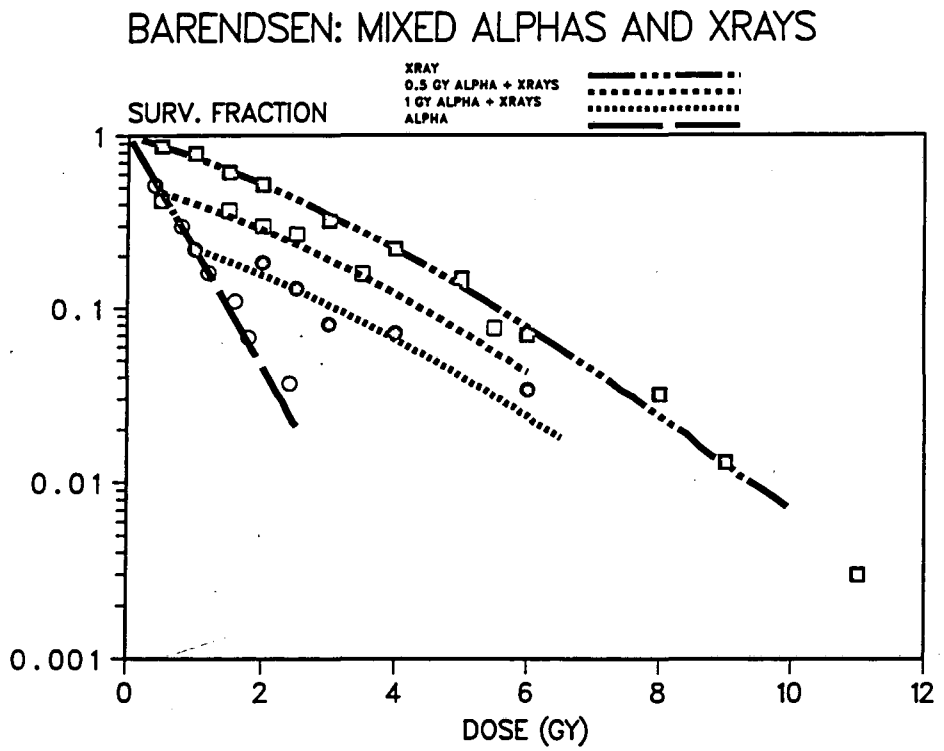


Fig. 1. Comparison of experimental cell survival data with theoretical predictions of LPL theory for mixed ^{210}Po alpha particles and X rays (Barendsen *et al.* 1960). Theoretical curves and data are for X rays alone, 0.5 Gy of alphas plus X rays, 1 Gy of alphas plus X rays and alphas alone. Parameter fitting was made only to obtain the pure alpha particle and X-ray curves.

particles with various doses of X rays. The lines are obtained by using eq. 5 with the values of the parameters from Table I.

3.2 ^{239}Pu Alpha Particles and X rays (Raju and Jett 1974)

In this experiment, a ^{239}Pu alpha particle source was used. The alpha particles of initial energy 5.1 MeV were degraded through air or nitrogen to 2.9 MeV at the cell surface. The cells although attached to plastic dishes were irradiated in an inverted position and the cell nuclei were considered to be 6 to 7 μm thick (M. R. Raju, private communication). The average LET was not determined by the authors but was considerably higher than in the above ^{210}Po experiments. A good fit to the alpha particle-only survival data was obtained by assuming an *average* LET of 210 keV/μm and a cross section of 27 μm^2 for the area of the radiosensitive material. The other parameters were held the same as for the ^{210}Po experiment except that k_0 was adjusted for the hypoxic experiment to that found in the previous analysis of the alpha particle data (Curtis 1986). The values of the parameters used are given in Table I. Fig. 2 gives a comparison of the experimental data for aerobic cells with the calculated curves for mixtures of 0, 11%, 45%, 64%, and 100% alpha particles. Fig. 3 presents the results for the hypoxic cells irradiated with the same alpha particle admixtures.

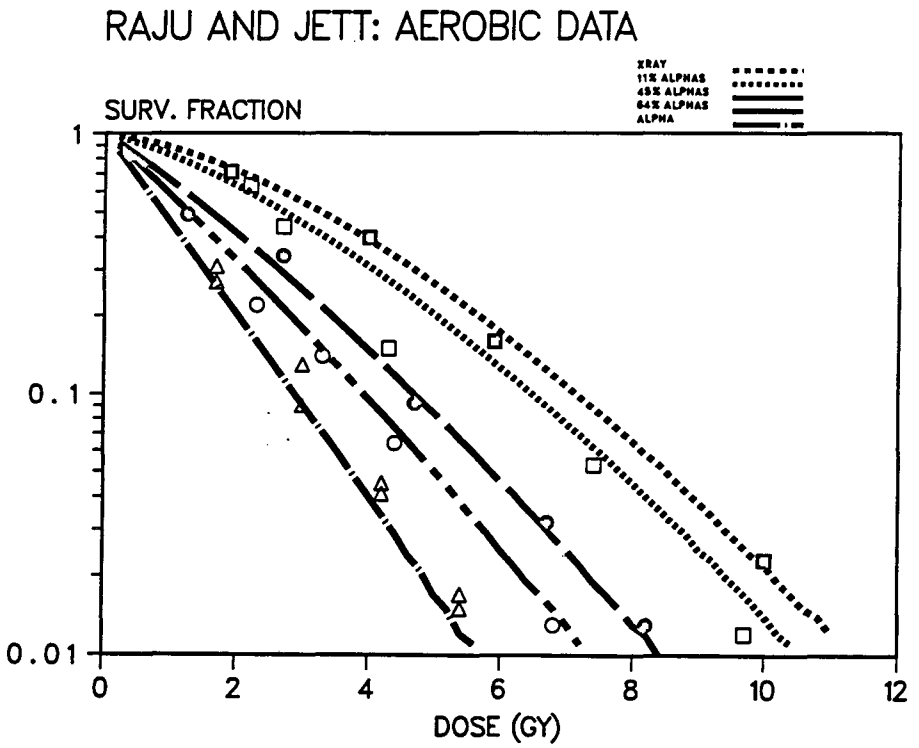


Fig. 2. Comparison of experimental *aerobic* cell survival data with theoretical predictions of LPL theory for mixed ^{239}Pu alpha particles and X rays (Raju and Jett 1974). Theoretical curves and data are for X rays alone, 11%, 45%, 64%, and 100% alpha particle admixtures. Parameter fitting was made only to obtain the pure alpha particle and X-ray curves.

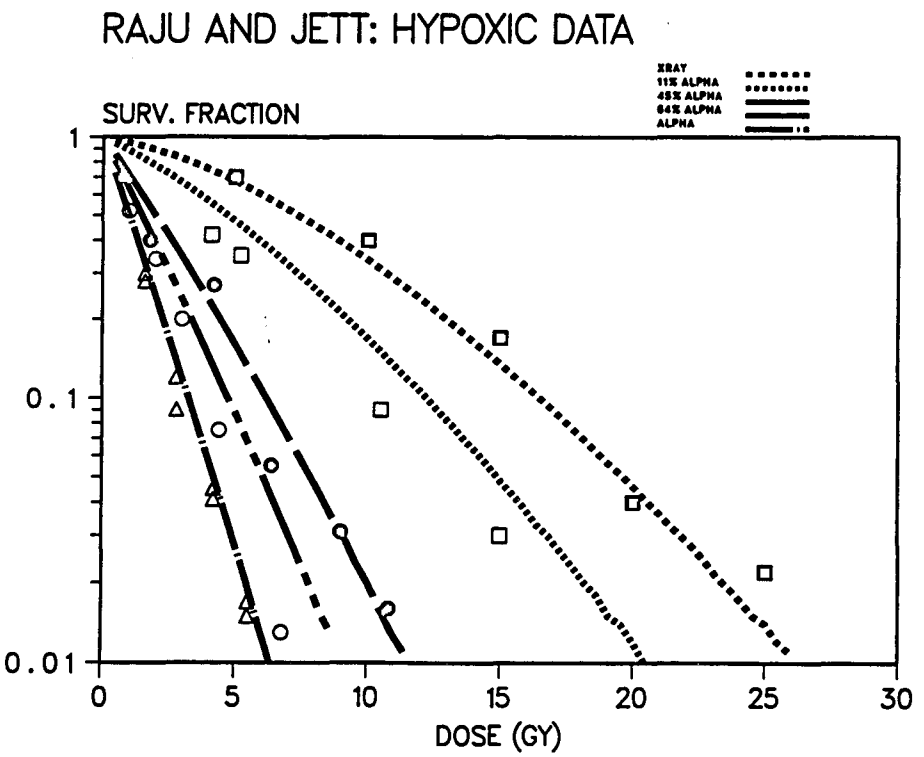


Fig. 3. Comparison of experimental *hypoxic* cell survival data with theoretical predictions of LPL theory for mixed ^{239}Pu alpha particles and X rays (Barendsen *et al.* 1960). Theoretical curves and data are for X rays alone, 11%, 45%, 64%. and 100% alpha particle admixtures. Parameter fitting was made only to obtain the pure alpha particle and X-ray curves.

3.3 Neon ions and X rays (Ngo *et al.* 1981).

The experiments with mixes of neon ions and X rays were performed with a neon ion beam near the Bragg peak region of the depth-dose curve, where the LET averaged over a track segment of 500 μm was stated to be 183 keV/μm. Using this value and returning the other charged particle parameter values to those used in the ^{210}Po alpha particle studies (see Table I), the neon ion survival curve given in Fig. 4 was obtained. The curve fitting code FIT yielded the η values given in Table I for the X ray curve also shown in Fig. 4.

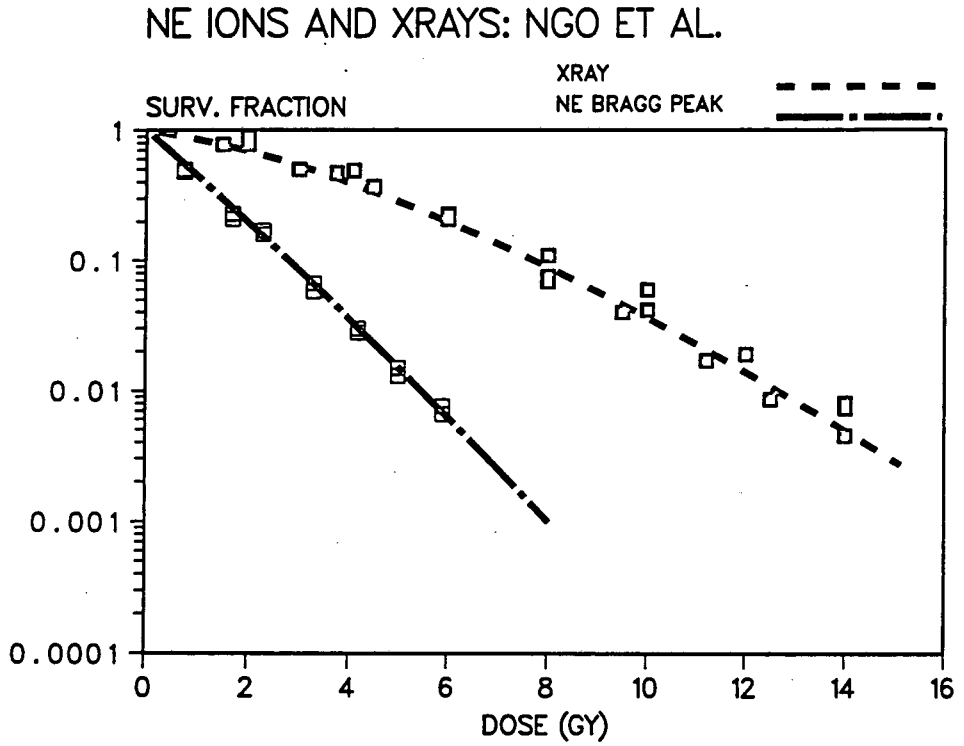


Fig. 4. Comparison of experimental cell survival data with theoretical predictions of LPL theory for the pure neon ion beam and X rays (Ngo *et al.* 1981). Parameters were obtained as described in the text.

In these experiments, the difference in sequence of irradiation was studied: irradiating with a priming dose of X rays, followed by neon ions, was compared with irradiating with a priming dose of neon ions, followed by X rays. Differences were found experimentally between the two sequences, with the *X ray-first* irradiations giving *lower* survival than the reverse sequence. From inspection of eq. 5, it is evident that the sequence is immaterial to the theoretical prediction, i.e., the theory in its present form does not predict a survival level that depends on which radiation is given first.

Comparison of the theoretical predictions with the experimental data obtained from a priming dose of 0.94, 2.36, 3.3, and 4.13 Gy of neon ions followed by a graded series of X-ray doses is shown in Fig. 5. A similar comparison from a priming dose of 0, 5, or 8 Gy of X rays followed by a graded series of neon ion doses is shown in Fig. 6. We note the discrepancy alluded to above particularly between the data and the theoretical prediction in the high dose (8 Gy) X-ray priming dose situation (the bottom curve in Fig. 6).

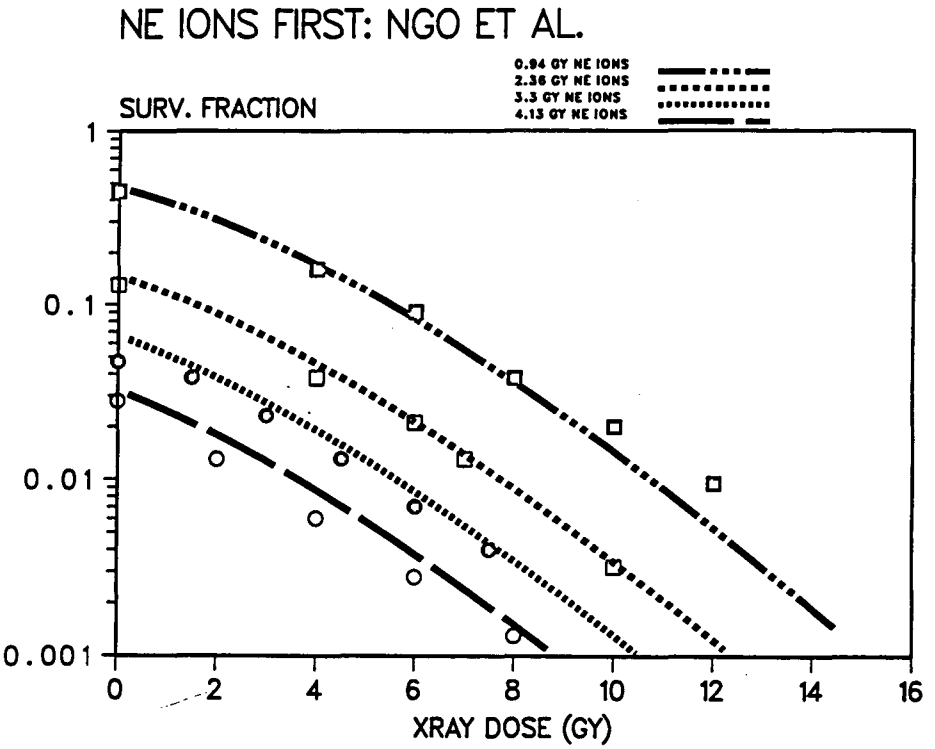


Fig. 5. Comparison of experimental cell survival data with theoretical predictions of LPL theory for mixtures of neon ions and X rays with the *neon ions given first* (Ngo *et al.* 1981). Theoretical curves and data are for priming (initial) doses of neon ions of 0.94, 2.36, 3.3, and 4.13 Gy.

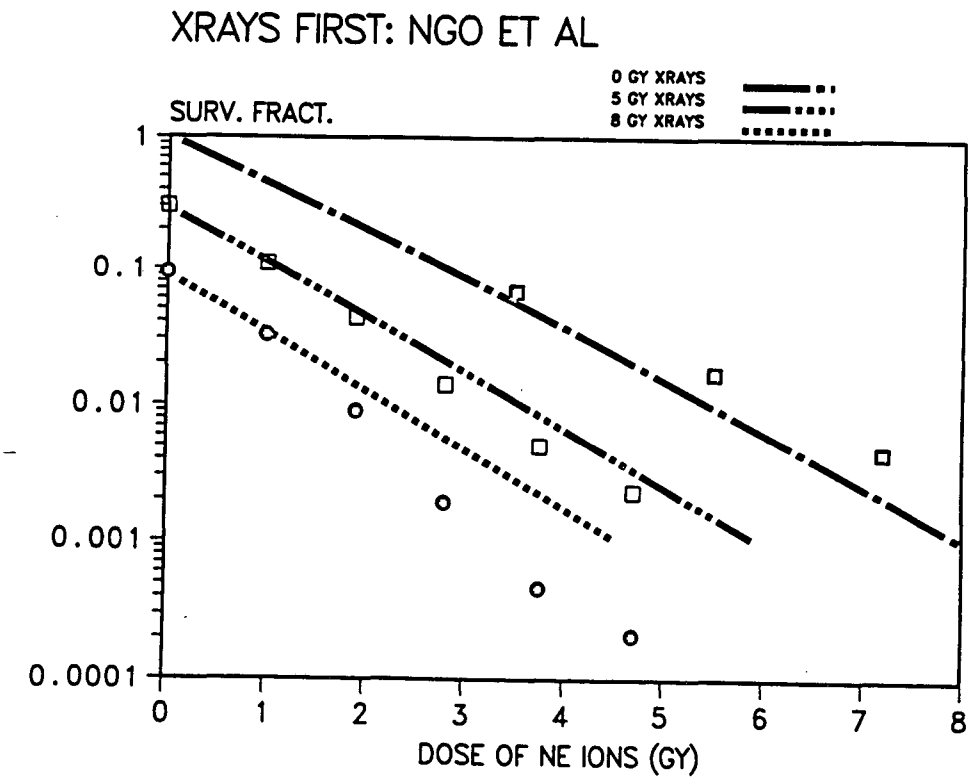


Fig. 6. Comparison of experimental cell survival data with theoretical predictions of LPL theory for mixtures of X rays and neon ions with the *X rays given first* (Ngo *et al.* 1981). Theoretical curves and data are for priming (initial) doses of X rays of 0, 5 and 8 Gy.

4. CONCLUSIONS

The LPL theoretical formulation hypothesizes that both high and low LET radiation produce lesions which can either be repaired correctly or can "interact" with each other to form a lethal lesion. The probabilities of lesion production as expressed by the inactivation cross sections vary as a function of LET, and in the present treatment, the z^{*2}/β^2 parameter is assumed to be a better descriptor of radiation quality than LET. This idea is very similar to that behind the suggestion of using restricted LET (L_{100}) (Harder *et al.* 1988) or primary ionization mean free path (Watt *et al.* 1985) as a such a descriptor. The more rapidly rising cross section for lethal lesions than for potentially lethal lesions causes the increase in survival curve slope as the LET increases. The assumption is made, however, that *potentially lethal* lesions produced by the high LET component can interact with similar lesions produced by the low LET component, thus providing a synergistic effect to the extent shown in the predicted curves. The success with which this hypothesis holds is shown by the extent to which the predictions match the experimental data in Figs. 1 through 6. It is concluded that the theoretical predictions compare favorably with the experimental data and the hypothesis holds, at least for the data sets chosen. The exception is that the difference in response depending on radiation sequence is not predicted by the theory. This is seen most strikingly in the lack of concordance between theory and experiment in Fig. 6. We are not aware, however, of any theory which addresses this dependence on radiation sequence.

In conclusion, the LPL theoretical treatment appears to predict with reasonable accuracy the interactive effects between high-LET charged particle radiation and X rays.

5. ACKNOWLEDGMENTS

It is a pleasure to acknowledge the help of Tennessee Gock-Yuan in the preparation of this manuscript. This work was supported by the Office of Health and Environmental Research of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

6. REFERENCES

Barendsen G W, Beusker T L J, Vergroesen A J and Budke L 1960 *Radiat. Res.* **13** 841

Curtis S B 1986 *Radiat. Res.* **106** 252

Curtis S B 1987 *Proc. 8th Int. Cong. of Radiat. Res.* eds E M Fielden, J F Fowler, J H Hendry and D Scott (New York: Taylor & Francis) pp 312-317

Curtis S B 1988 *Quantitative Mathematical Models in Radiation Biology* ed J Kiefer (Berlin, Heidelberg: Springer-Verlag) pp 137-148

Harder, D, Blohm R and Kessler M 1988 *Radiat. Res.* **23** 79

Ngo F Q H, Blakely E A and Tobias C A 1981 *Radiat. Res.* **87** 59

Raju M R and Jett J H 1974 *Radiat. Res.* **60** 473

Watt, D E, Al-Affan A M, Chen, C Z, Thomas, G E 1985 *Radiat. Prot. Dosimetry* **13** 285

LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA
INFORMATION RESOURCES DEPARTMENT
BERKELEY, CALIFORNIA 94720