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RBE-Dose Relations for Neutrons and Pions

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RBE-Dose Relations for Neutrons and Pions

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Abstract
RBE-Dose relations have been calculated from cellular radiosensitivity parameters and theoretical particle-energy spectra in tissue, of the secondary particles from neutron and negative pion irradiations. The theoretical results are compared with clinical and radiobiological data for normal tissue, tumors, and cells in culture. Formulae for calculation, cellular parameters, and the needed properties of equivalent "track-segment bombardments" are given, for several mammalian cells irradiated with pions and with neutrons of several energies.

1. Introduction

From the algorithms of the theory of track structure RBE-Dose relations have been calculated for neutrons of several different energies, and the results compared with clinical data, to good effect. The results here achieved may be reproduced from a simple formula, based on the concept of an "equivalent track segment bombardment." The consistency of these calculations with observed values of the RBE, for neutrons of several energies, and for normal tissue, tumors, and cells in culture, suggests their application to treatment planning with neutrons of all energies and with negative pions.

2. The cellular radiosensitivity parameters

The radiosensitivity parameters used in the present investigation were fitted visually to survival data for cells of various types, human kidney (Todd 1967), HeLa (Deering and Rice 1962; Nias, Greene, Fox, and Thomas 1967), Chinese hamster (Skarsgard, Kihlman, Parker, Pujara, and Richardson 1967), murine leukemia (Berry 1970), and mouse bone marrow (Broerse, Engels, LeLieveld, van Putten, Duncan, Greene, Massey, Gilbert, Hendry, and Howard 1971). A preliminary statistical evaluation of the radiosensitivity parameters yields an uncertainty (95% confidence limit) of about 15% in the parameters for aerobically irradiated kidney, HeLa, and hamster cells, where the survival data were obtained with X-rays and several HILAC bombardments. The data are less complete for the anoxic irradiation of these cells, with a corresponding increase in the parameters' uncertainties. Parameters for leukemia cells are from a more limited range of cyclotron bombardments. Parameters for bone marrow cells are for CA and BD cells irradiated at Manchester with γ-rays and neutrons, and are not representative of other bone marrow data reported in the same paper. Our calculations have been made from all of these parameters, for completeness, for the available mammalian cell data are quite limited. The cellular parameters are listed in Table 1, together with the values of the characteristic properties of the equivalent irradiations for several neutron and pion fields. Except for mouse bone marrow cells, the parameters have been reported earlier (Katz and Sharma 1973).

Table 1. Cellular radiosensitivity parameters for mammalian cells and "equivalent irradiations" for neutrons and pions.

Cell		Parameters				n energy (MeV)								MRC		Pion stars	
						0.5		1.0		2.0		14					
		m	κ	$E_0 \times 10^{-4}$ (erg cm–3)	$\sigma_0 \times 10^{-7}$ (cm2)	L†	P	L†	P	L†	P	L†	P	L†	P	L†	P
Hamster	O_2	2.5	1400	1.9	4.6	4.53	0.651	5.99	0.489	5.40	0.300	15.3	0.235	10.5	0.196	13.4	0.146
HeLa	N_2	3.0	1100	3.7	5.6	4.62	0.707	5.99	0.526	5.44	0.323	15.4	0.243	10.5	0.205	13.5	0.158
	O_2	3.0	750	1.4	5.6	4.81	0.840	5.95	0.650	5.34	0.430	12.6	0.273	8.48	0.249	11.2	0.206
Kidney	N_2	2.5	1300	4.6	6.7	4.59	0.682	5.97	0.510	5.38	0.317	14.8	0.240	10.0	0.204	12.9	0.154
	O_2	2.5	1000	1.7	6.7	4.72	0.774	5.95	0.592	5.32	0.385	12.9	0.261	8.68	0.232	11.4	0.185
Leukemia	N_2	2.5	2100	3.5	5.8	4.25	0.493	6.07	0.378	5.45	0.219	18.2	0.206	13.1	0.163	16.0	0.106
	O_2	2.5	1750	1.5	5.8	4.38	0.564	6.03	0.426	5.43	0.252	16.9	0.218	11.8	0.177	14.8	0.123
Bone marrow	O_2	2.5	500	0.91	4.2	4.94	0.945	5.85	0.801	4.97	0.601	8.29	0.325	5.32	0.332	7.99	0.278

† L stands for LET∞ × 10^{-2} (MeV g^{-1} cm^2)

As indicated elsewhere (Katz and Sharma 1974a), the four radiosensitivity parameters are m and E_0, the extrapolation number and the extrapolated D-37 dose of the survival curve after γ-irradiation, σ_0, the plateau value of the inactivation cross-section for heavy ion bombardment where $z^2/4\beta^2 = \kappa$, when cells are bombarded with heavy ion beams of different effective charge number z, when the ions move at a speed of $v = \beta c$ where c is the velocity of light.

3. Comparison of theory and experiment

A recent study of the survival of Chinese hamster ovary cells, after sequential exposure to 14 MeV neutrons and γ-rays (Railton, Porter, Lawson, and Hannan 1974), provides a test of the theory of cell survival in a mixed radiation environment (Katz and Sharma, 1974b). The survival curves measured with CHO cells match those calculated with kidney cell parameters (in the absence of CHO parameters) with sufficient accuracy for kidney parameters to be used to represent the radiosensitivity of CHO cells. The calculated values of the RBE and OER (at 10% survival) are in excellent agreement with measured values, as the fraction of the dose delivered as γ-rays ranges from 0 to 1.

Experimental values of the RBE as a function of the neutron dose have been measured at neutron energies of 0.43, 1.8, and 14 MeV, with cataract formation in mice as the end-point (Bateman, Rossi, Kellerer, Robinson, and Bond 1972). For comparison with these data, RBE-Dose relationships are calculated for 0.5, 2.0, and 14 MeV neutrons, using theoretical secondary particle-energy spectra in tissue (Caswell and Coyne 1972, 1973), with the results shown in Figures 1–3. The large uncertainties in the clinical data do not permit the selection of a "best set "of radiosensitivity parameters to represent cataract formation, but the calculations agree with the data to the precision of the data.

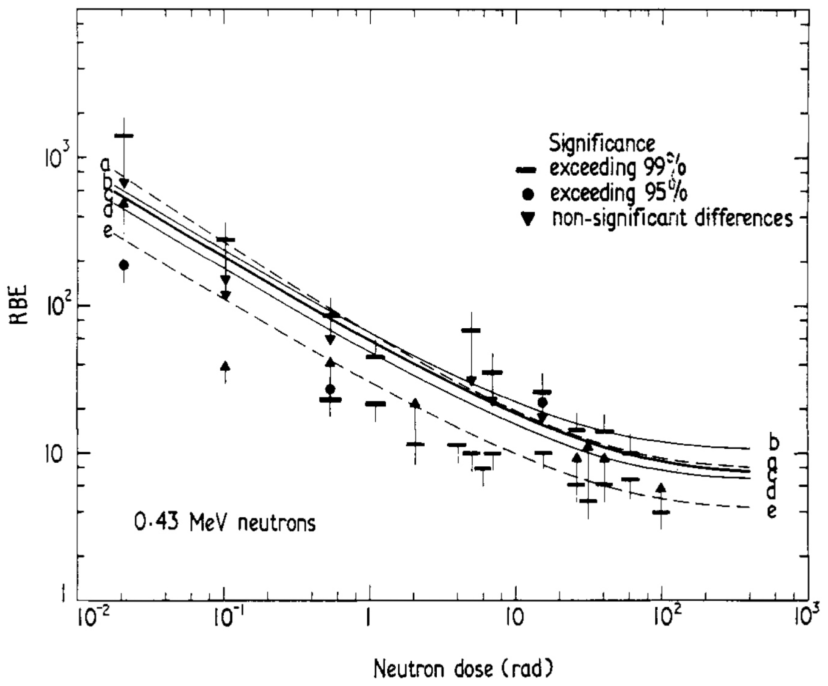

Figure 1. RBE-Dose relations for 0.43 MeV neutrons measured for cataract formation in mice (Bateman *et al.* 1972) as compared with the curves calculated for mammalian cells irradiated aerobically with 0.5 MeV neutrons. Confidence limits for the experimental data are shown. Curves are: a = HeLa; b = kidney; c = hamster; d = leukemia; e = mouse bone marrow.

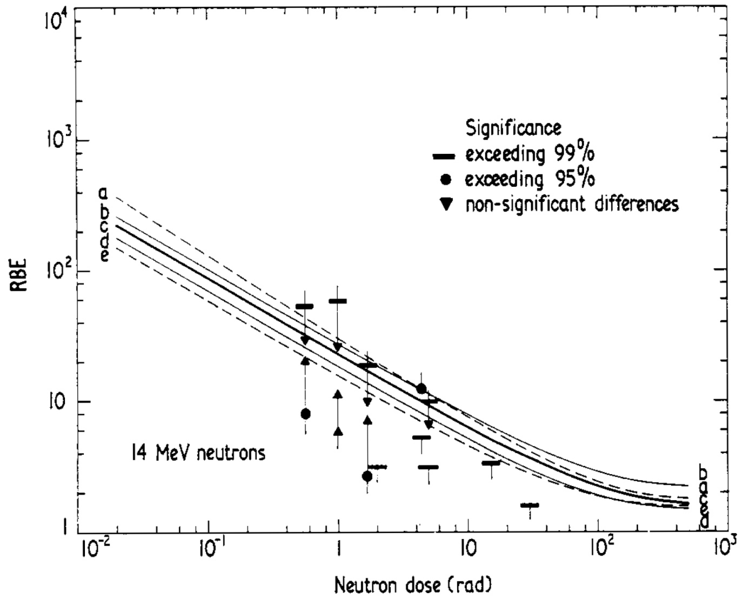

Figure 2. Data for 1.8 MeV neutrons are compared with calculations for 2 MeV neutrons (see caption to Figure 1).

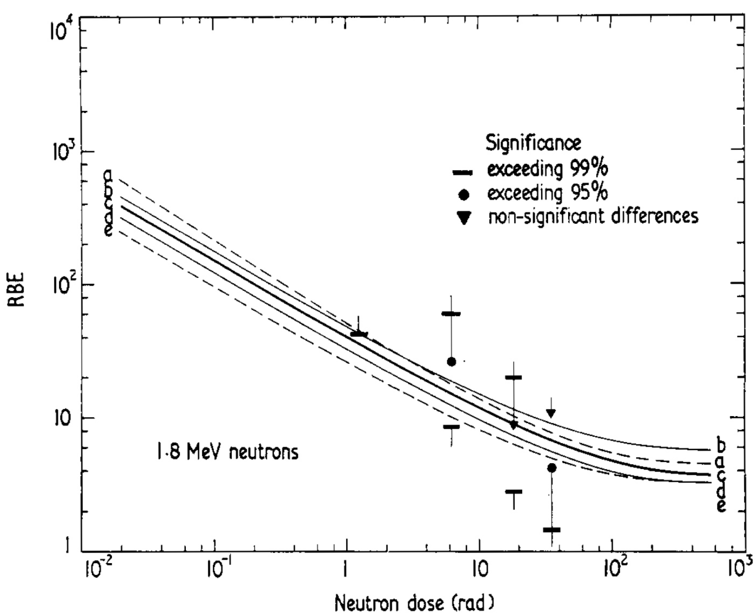

Figure 3. Data for 14 MeV neutrons are compared with calculations for neutrons of the same energy (see caption to Figure 1).

Experimental values of the RBE as a function of the neutron dose have been measured at 15 MeV, using mouse intestinal crypt cells, rat capillary endothelium, rat spinal cord, and rat skin as test objects (Broerse and Barendsen 1973). These data are compared with calculated values for 14 MeV neutrons, in Figure 4. Below neutron doses of about 500 rad, the data are entirely consistent with the results calculated for HeLa cells. Above 500 rad the data depart systematically from the theoretical values.

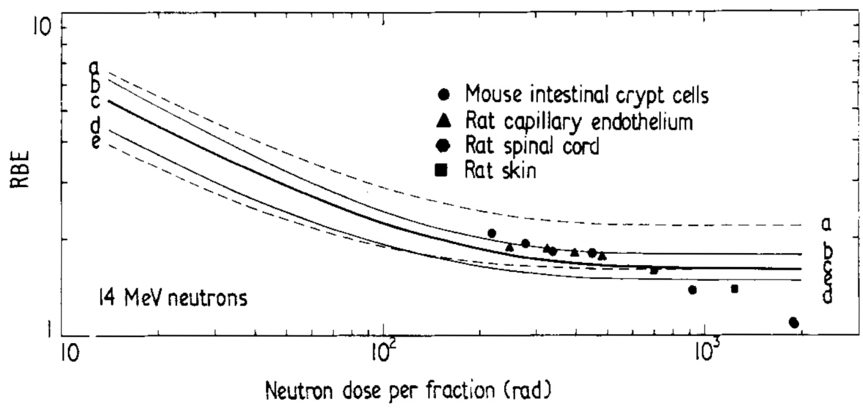

Figure 4. RBE-Dose data for 15 MeV neutrons with mouse intestinal crypt cells, rat capillary endothelium, rat spinal cord, and rat skin (Broerse and Barendsen 1973) are compared with calculations for 14 MeV neutrons on aerobically irradiated mammalian cells. Curves are: a = kidney; b = HeLa; c = hamster; d = leukemia; e = mouse bone marrow.

Experimental values of the RBE as a function of the neutron dose per fraction have been measured for human, pig, rat, and mouse skin, as well as for hemopoetic tissue, growing cartilage, and intestine, and for rat sarcoma, lymphocytic leukemia, Ehrlich ascites tumor, and C_3H mammary carcinoma in estrogen-fed male mice, at the MRC generator at Hammersmith Hospital, with neutrons of mean energy about 7 MeV (Field and Hornsey 1971). The data are compared with calculations based on theoretical particle-energy spectra in tissue for the MRC neutron spectrum (Dennis 1972, private communication). In Figures 5 and 6, the calculated curves are based on the radiosensitivity parameters for aerobically irradiated cells, and the data are for skin and for other normal tissue. In Figure 7, the calculated curves are based on the radiosensitivity parameters for anoxically irradiated cells, and the data are for tumors. Once again, the data for normal tissue depart from the calculated curves above

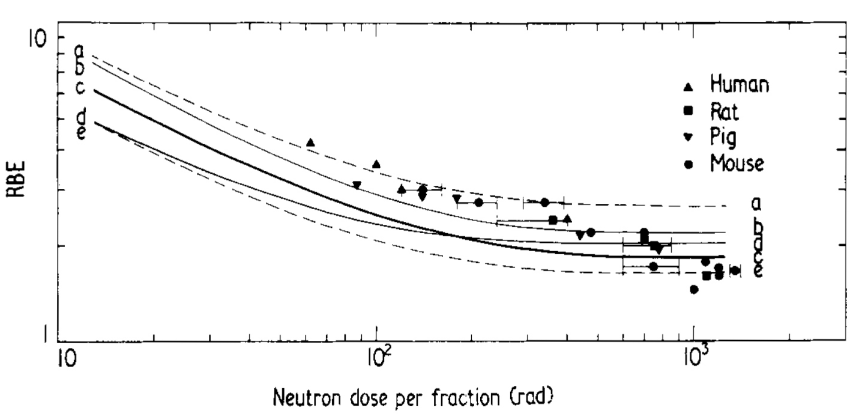

Figure 5. RBE-Dose per fraction data for MRC neutrons with human, pig, rat, and mouse skin (Field and Hornsey 1971) are compared with calculations for aerobically irradiated mammalian cells. Curves are: a = kidney; b = HeLa; c = hamster; d = mouse bone marrow; e = leukemia.

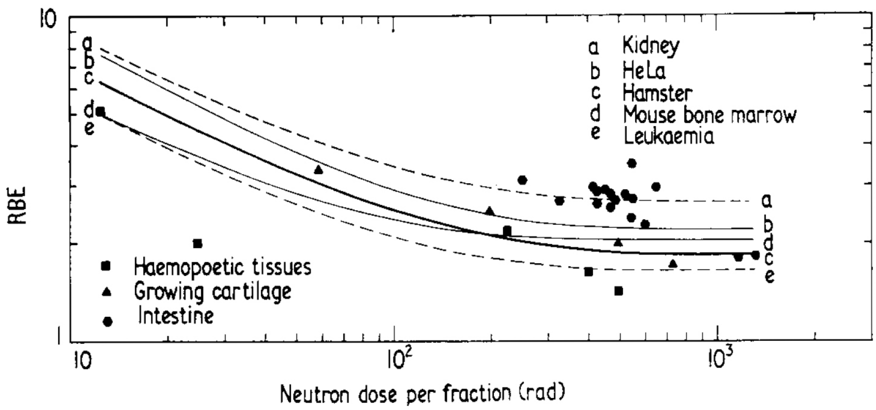

Figure 6. Data for hemopoetic tissue, growing cartilage, and intestine for MRC neutrons are compared with theoretical calculations for aerobically irradiated mammalian cells (see Figure 5).

doses of 500 rad per fraction. At lower doses the clinical data for skin are bracketed between curves calculated for aerobically irradiated kidney and HeLa cells, the data for intestine cluster about calculations for kidney cells, the data for cartilage are reasonably represented by calculations for HeLa cells, and the data for hemopoetic tissues are reasonably represented by calculations for leukemia cells, though the uncertainties are large. The tumor data, in Figure 7, are consistent with calculations for anoxically irradiated HeLa and leukemia cells.

None of the calculated RBE-Dose relations display the slope –½, nor the saturation of RBE at low dose levels demanded by the "theory of dual radiation action" (Kellerer and Rossi 1972).

4. Equivalent irradiations for neutrons and pions

The preceding results are calculated quite simply from equivalent track segment bombardments, once the ion-kill probability P and the stopping power L of the equivalent irradiation is evaluated, as given in Table 1. For purposes of calculation, the equivalent track segment bombardments specified by P and L need not be phys-

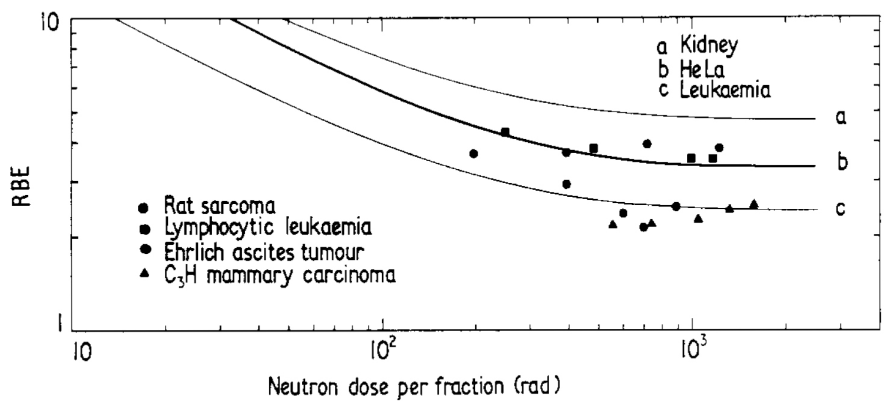

Figure 7. Data for rat sarcoma, lymphocytic leukemia, Ehrlich ascites tumor, and mammary carcinoma in estrogen-fed male mice, irradiated with MRC neutrons, are compared with theoretical calculations for anoxically irradiated mammalian cells.

ically realizable. For the equivalents of Table 1, we have required that Π_i and Π_γ, the probabilities for survival at the same dose in the ion-kill and the gamma-kill modes, respectively, be equal for the track segment and the neutron (or pion) irradiation.

The surviving fraction of cells after a dose D is deposited is given by the following equations (Katz and Sharma 1973):

$$N/N_0 = \Pi_i \times \Pi_\gamma \tag{1}$$

$$\Pi_\gamma = 1 - \{1 - \exp[-(1 - P)D/E_0]\}^m \tag{2}$$

$$\Pi_i = \exp(-\sigma_0 PD/L\rho) \tag{3}$$

where ρ is the density of the absorber. From knowledge of the radiosensitivity parameters for a particular cell line (given in Table 1), and the Π_γ and Π_i for a neutron (or pion) irradiation of this cell line at a given dose, equation (2) can be solved to find the equivalent track-segment value of P. This P value is substituted into equation (3) to calculate the corresponding equivalent stopping power L.

Once the equivalent irradiations are known, the relevant calculations are reduced to slide rule complexity.

The surviving fraction N/N_0 of a cellular population exposed to a dose D from a mixed radiation field, in which the fraction α is from low LET radiations (γ-rays, electrons, muons, or pions in motion), and the fraction (1 – α) is from high LET radiations (neutrons or pion stars), may be calculated from the expression

$$N/N_0 = \exp[-(1 - \alpha)D\sigma_0 P/L_\rho](1 - \{1 - \exp[-(1 - P + \alpha P)D/E_0]\}^m \tag{4}$$

The "biologically equivalent dose" D_X of X-rays yielding the same survival is found from the multi-target single-hit equation as

$$D_X = -E_0 \ln[1 - (1 - N/N_0)^{1/m}]. \tag{5}$$

The RBE of the radiation field, as experienced by the cell line whose radiosensitivity parameters are E_0, σ_0, and m, is found from these results as

$$\mathrm{RBE} = D_X/D. \tag{6}$$

The fourth radiosensitivity parameter κ is not used in these equations, except implicitly, in the evaluation of P and L for the particular radiation field.

More generally, if f_i is the fraction of the total dose D, delivered in a mode characterized by P_i and L_i, equation (4) may be written

$$N/N_0 = \exp[-(\Sigma f_i P_i/L_i)\sigma_0 D/\rho]\,[1 - (1 - \exp\{-[\Sigma(1 - P_i)f_i]D/E_0\rho\})^m]. \tag{7}$$

For a mixture of a fraction $f_n = 1 - \alpha$ of neutrons and $f_\gamma = \alpha$ of gamma-rays, and with $P_\gamma = 0$, equation (7) reduces to equation (4). Equation (7) may be used, for example, to describe the effect of a mixture of pion stars, neutrons, and a complex of "low LET radiations."

From these formulae, we have calculated the RBE-Dose relations for 14 MeV neutrons and for negative pions admixed with low LET radiations, as shown in Figures 8 and 9, respectively. In the case of the pion irradiation, we have also plotted the value of the RBE resulting from assigning an RBE of 3 to the star dose (independent of dose), and an RBE of 1 to the low LET dose fraction, as used in some preliminary treatment planning calculations (Li, Boyd, and Schwettman 1974). The calculations for Figures 8 and 9 are based on the radiosensitivity parameters for aerobically irradiated human kidney cells.

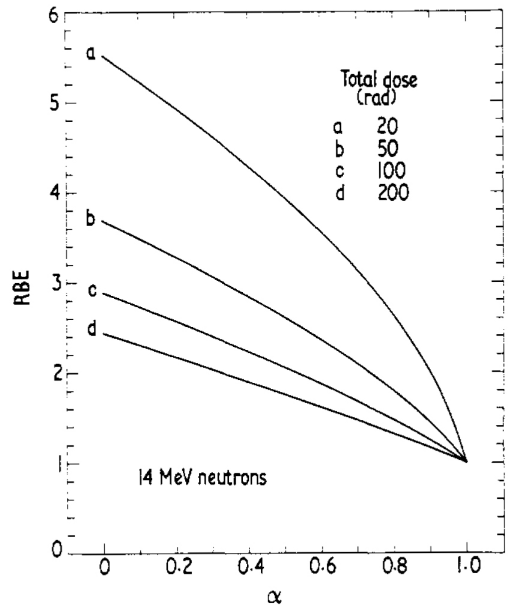

Figure 8. Calculated RBE-Dose per fraction relations for 14 MeV neutrons on aerobically irradiated kidney cells, as a function of the fraction α of the total dose delivered as γ-ray contamination, at total delivered doses of 20-200 rad per fraction.

As a first approximation, an equivalent irradiation may be taken to be one which produces a survival curve (nearly) congruent to the neutron (or pion) field. Such an approximation may be found experimentally, using HILAC or BEVALAC ions. In this case, the ion-kill and gamma-kill survival probabilities of the two fields need not

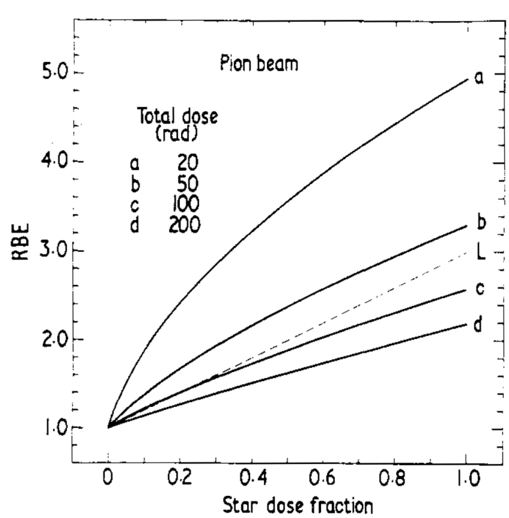

Figure 9. Calculated RBE-Dose per fraction relations for pions on aerobically irradiated kidney cells, as a function of the fraction of the total dose delivered as pion stars, at total doses of 20-200 rad per fraction. Also shown is a linear RBE-Dose relationship *L*, obtained when the star dose is assigned an RBE of 3 (independent of dose), while the low LET component of the dose field is assigned an RBE of 1 (Li, Boyd, and Schwettman 1974), as used in preliminary treatment planning.

necessarily be equal. In earlier work (Katz, Sharma, and Homayoonfar 1972), it was found that Li bombardments of different energies were equivalent to 14 MeV neutrons or stopped pions, in the sense of congruence of the survival curves. Values of the RBE found for neutron (or pion) fields diluted with low LET radiations calculated for Li bombardments lie within 5–10% of the values found from Table 1. This suggests that experimental cell survival curves, obtained in a field whose secondary particle spectrum is not known, may be used to find equivalent irradiations.

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Résumé

Rapports EBR-dose pour neutrons et pions

A partir des paramètres de la radiosensitivité cellulaire et du spectre théorique, dens le tissu, de l'énergie d'atomes secondaires provenant d'irradiations de neutrons et de pions négatifs, on a calculé les rapports EBR-dose. Les résultats théoriques sont comparés aux données obtenues par des expériences cliniques et radiobiologiques sur du tissu normal, des tumeurs, et des cellules de culture. On donne les formules utilisées pour le calcul, les paramètres cellulaires et les propriétés nécessaires à des bombardements équivalents, concernant plusieurs cellules de mammifères, irradiées avec des pions et des neutrons de plusieurs énergies.

Zusammenfassung

RBW-Dosis-Verhältnisse für Neutronen und Pi-Mesonen

Aus Zellen-Strahlenempfindlichkeitsparametern und theoretischen Spectra der Teilchenenergie im Gewebe von Sekundärteilchen für Bestrahlungen mit Neutronen und negative Pi-Mesonen sind RBW-Dosis-Verhältnisse berechnet worden. Die theoretischen Resultate werden verglichen mit klinischen und radiobiologischen Daten für normales Gewebe, Geschwülste, und Zellen in Kulturen. Formeln für Kalkulationen, Zellenparameter und die benötigten Eigenschaften von "äquivalenten Spur-Segment-Bestrahlungen"werden gegeben für verschiedene Säugetierzellen, die mit Pi-Mesonen und Neutronen verschiedener Energien bestrahlt wurden.

Резюме

Отношения ОБЭ-доза для нейтронов и пи-мезонов

Расчитывлись отношения относительной биолгической эффективноси к дозе для вторичных частиц из облучений нйтронами и отрицательными пи-мезонами, на основании параметров клеточной чувствительности к облучению и теоретических спектров энергии частицвткани. Теоретические результаты сравниваются с клиническими и радиобиологи-ческими данными для нормальной ткани, опухолей и клеток в культуре. Даются фомулы для расчета, клеточныепа раметрыи необходимы свойтва "эквивалентных бомбардировок на отрезке следа" для нескольких клеток млекопитающих животных, облучаемых пи-мезонами и нейтроами разной энергии

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