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BIOLOGICAL EFFECTS OF ^{252}CF NEUTRONS*

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ABSTRACT

The biological effects of ^{252}Cf neutrons have been studied with cultured cells, and with intact tissues. Measurements available to date, of the relative biological effect (RBE) and of the oxygen enhancement ratio (OER), are summarized and discussed.

INTRODUCTION

The biological effects of ^{252}Cf neutrons have been studied on the chromosomal level, with single cell cultures, and on intact tissues. Careful consideration of these data is required before embarking on clinical trials, since the relative lack of repair evidenced after ^{252}Cf irradiation produces a biological effect greater than that observed with X and γ ray sources in general use. Additional problems are introduced since the composition of the mixed neutron-γ radiation field is a function of source incapsulation, depth in tissue, and extent of surrounding hydrogenous material. Also, experiments must be conducted at low dose rates used in therapy.

The effect of ^{252}Cf neutrons is generally measured relative to the effect produced by ^{226}Ra or ^{137}Cs γ rays. In order to obtain meaningful comparisons, RBE values must be obtained for the neutron component alone. For survival curves, the slope of the mixed radiation survival curve can be related to the slope for neutron and γ components alone:

$$\frac{1}{D_o\ (n+\gamma)} = \frac{F_n}{D_o\ (n)} + \frac{F_\gamma}{D_o\ (\gamma)}$$

where F_n and F_γ represents the fraction of total absorbed dose delivered by neutrons and gamma rays respectively. In general, D_o (γ) will not be known. If it is assumed that D_o (γ) equals D_o for the electromagnetic radiation relative to which the RBE is being calculated, the equation for RBE reduces to

$$RBE = \frac{D_{em} - D_\gamma}{D_n}$$

Here, D_{em}, and $D_n + D_\gamma$ are doses from standard electromagnetic radiation, and the mixed ^{252}Cf field, respectively, which produce the same end point in the same irradiation time.

RELATIVE BIOLOGICAL EFFECT (RBE)

Table 1 presents the RBE data available to date (1). Where necessary, the data has been manipulated to produce the RBE for neutrons alone, as outlined above. Data in Table 1 demonstrate an increase in RBE with decreasing dose rates. However, a comparison of results is complicated by the fact that RBEs can be quite sensitive to the γ standard dose rate used. This is caused by repair, as well as possible multiplicity changes. An examination of Table 1 shows that RBEs were not always obtained from the ratio of doses needed for equal effects and equal exposure times. Also, some cultured cell survival curve data indicate a lower RBE than that obtained with *in vivo* tissue systems. While this effect could be explained in the case of HeLa cells by their relatively low capacity for repair , this would not explain the RBE of 3.94 measured with hamster cells at 37° (1).

Evaluation of radiation effects on tissues have given higher RBE's. Withers *et al*., found an RBE of 5 for mouse jejunal crypt cells, which he extrapolated to approximately 7 for ^{226}Ra at 35 rads/hour. Atkins *et al*., reported an RBE of 6.6 for pig skin, relative to ^{137}Cs at 50 rads/hour.

Effects on the hemopoietic system have been studied by Carsten. In a study on spleen colony-forming ability the RBE for californium neutrons was 2.44 compared to gamma irradiation. Dose rates were 10.81 rads/hour (n + γ) from ^{252}Cf and 42.9 rads/hour from ^{182}Ta. This is consistent with a somewhat lower RBE for hemopoietic tissues compared to other tissues for neutrons as shown by Field.

The higher RBEs such as those obtained with tissues (Fig. 1, ref. 2) or with hamster cells at 22°C have been used in devising a dosage scheme for radiotherapy. Thus it has been suggested that 890 rads of ^{252}Cf neutrons in close to 7 days is equivalent to 6000 rads of radium γ rays in 7 days, and that the dose rate used to compute the treatment time necessary to deliver the 890 rads should be: Cf neutron dose rate + 1/10 (Cf γ-ray dose rate) (3).

OXYGEN ENHANCEMENT RATIO (OER)

Another measurement of the biological effect of ^{252}Cf neutrons is obtained by the ratio of doses which give the same effect in the absence and presence of oxygen (OER). OER measurements are of particular interest, since the rationale supporting neutron therapy pre-supposes that the efficacy with which neutrons act upon anoxic cells is greater than that of X or γ rays used in conventional radiotherapy.

Determinations of OER with californium-252 have been consistent with other determinations performed with various sources of fast neutrons. Since OER is not a sensitive function of the ^{252}Cf gamma component, reports have in general been made on the basis of total dose (n + γ). Measurements with californium-252 have been made using growth of Vicia faba seedlings, chromosome aberrations in Chinese hamster cells and survival of P-388 leukemia cells, HeLa cells and hamster cells (Fig. 2). OER measurements (shown in Table 2) show quite good agreement, with values generally ranging from 1.4 to 2.0. A trend toward higher OERs is noted with higher dose rates, due presumably to an increasing contribution from the γ component. Clinical experience to date has been at the lower dose rates, such that the therapeutic gain factor (TGF = $\frac{\text{OER of test radiation}}{\text{OER of standard radiation}}$) is (with the exception of the recent work by Nias et al) significantly greater than 1.

Thus there is good biological evidence for an enhanced effect of californium-252 on tumors because of a reduced necessity for the presence of oxygen during the period of irradiation.

HAZARDS

Biological considerations suggest caution in the use of californium-252 in a hospital environment. The lack of recovery from cellular damage due to neutrons results in high values for relative biological effectiveness, particularly for low doses and low dose rates. This situation exists outside the treatment volume in interstitial implants with californium. Therefore it is not a simple matter to extrapolate from the experience with radium and other gamma sources insofar as effects on non-tumor tissue is concerned.

This is particularly true, as well, in assessing the hazards to personnel who may be exposed to low doses over a long period of time. The RBE values for cancer induction (approximately 20), lens opacification (10-1000) and genetic damage (20) can be extremely high and should be kept in mind in the design of facilities for handling and storage.

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FIGURE LEGENDS

1. The relative biological effect of californium-252 neutrons, as measured by pig skin tolerance (compared to ^{137}Cs or ^{226}Ra for equal irradiation times).

2. Chinese hamster cell survival under oxygenated and anoxic conditions, after irradiation by ^{137}Cs and ^{252}Cf. OER = 2.5, and 1.7, respectively (1).

Table 1

RBE of ^{252}Cf

Biological system	Temp.	^{252}Cf total dose rate (rads/h)	n/γ for ^{252}Cf radiations	γ Dose rate of ^{137}Cs or ^{226}Ra standard	RBE (total dose)	RBE (neutrons only)	Author
HeLa Cells	37°C	16.0	1.7	31	2.89	3.95	Fairchild, Drew + Atkins 1969
HeLa Cells	30°C	20	1.95	60	2.15	2.74	Djordjevic, Anderson + Kim 1973
HeLa Cells	37°C	~13	1.7	37.3		4.38	Atkins, Fairchild + Drew 1973
Hamster Cells	37°C	1.27-5.21	1.23-1.59	11.7-52.5	10-5	16-7.7	Hall, Rossi + Roizin 1971
Hamster Cells	22°C	1.14-21.6	1.23-1.59	11.7-52.5	4.3 (^{226}Ra=35.3 rads/h)	6.7	Hall, 1972
Hamster Cells	37°C	~13.5	1.33-1.7	37.3		3.94	Atkins, Fairchild + Drew, 1973
Hamster Cells	20°C	18	2.0	50	3.5	5.9	Hall, Roizin-Towle + Colvett, 1973
Hamster Cells	22°C	15	1.17-2.0	100	3.5-6.7		Nias, Howard, Greene + Major 1973
Hamster Cells		167	2.09	79	1.72-2.28		Bushong, Prasad, Briney + Oliver 1970
Chromosome Aberration Frequency		406-522	1.95	327	3.44-4.34		
P-388 Leukaemia Cells	37°C	200-260	?	300-420	2.7-3.5		Berry, 1971

Biological system	Temp.	^{252}Cf total dose rate (rads/h)	n/γ for ^{252}Cf radiations	γ Dose rate of ^{137}Cs or ^{226}Ra standard	RBE (total dose)	RBE (neutrons only)	Author
Vicia Faba	22°C	16.02	1.32	46.9	6.5-5.3	10	Hall + Fairchild 1970
Mouse Jejeunal Crypt Cells		43.5	1.55	160	3.2	5	Withers, Oliver + Glenn 1971
Pig Skin		12-53 11.1	1.7	35-192 50		7.4-5.4 6.6	Ackins, Fairchild + Robertson 1972
Mouse Spleen Colony		10.81	1.32	42.9	1.81	2.44	Carsten, 1972

TABLE 2

OER of ^{252}Cf

Biological System	Temp.	^{252}Cf total dose rate (rads/h)	Cf OER	γ (^{137}Cs or ^{226}Ra) dose rate (rads/h)	γ OER	Acute X-ray exposure OER	Author
Vicia Faba	22°C	16.02	1.66	46.9	2.02	2.7	Hall + Fairchild 1970
Hamster Cells		60.4	1.75				Bushong, Prasad, Briney + Oliver, 1970
Chromosome Aberration Frequency							
"		167	1.76	79	2.32		} " 1973
"		406-522	1.81	327	2.29		
P-388 Leukaemia Cells	37°C	200-260	2.0	300-420	2.6		Berry, 1971
HeLa Cells	37°C	19.4	1.55	37.3	2.5	3.0	Drew, Fairchild + Atkins 1972
"	30°C	20	1.70	60.2	2.53	3.1	Djordjevic, Anderson + Kim 1973
Hamster Cells	22°C	16.5	1.4				Hall, 1972
"	37°C	27.0	1.7	37.3	2.5		Atkins, Fairchild, + Drew 1973
"	20°C	18	1.42	50	2.0	2.4	Hall, Roizin-Towle + Colvett 1973
"	22°C	15	2.18	100	1.42	3.2	Nias, Howard, Greene and Major 1973

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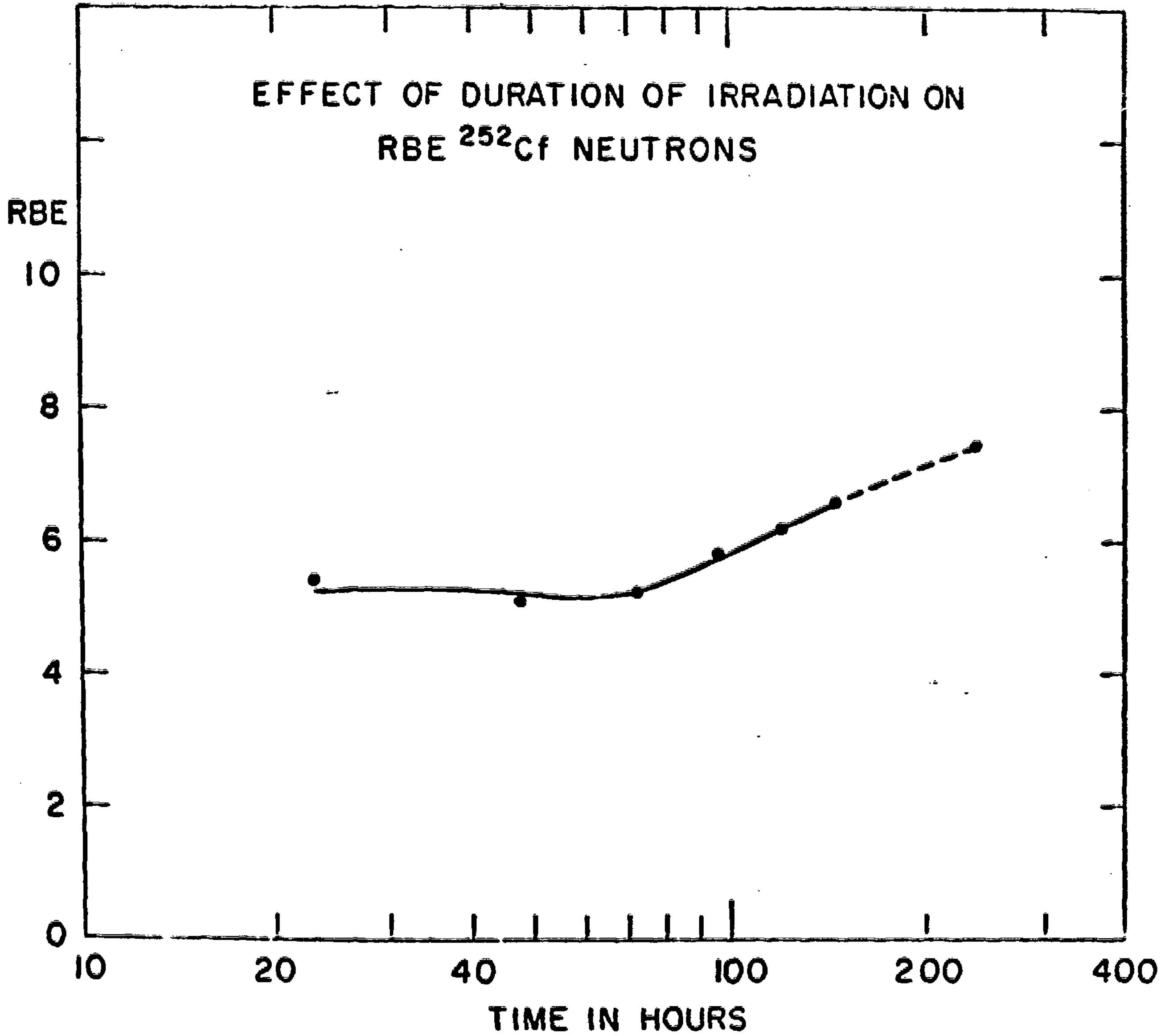

FIGURE 1

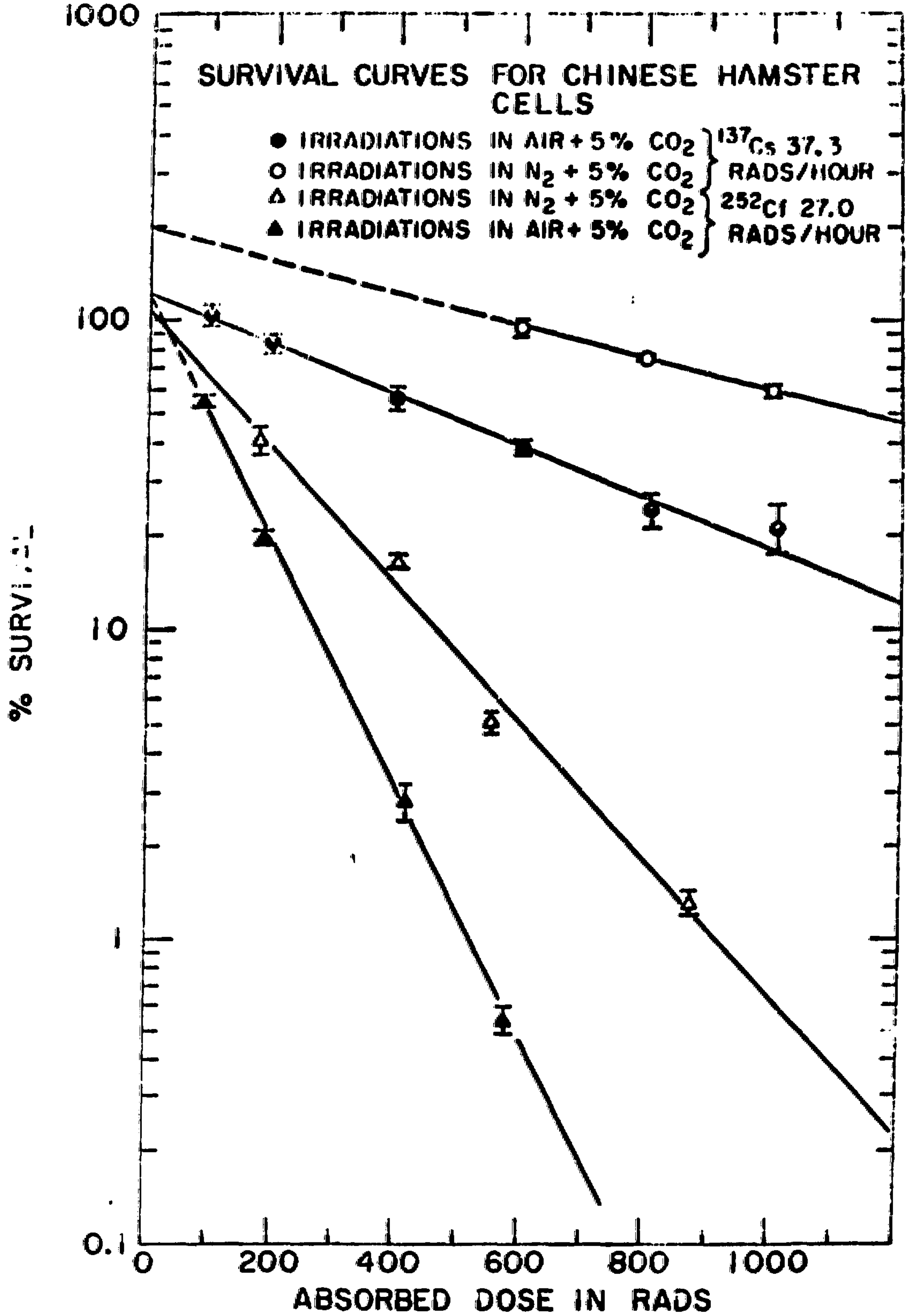

FIGURE 2

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