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Biophysical Factors in Brachytherapy with Low- and High-LET Radiations[1]

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ABSTRACT—The biophysical factors in brachytherapy with particular reference to differences between gamma and neutron emitters are analyzed. Physical parameters are source strength, distance, and time; biological factors are repair of sublethal damage, cell proliferations, and the nature of the dose–effect relationship. The principal relationships are considered on the basis of the theory of dual radiation action. Experimental results with a model system are in substantial agreement with predictions. The most important practical conclusion is that the biological effect decreases much more slowly with distance from an implant in the case of neutrons.

INDEX TERMS: Californium, Radioactive • Neutrons • Radiobiology, cell and tissue studies • Radiobiology, growth studies • Radium • Relative Biological Effectiveness • Therapeutic Radiology, physics

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SEVERAL major radiotherapy centers are in the process of evaluating ^{252}Cf for the interstitial or intracavitary treatment of malignant lesions because of the expectation that anoxic tumor cells are relatively less resistant to the neutrons emitted by this nuclide. The choice of treatment parameters will probably be influenced by the long experience accumulated with radium and other materials emitting gamma radiation, but it is evident that there are a number of aspects of radiotherapy with ^{252}Cf that require fundamental modification. These are the different dependence of absorbed dose rate on distance from the source, a different effect of dose rate variations and an RBE that is not only different from 1 but also depends on dose and dose rate. These factors combine to modify the pattern of cellular injury at various distances from a ^{252}Cf source compared to that obtained with gamma emitters. This has already been noted by Hall *et al.* (4) but the discussion on this point was incomplete and also, as will be seen, partly incorrect.

Because of the practical importance of the subject, we shall analyze in some detail the various factors and their interrelation. This can be done more effectively if one first considers the principal biophysical relations. These will be primarily derived on the basis of the theory of dual radiation action (6). Modification of the principal relationships between parameters that results when growing cultures of mammalian cells are continuously irradiated will be considered in a separate section.

PRINCIPAL RELATIONS

The Theory of Dual Radiation Action: This postulates that inactivation of the cells of higher organisms by ionizing radiation is caused by elementary lesions whose yield is proportional to the square of the specific energy, z, (which is simply the ratio of energy absorbed and mass) in sites having dimensions comparable to those of cell nuclei. Observed effects may depend on the yield of elementary lesions through various factors independent of the pattern of primary energy depositions. These factors determine the shape of the dose–effect relation but cancel if the RBE (relative biological effectiveness) is considered.

It can be shown (7) that at any value of the absorbed dose, D, the average value of the square of the specific energy is given by

$$\overline{z^2} = \zeta D + D^2 \qquad (1)$$

where ζ is a constant[2] characterizing radiation quality. It follows that the yield of elementary lesions is given by

$$\epsilon(D) = k(\zeta D + D^2) \qquad (2)$$

The constant appears to be primarily related to the nature of the biological effect and to be largely independent of radiation quality.

For mammalian cells ζ is typically of the order of tens of rads for x or γ rays and roughly thousands of rads for fission neutrons. From this it follows that in the dose range relevant to radiotherapy one may in a first approximation assume

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[2] ζ is the dose average specific energy for single events as given by $\zeta = {}_0\int^\infty z d(z)\, dz$; where $d(z)$ is the distribution of absorbed energy in the specific energy z produced in individual particle passages (7). ζ depends on the radiation quality and on the size of the reference site. It is largest for small sites and for densely ionizing radiation. shan

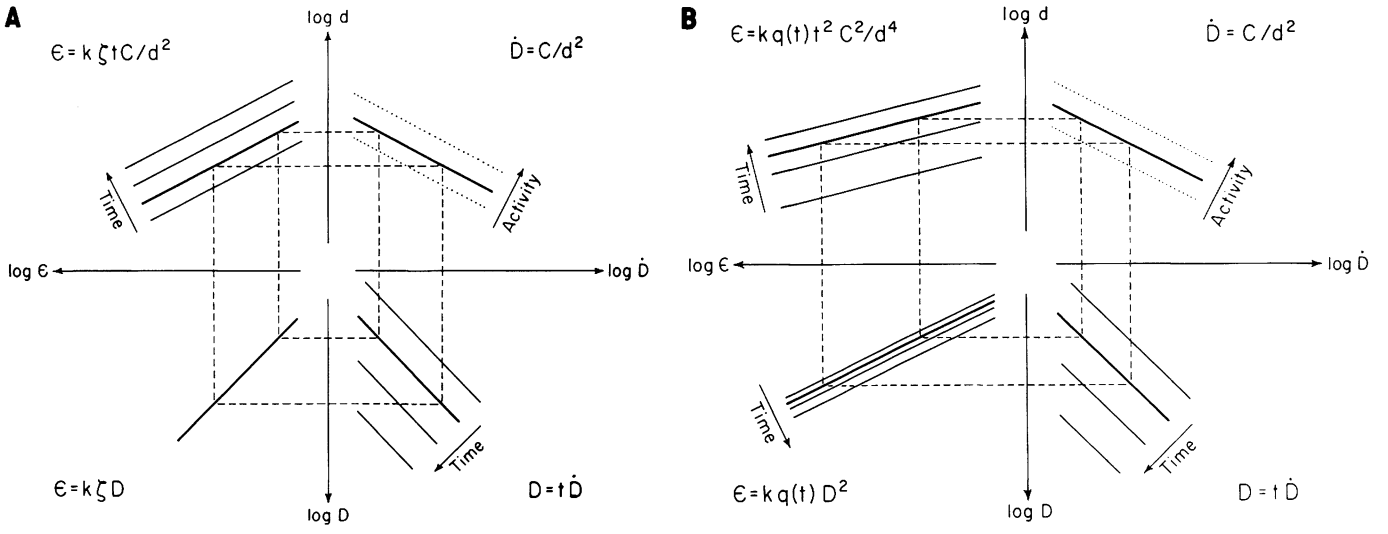

Fig. 1. Schematic representation of the interdependence of the biophysical factors of source strength (activity), distance, dose rate, dose, time, and biological effect.
A. Neutrons.
B. γ rays.

that on the right hand side of Equation 2, only the second term is significant for γ rays and only the first term is of importance for neutrons. Thus

$$\epsilon(D_x) \simeq kD_x^2 \tag{3}$$

and

$$\epsilon(D_n) \simeq k\zeta D_n \tag{4}$$

This implies that elementary lesions are due to single secondary particles (usually protons) produced by neutrons. On the other hand the quadratic dependence for gamma rays implies that more than one electron secondary to gamma rays is necessary to induce a lesion. Although not strictly proved the assumption may be made that two electrons produce each elementary lesion; but even if more electrons were involved in the second order reaction, the following argument would be unaffected:

From Equations 3 and 4, it may be concluded that

(*a*) The production of lesions is proportional to neutron dose but depends on the square of the γ-ray dose. By equating Equations 3 and 4 and setting the RBE (the inverse ratio of absorbed doses for equal effect) equal to D_x/D_n it is a simple matter to show that the RBE is proportional to D_x^{-1} or $D_n^{-1/2}$.

(*b*) Since neutrons produce elementary lesions in a single step, no repair of sublethal damage has to be considered. On the other hand if there is an increasing period of time between the arrival of the two electrons responsible for the production of the elementary lesion, the probability for repair from the effects of the first electron increases. Thus an absorbed dose D delivered in time t is less effective than if delivered instantly. According to the theory of dual radiation action, this is described by a modified form of Equation 2 (8):

$$\epsilon(D) = k(\zeta D + q(t)D^2) \tag{5}$$

where the reduction factor $q(t)$ depends on the length t of the irradiation time. Thus while Equation 4 for neutrons remains unchanged, one has the modified equation

$$\epsilon(D) = kq(t)D^2 \tag{6}$$

in the case of gamma rays. If various doses are delivered in the same time (by variation of dose rate) the reduction factor is constant, and the quadratic dependence of effect on dose is therefore preserved. One notes that this is not the case if the dose rate is kept constant and the time is varied.

The General Quadrant Plot: It so happens that all the basic biophysical parameters of brachytherapy are principally related by power functions and that consequently their interrelation can be represented by straight lines on logarithmic plots. In Figure 1, A and B show the resulting schemes for neutrons and gamma radiation, respectively.

Beginning with the upper right hand corner, the relation between d, the distance from a source, and $\dot{D}$, the absorbed dose rate, is in the logarithmic representation given by a line of slope $-1/2$ in accordance with the inverse square law. A change of source strength results in a proportional displacement of this line:

$$\dot{D} = \frac{C}{d^2} \tag{7}$$

If one considers a fixed irradiation time t, the absorbed dose D is proportional to the dose rate $\dot{D}$:

$$D = t\dot{D} \tag{8}$$

Thus in the second quadrant one has lines of slope +1 with a parallel shift proportional to time. This merely expresses the linear increase of the physical quantity *absorbed dose* with time.

The first two quadrants refer to the physical quantities and their principal interdependence which is the same for either radiation. The second two quadrants involve biological responses that are different for the two radiations.

For neutrons, the production of elementary lesions is proportional to D (Equation 4):

$$\epsilon_n = k\zeta D \tag{9}$$

This relation appears as a line of slope +1 in the third quadrant of Figure 1, A. There is only one line because ϵ is independent of the time in which the dose is delivered. For gamma rays, the dependence is quadratic (Equation 6) and one therefore has lines of slope 0.5 in the third quadrant which are shifted parallel with varying values of t:

$$\epsilon_x = kq(t)D^2 \tag{10}$$

The shifts represent the biological consequence of changing the length of the irradiation period. Since $q(t)$ decreases with increasing t, the effect of time is opposite to that in the second quadrant.

By a stepwise connection of the lines in quadrants *1* to *3* one obtains the resulting line in quadrant *4*. For gamma rays one finds the slope $-1/4$, or according to Equations 7, 8, and 10:

$$\epsilon_x(d) = kq(t)t^2C^2/d^4 \tag{11}$$

For neutrons, on the other hand, the resulting line has the slope $-1/2$, or corresponding to Equations 7, 8 and 9:

$$\epsilon_n(d) = k\zeta tC/d^2 \tag{12}$$

The quadrant plot therefore demonstrates the basic result that the effect of a neutron source decreases only with the square of the distance, while for a gamma source, it decreases with the fourth power of the distance.

ACTUAL RELATIONS OBSERVED IN TISSUE CULTURES CONTINUOUSLY IRRADIATED BY RADIUM AND CALIFORNIUM SOURCES

Deviations from Idealized Conditions: It appears that the only available series of experiments that can be tested against the theoretical predictions is that of Hall *et al.* (4) in which growing cultures of hamster cells were irradiated continuously. The relevance of these experiments to tumor therapy is of course limited, but they present a feasible model system and they may also serve to illustrate the general modifications required if the theoretical considerations are applied to practical cases.

There are a number of physical aspects that are different in practical situations. In order to achieve optimum dose uniformity, tumors are usually irradiated by arrays of sources and if the distance d in the quadrant plot is that to the geometrical center of the array, the dose rate decreases more slowly than the inverse square of d in the vicinity of the array, although the inverse square dependence is approached at more distant locations (*e.g.*, normal tissue beyond the tumor). A factor operating in the opposite direction is attenuation of radiation. In the modified plots given below, a single needle-shape source is implied. The appropriate modifications for other types can be readily performed.

The neutrons emitted by ^{252}Cf have energies of the order of 1 MeV and may be regarded as high-LET radiation in the sense that first order inactivation predominates. However the ^{252}Cf sources employed in brachytherapy emit not only neutrons but also gamma rays and the neutron capture by hydrogen in the surrounding tissues results in additional gamma radiation. Thus the absorbed dose rates of the two types of radiation are comparable. However, the RBE of the neutrons is high and in order to avoid the complexities of its variation with dose, dose rate, and a varying neutrons-to-gamma ratio with distance, the gamma radiation has been ignored in the first quadrant of the neutron plot. Its influence on the experimental curves in the other quadrants should be minor.

There is strong indication that ^{252}Cf inactivates cells in single events. The growth curves for viable cells in Figure 1, B in Hall *et al.* (4) appear to be proportional to $e^{(\mu - \dot{D}/D_0)t}$ where μ is the multiplication rate ($\sim$0.06 hr^{-1}), and D_0 the dose required for a survival ratio of e^{-1} ($\sim$60 rad). The decline which occurs several days after the beginning of irradiation—presumably because cells stop dividing in the stationary phase—is also rather accurately proportional to $e^{-\dot{D}/D_0 t}$. The curves for radium irradiation (Fig. 1, A of the reference) exhibit the differences one might expect qualitatively in that they seem less linear and show a more pronounced dependence on dose rate. However, because of the complexities of the inactivation mechanism and in view of various imponderables (especially division delay), a numerical analysis seems impractical.

The dependence of RBE on neutron dose is that postulated by theory. The lines in Figure 3 in

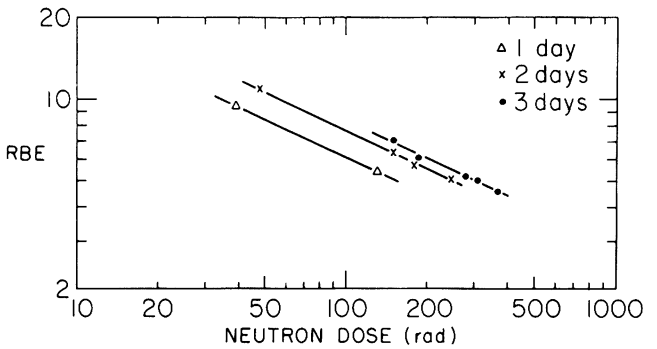

Fig. 2. Dependence of RBE on neutron dose for cell irradiations protracted over various periods [after Hall *et al.* (4)].

Hall *et al.* (4) give the RBE as a function of dose rate for various periods of irradiation. Multiplication by the duration of these periods of the dose rates on the abscissa produces the relations between RBE and dose in our Figure 2. The figure represents lines of the same slope shifted to higher neutron RBE as irradiation is protracted. This is in accord with the theoretical results given above, as is the slope which at -0.47 is near the predicted value of -0.50. Even the slight discrepancy (although within experimental error) is in the right direction if the gamma contamination of the ^{252}Cf source is taken into account.

There is one difference between the basic theoretical relations and the actual behavior of this dynamic system in that there may be a slight dose rate effect with Cf [cf. Fig. 4 in Hall *et al.* (4)]. The accuracy of the data is in fact such that it is not certain whether the three curves in the third quadrant of our Figure 3, B, which will be discussed in the next section, are different. If they are, this may be due to contaminant gamma radiation or to some other cause, such as sensitivity shifts with increasing age of the population.

The Specific Quadrant Plot: The actual quadrant plots for the case of continuous irradiation of growing cultures of hamster cells are given in Figures 3, A and 3, B for encapsulated sources of ^{226}Ra (and its decay products), and ^{252}Cf (and its fission products).

As stated above, the sources are assumed to be single needles, and the curves in the first quadrant are based on data by Goodwin *et al.* (2) and Colvett *et al.* (1), respectively.

Comparison between theory and experiment involves the relationship between $\epsilon(D)$ and $S(D)$, the cell survival. The simplest assumption is that at any survival the number of survivors decreases in proportion to the number of lesions produced, leading to

$$S = e^{-(\epsilon D)} \tag{13}$$

The quantity ϵ on the fourth axis in the quadrant plot is therefore set equal to $-ln\ S$ where S is the observed surviving fraction.

Figure 3 is in substantial agreement with Figure 1.

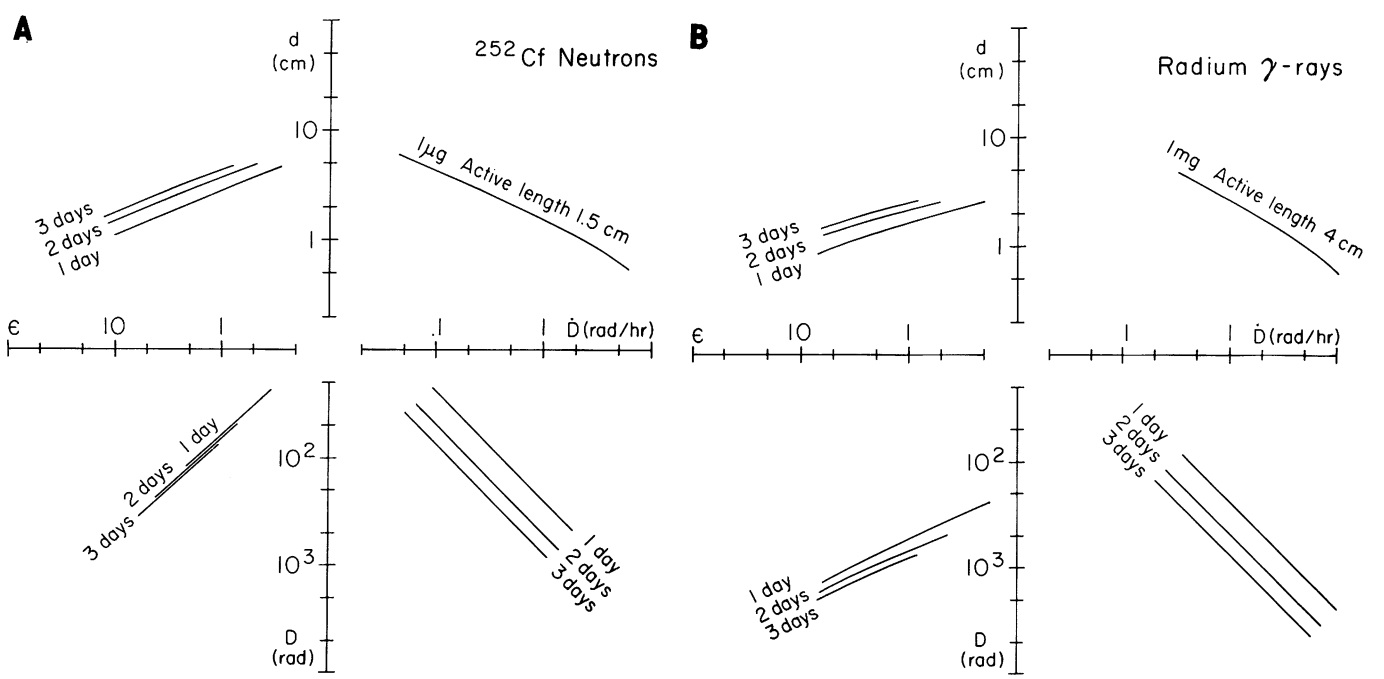

Fig. 3. Actual dependence of the factors in Figure 1 as observed in continuous irradiation of growing cultures of mammalian cells [after Hall *et al.* (4)].
A. Neutrons.
B. γ rays.

DISCUSSION

The most important practical consequence of these considerations is that tissue damage at some distance from a brachytherapy implant is likely to be more severe for ^{252}Cf than for gamma emitters. Good design of the source array may lessen the hazard and avoid the entire differential in the killing rates for single point sources. In addition, the doses applied in radiotherapy may be larger than those employed in the experiments of Hall *et al.* (4). If this results in an appreciable contribution of the second order term for *neutrons*, the curves in the third quadrant of Figure 3, A and B become more alike at high doses. Nevertheless, the problem is likely to be serious in certain practical situations. An example would be damage to rectum or bladder in treatment of carcinoma of the cervix uteri.

It also follows that in addition to posing a greater hazard to the normal tissues of the patient, neutron brachytherapy involves greater risks to other persons in proximity to the patient. Current radiation protection rules allow for this to a limited extent by imposing a quality factor Q of 10 (5, 9) which is somewhat higher than the RBE values applicable for therapy (3). However the considerations presented here suggest that this may not adequately reflect the dependence of RBE on dose. Although a sufficient margin of safety may be afforded by the low levels of MPD currently employed, this margin is likely to be less for neutrons and careful attention to radiation protection is indicated.

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