PROGRESS REPORT

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BIOLOGICAL EFFECTS OF RADIATION AND RELATED BIOCHEMICAL

AND PHYSICAL STUDIES

Proposal #1: Radiation Studies; Theoretical Investigation
of LET Spectra and Dose Relationship

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RADIATION STUDIES

Theoretical Investigation of LET Spectra & Dose Relationship

A. High-Intensity Pulsed Radiations

The analysis and testing of a biophysical model of oxygen diffusion into a monocellular aqueous layer after exposure to an ultra-high intensity pulse of electrons has been carried out and completed by comparing the oxygen concentration calculated on the basis of the model with the corresponding experimental data (Epp, Section 7501). These data (1) give the concentration of oxygen, as a function of time after the pulse, diffusing into the layer (which was rendered anoxic by the pulse) from an oxygen-containing gas above. The cells are drenched in an aqueous solution and are resting on top of a millipore filter that is permeable to water but not to cells. The cellular layer's thickness is estimated at about one micron, only slightly more than the average cell diameter, since there is very little solution above the cells. The thickness of the filter, on the other hand, is about two hundred microns and can be considered infinitely thick relative to the bacterial layer. The data shows a marked delay and depression of oxygen concentration at intermediate times that suggests the presence of a competing oxygen absorption process. In addition, the diffusion process covers over five decades in time. These features are not obtained and cannot be explained by a simple diffusion process. The model assumes the existence of a set of relatively long-lived agents initiated by the radiation pulse which react slowly with and are neutralized by the diffusing oxygen molecules so that the latter are tied-up and are no longer available to the cells. Thus, the concentration, R , of these agents, which is a maximum, R , at the end of the pulse, will decrease monotonically to zero after a sufficiently long time, after which oxygen will diffuse unimpeded. When this concentration is expressed mathematically and the rate of oxygen absorption proportional to this concentration, the flux of diffusing oxygen and the interaction cross-section, σ , is introduced into the diffusion equation for oxygen, the solution, by the iteration method, exhibits closely the transient oxygen absorption at intermediate times indicated by the data.

The model and its mathematical interpretation contain five physical parameters that influence the oxygen diffusion in time: 1. The depth, x , in the cellular layer, at which the mathematical solution is evaluated, 2. The diffusion coefficient, D , 3. The initial concentration, R_0 , of the oxygen reacting agents, 4. The interaction cross-section, σ , 5. The oxygen concentration, C_0 , of the gas in contact with the cellular layer.

The model predicts a non-trivial dependence of the oxygen concentration in the layer on the radiation dose (propor-

tional to R_0) and on the oxygen concentration in the gas. In order to test the predicted behavior, experimentation was extended to cover three oxygen gas concentrations (8,6,4%) and two radiation doses.

The calculation was performed at a depth of 0.4 microns from the surface of the layer (approximately at the center). Comparison with the data for a 6% gaseous oxygen concentration at short times yields the value of the diffusion coefficient, $D=0.4 \times 10^{-5}$ cm/sec. This value is significantly lower than that of pure water, and shows a decreased oxygen mobility offered by the cells. The values of the parameters R_0 and ϕ obtained by matching the experimental and theoretical curves at the time of maximum oxygen absorption (about 10^{-2} seconds). The value of C_0 was the same as the experimental one. With these values, the calculated curve was in very good agreement with the experimental one at most times (Fig.1).

The determination of the physical parameters in the 6% case predetermines them for all the other cases as well, since X , D , ϕ should be the same and R_0 and C_0 should be proportional to the experimental dose and gaseous oxygen concentration respectively. Thus, the calculated curve for the 8% case with the prescribed values of the parameters is shown in Fig.2, together with the data. Agreement is again good. The predicted dose dependence was tested by repeating the 6% calculation with a 50% dose increase (50% increase of R_0), and comparing with the corresponding experimental data (Fig. 3). The increased concentration, R_0 , of oxygen absorbing agents results in a depressed oxygen diffusion at most times, in very good agreement with the data.

The 4% gaseous oxygen concentration was considered last and the results are shown in Fig. 4. It was repeated for a dose 100% higher (Fig. 5). Agreement between theory and experiment is not as close as before, but it is still adequate, with the shapes and trends in both curves being similar. In the first of the 4% cases, if R_0 is assigned an alternate value that will give agreement with the data at a single point in time (in the millisecond region), very good agreement with the data is obtained at all other times, except at the very short ones. This alternate value, however, boosted by 100% for the second 4% case, gives a curve that falls somewhat below the experimental one.

In conclusion, the model is seen to be general enough and powerful enough to reproduce and predict the available experimental data, without making any specific or arbitrary assumptions on the nature of the oxygen-reacting agents and on the details of their interaction with oxygen.

A detailed presentation of the theoretical and experimental procedures and results is the subject of a series of two papers that are expected to appear in the May 1973 issue of Radiation Research.

B. RBE and OER Studies in Water for Cyclotron-Produced Neutron Beams

Studies at our Institute and elsewhere indicate that neutron beams can be particularly effective in clinical cases of deep-seated anoxic (radio-resistant) tumors. This is because neutrons result in elevated value of the index of radiobiological effectiveness (RBE) combined with a low value of the oxygen enhancement ratio (OER) compared to those of x- and gamma rays. The main object of this work is to obtain a quantitative description of the dependence of RBE and OER on the spectrum of LET at various points in a tissue like medium arising from a variety of cyclotron produced neutron beams incident to the medium. Such beams can differ substantially in the spectrum of their incident neutrons depending on the mode of their production, and to some extent, the presence or absence of collimation. Each beam results, at any depth, in specific LET spectrum of the various recoil particles. The fast and slow protons, the alpha particle recoils, the oxygen atom recoils (and whatever other elements the medium may have) and the fraction due to gamma-rays from (n- γ) reactions. These components of the LET spectrum are nearly separable on the LET scale. This facilitates the study of the dependence of RBE and OER on these components, as they change with incident neutron spectrum. The average RBE, at the point of interest in the medium, is obtained by weighting the RBE versus LET curve for mono-LET spectrum at that point. The average OER is similarly obtained. This RBE versus LET curve is nearly unity up to about 10 keV per micron. It rises to its maximum value at LET of about 100 keV per micron and decreases fast at still higher LET values (2,3,4). The details of this curve may change from one biological system to another, but its essential features remain the same. The OER versus LET curve for mono-LET spectrum is maximum (2.5 or more) at the minimum LET (1 keV per micron or less), and decreases slowly up to LET of 30 KeV/ and subsequently much faster, the steepest decrease occurring in the range LET around 100 KeV per micron (near the maximum LET for protons). Beyond this LET, the OER approaches and remains at unity. If we denote RBE by $R(L)$ and OER by $O(L)$ and the spectrum by $F(L)$, normalized to unit dose, we have

$$\langle R \rangle = \int_{\text{all } L} dL F(L) R(L)$$

And similarly, for $\langle O \rangle$. Since the gamma-ray, proton and heavy ion spectrum components are nearly separable on the LET scale, we can write

$$F(L) = F_{\gamma}(L) + F_p(L) + F_h(L)$$

where F_{γ} , F_p and F_h are the gamma, proton and heavy ion spectrum components respectively. Then:

$$\langle R \rangle = \int_{\text{all } L} dL R(L) [F_{\gamma}(L) + F_p(L) + F_h(L)] \equiv \langle R \rangle_{\gamma} \lambda_{\gamma} + \langle R \rangle_p \lambda_p + \langle R \rangle_h \lambda_h$$

where

$$\langle R \rangle_{\gamma} \lambda_{\gamma} \equiv \int dL R(L) F_{\gamma}(L), \text{ etc.}$$

and $\lambda_{\gamma}, \lambda_p, \lambda_h$ are the γ , proton and heavy ion dose fractions (adding)

up to unity) and $\langle R_V \rangle$, $\langle R_p \rangle$, $\langle R_h \rangle$ are the average RBE values of the gamma proton and heavy ion components respectively. Exactly analogous expressions apply for OER. This investigation employed a variety of different dose fractions and partial RBE averages simulating the effects of different incident neutron beams and depths of interest. In this calculation, in which the proton component is dominate, but the others are also important, a softer incident neutron beam or a larger depth corresponded (on the basis of pilot calculations by this investigator and information in the literature (5,6,7,8) to a somewhat larger value of R_p . The resulting overall RBE averages for all cases considered remained nearly constant in value with a slight tendency (a few percent) of RBE to increase with increasing depth or with softer incident neutron beam. This was so because the variation in the proton and gamma ray components pulled the RBE value in opposite directions nearly cancelling each other. The latest experimental data from our laboratory, which is still incomplete, indicates, however, a slight hardening rather than softening of the proton component with increasing depth. This can occur when the incident neutron spectrum is rich in the range of 0.1 to 5 MeV neutrons and relatively weak above and below this range (such as the spectra from our cyclotron).

Under these conditions, neutrons in the range 0.1 to 5 MeV, which are known to have substantially increased probability of absorption than neutrons either above or below this range, will appear with relatively decreasing intensity at greater depths. This effect can be just strong enough to overbalance the overall tendency of the proton spectrum toward lower energies (i.e., higher LET). This will result in a small decrease of RBE with increasing depth. Preliminary calculations show a possible decrease of 1-10%. This conclusion is in agreement with experiments (11) showed a small increase or no increase at all.

A similar analysis of OER variations to date showed that it is less sensitive than RBE to spectral changes and remains nearly constant for a variety of LET spectra. This is also in agreement with recent experimental evidence from our laboratory. (9)

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Fig. 1 Theoretical and experimental time diffusion curves
6% [O₂]

Fig. 2 Theoretical and experimental time diffusion curves
8% [O₂]

Fig. 3 Theoretical and experimental time diffusion curves 6% $[O_2]$, increased dose

Fig. 4 Theoretical and experimental time diffusion curves 4% [O₂], increased dose

Fig. 5 Theoretical and experimental time diffusion curves 4% $[O_2]$, 100% dose increase