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HIT THEORY FOR LOW-LET RADIATION*

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Hit theory has had a long and useful history in radiobiology (c.f. Zimmer, 1961). Its chief drawbacks have been the "all-or-nothing" character that was ascribed to the hits, with consequent lack of consideration of hit effectiveness with particle type, chemical agents, or pre- or post-irradiation treatment, and the lack of any allowance for time-dependent interactions between hits. None of these characteristics is inherent in the theory. The "all-or-nothing" assumption is easily dropped (c.f. Zimmer, 1961, pp. 56-57), although the consequences of being able to do so have not been much explored (Roesch, 1967). Roesch (1967) described how time-dependent phenomena could be included in a hit theory. His equations are difficult to evaluate numerically in the case of low-LET radiations such as x or gamma rays, where large numbers of hits have to be considered. The purpose of this paper is to describe an approximation of good accuracy that permits ready application of Roesch's theory to low-LET radiation.

Basic Equations

The basic equation in Roesch's theory is

$$S = \sum m^n e^{-m} (n!)^{-1} S_1^n R_n \quad (1).$$

The survival, S , is the sum of the fractions of the population surviving n hits. The factor $m^n e^{-m} (n!)^{-1}$ is the Poisson probability of receiving n hits when the mean number received is m . S_1 is the probability of surviving death from a single hit due to effects that neither influence nor are influenced by the effects of other hits; S_1^n is the corresponding probability of surviving such effects for n hits. R_n is the probability of surviving the effects of n hits that do spread their influence from one hit to another.

Further development of the theory requires adding specific assumptions that permit establishing an equation for R_n . The simplest assumption that one can make is that every pair of hits has the same chance of some lethal interaction occurring between their products. Further, this chance of interaction should decrease with the time between the two hits, i.e. the chance of surviving such interactions should approach 1.0 with time. The form

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$(1 - a e^{-bt})$ for the chance of survival, where a and b are constants and t is the time between the hits, is the form expected when the first hit leaves a product such as a radical or a DNA strand break that may disappear or be repaired at a random time with a probability b per unit time before another hit occurs that may render the result lethal. It is also a convenient form for mathematical analysis. These assumptions lead to

$$R_n = (n!/T^n) \int_0^T dt_n \int_0^{t_n} dt_{n-1} \dots \int_0^{t_2} dt_1 \prod_{j=i+1}^n [1 - a e^{-b(t_j - t_i)}] \quad (2).$$

Here T is the irradiation period and the t_i enter as the times at which the hits occur.

This expression for R_n can, in principle, be integrated. For example

$$R_2 = 1 - (2a/b^2 T^2)(bT - 1 + e^{-bT}) \quad (3).$$

The author also has the integrated expressions for R_3 and R_4 . Further integrations would be too laborious: there are 320 terms that must be evaluated to obtain R_4 , there would be 5120 for R_5 . A computer program was prepared that does the algebra of multiplying out the product in Eq. (2), taking the Laplace transform, expanding the transform in partial fractions, and inverting the transform. With this program it was possible to evaluate R_5 numerically in a reasonable time. It took several minutes to do R_6 (on a Univac 1108), which is unreasonable for any considerable amount of computing. Clearly some approximate way of evaluating the equation for R_n is needed whenever the number of hits to be considered is large.

Number of Hits for Low-LET Radiation

The concept of a "hit" is the same as that called an "event" in microdosimetry. Therefore, data from microdosimetry can be used to estimate the number of hits that occur during radiobiological phenomena. Rossi (1968 [his Fig. 24]) gave distributions in local energy density (now called specific energy [ICRU, 1971]) for ^{60}Co radiation in spheres of diameters 1 and 7 microns. The mean local energy densities for the two spheres were about 5 and 0.1 rad. Thus for a phenomena requiring a dose of 100 rads, for example, there would have to be on the average 20 hits in a 1-micron sphere and 1000 in a 7-micron sphere. The number of hits then is usually very large.

It is not customary to think of even low-LET radiation as requiring so many hits. This is probably due to our conditioning by use of the usual hit theory, where it is customary to consider small numbers of hits. Complementary to the need to consider large numbers of hits is the need to assign them low probabilities of producing death. The probability of death from single hits, $1 - S_1 = \lambda$, may typically be of the order of 10^{-3} . The interaction probability, a , may typically be of the order of 10^{-6} .

Survival for Low-LET Radiation

All of the factors under the integrand of Eq. (2) increase monotonically with the time between the hits. It was found possible to exploit this fact to construct particular upper and lower bounds to R_n . It was then found that for the large values of n typical of low-LET radiation the two bounds converged to

$$R_n \approx \exp [-an^2(bT - 1 + e^{-bT})/b^2T^2] \quad (4).$$

This expression for R_n can now be substituted into Eq. (1) to give the surviving fraction of the population. It is both convenient and accurate to replace S_1 also by its exponential approximation, $S_1 = 1 - \lambda = e^{-\lambda}$. Then

$$S \approx \sum m^n e^{-m} (n!)^{-1} \exp [-\lambda n - an^2(bT - 1 + e^{-bT})/b^2T^2] \quad (5).$$

This sum can be evaluated by replacing the Poisson probability by its normal approximation and then approximating the sum by an integral. The result is

$$S \approx \exp [-\lambda m - am^2(bT - 1 + e^{-bT})/b^2T^2] \quad (6)$$

provided $ma \ll 1$ and $m\lambda^2 \ll 1$.

A number of different forms for this survival equation result from making various substitutions. The mean number of hits, $\underline{m}$, is given by $m = cT$, where c is the mean hit rate. Thus

$$S \approx \exp [(ac^2/b^2)(1 - e^{-bm/c}) - (\lambda + ac/b)m] \quad (7),$$

or

$$S \approx N^{(1 - e^{-bm/c})} e^{-(\lambda + ac/b)m} \quad (8),$$

where the extrapolation number, N , is

$$N = \exp (ac^2/b^2) \quad (9).$$

From microdosimetry, the absorbed dose, D , is given by $D = m\langle z \rangle_1$, where $\langle z \rangle_1$ is the mean value of the specific energy (see local energy density), z , in single hits. The dose rate, dD/dt , is then $dD/dt = c\langle z \rangle_1$. Hence,

$$S \approx \exp \left[(ac^2/b^2)(1 - e^{-bD/(dD/dt)}) - (\lambda + ac/b)D/\langle z \rangle_1 \right] \quad (10)$$

$$\approx N(1 - e^{-bD/(dD/dt)}) e^{-D/D_0} \quad (11),$$

where the asymptotic-mean lethal dose, D_0 , is given by

$$D_0 = \langle z \rangle_1 / (\lambda + ac/b) \quad (12).$$

Heuristic Derivations

The substitutions

$$k = (\lambda + ac/b) / \langle z \rangle_1 \quad (13.a)$$

$$\alpha = ac^2/b^2 \quad (13.b)$$

$$\beta = b/(dD/dt) \quad (13.c)$$

change Eq. (10) into

$$S \approx \exp [-kD + \alpha(1 - e^{-\beta D})] \quad (13.d).$$

This same equation was derived heuristically by Hug and Kellerer (1963) and by Haynes (1964, 1966). In both derivations it was assumed that radiation could produce damage which could be partially or completely "compensated" (Hug and Kellerer) or "reactivated" or "repaired" (Haynes). The rate of formation of defects with dose is $\underline{k}$, and $\underline{\alpha}$ is the maximum number of reparable lesions (Haynes).

The present derivation of Eq. (13.d) has been a stochastic one. To compare with the earlier, heuristic derivations, it is easier if one makes an approximate, non-stochastic derivation based on assumptions concerning time dependences similar to those used above. Suppose each hit produces M "defects" of some sort and the number left at a time t after the hit is $M e^{-bt}$. Then hits arriving at a mean rate $\underline{c}$ will produce a mean number of defects $M(c/b)(1 - e^{-bt})$ after irradiation for a time $\underline{t}$. Suppose that the number of deaths produced by a hit is proportional to the number of defects present when the hit occurs and to the number it produces, i.e. death is assumed to result from interactions. Then the mean death rate is $K M^2(c^2/b)(1 - e^{-bt})$, where K is a constant. The mean number of deaths during an irradiation of ^{length} T is then $K M^2(c^2/b^2)[T - (1 - e^{-bT})/b]$. With the substitutions $a = KM^2$ and $m = cT$, this becomes: $a(c/b)m - a(c^2/b^2)(1 - e^{-bT})$. Identifying the survival with the negative exponential of the mean number of deaths leads to Eq. (7), except for the provision for deaths ^{occurring} by the non-interactive processes; Eq. (7) leads to Eq. (13).

Both of the heuristic theories attributed the $\alpha(1 - e^{-\beta D})$ term in Eq. (13.d) to a decrease in the effectiveness of the compensation or repair mechanism with dose. They emphasized dose where the present paper uses time; these viewpoints are equivalent for a constant dose rate, because dose and time are then proportional. The present theory, however, assumes a repair mechanism, characterized by the e^{-bt} factor, that is the same for every defect; i.e. there is no decrease in the effectiveness of the repair process. In terms of the approximate theory of the preceding paragraph, the effect of the repair process is to make the number of defects approach a limiting value; thereafter the death rate due to interactions among the defects is constant. The $\alpha(1 - e^{-\beta D})$ term is the modification to the interaction rate to correct for the period before the interaction-death rate has become constant.

The inclusion in the present paper of the non-interactive death process characterized by λ is not a fundamental difference from the earlier work. Such a process could reasonably be envisaged as included within the parameter k . The present theory does show, however, how the part of k connected with the interactive processes is connected with α and β , thus permitting unraveling of the more fundamental parameters λ , a , and b from the k , α , and β that can be found by curve fitting.

Comparison with Experiment

The discussions by Hug and Kellerer (1963) and Haynes (1964, 1966) and by numerous authors drawing on Haynes's work have shown the usefulness of Eq. (13.d) -- and hence of the results of this paper -- in studying experimental data. Figure 1, therefore, is shown merely for further illustration. The figure shows the results of Sinclair and Morton (1966) for the survival of synchronized Chinese hamster cells to x rays at different times after synchronization. Evidently the curve shapes predicted by the theory are about right.

Dependence on Dose Rate

At first sight, the results of this paper for the survival appear to depend strongly on the dose rate (i.e. either on $\dot{c}$ or on dD/dt). Actually the values for the survival are not very sensitive to the rate until high doses are reached. If the exponential within the exponential in Eq. (7) is expanded in a series, the result is

$$S \approx \exp \left[-\lambda m - \frac{1}{2} a m^2 + (ab/6c) m^3 \dots \right] \quad (14.a)$$

or

$$S \approx \exp \left[-(\lambda / \langle z \rangle_1) D - (a/2 \langle z \rangle_1^2) D^2 \right]$$

$$+ (ab/6\langle z \rangle_1^2 (dD/dt)) D^3 \dots] \quad (14.b)$$

The second and the third terms in the exponent of this equation are equal at a dose of $3(dD/dt)(1/b)$. For example, for a dose rate of 100 rad/min and $b^{-1} = 10$ min (values that might apply to the Sinclair-Morton data in Fig. 1), equality occurs at 3000 rad. Below this dose the terms linear and quadratic in the dose dominate the exponent; these terms do not depend on the dose rate. Above this dose the survival begins to depend strongly on the dose rate. This is also evident from Eq. (9) for the extrapolation number, which depends exponentially on the square of the rate, and from Eq. (12) for the asymptotic-mean lethal dose, which depends inversely on the dose rate; these parameters characterize the survival curve for large doses.

The data in Fig. 1 are principally in a dose region that is not very sensitive to dose rate. However, when they were fitted by a least-squares procedure, they did give values of b^{-1} and the values were about 10 min. The uncertainty is about a factor of two, either way, reflecting the lack of sensitivity to the dose rate. The value is, however, about what one expects from fractionation phenomena; see below.

Fractionation

Suppose a population is exposed to low-LET radiation in two periods, T_1 and T_2 , separated by a time U . The survival can be calculated by the methods used above; the time U is included in the recovery factor, e^{-bt} . The result is

$$S \approx N(1 - e^{-bT_1})(1 - e^{-bT_2})(1 - e^{-bU}) S^* \quad (15),$$

where S^* is the survival when there is no intervening interval, i.e. there is a continuous irradiation for a time $T_1 + T_2$, and N is the same extrapolation number defined in Eq. (9). Figure 2 shows three examples: a survival curve in the absence of fractionation and two for different fixed intervals, U , between an irradiation of fixed length, T_1 , and variable length, T_2 .

If the two irradiation periods are long enough, then

$$S \approx N(1 - e^{-bU}) S^* \quad (16),$$

and the survival rises from S^* to N times S^* as the separation between the irradiations increases. This is what is observed experimentally (Elkind and Sutton, 1959). The time resolution of fractionation experiments is not good enough to yield a good value for the decay time, $1/b$; the best that can be

said is that they indicate times of about 15 to 30 minutes as compared to the 10 min noted above. Fractionation experiments are also strongly influenced by movement of the cells through their cycle; after the initial rise in survival indicated by Eqs. (15 & 16), oscillations due to movement of the cells through their life cycle are observed.

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Fig. 1

Fig. 2