

A HYPOTHETICAL STOCHASTIC MECHANISM OF
RADIATION EFFECTS IN SINGLE CELLS

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ABSTRACT This paper is in continuation to an earlier paper (Neyman and Puri, 1976), which deals with a hypothetical structural stochastic model of radiation effects in living cells. This model incorporates, among others, two important details of the mechanism, overlooked in its mathematical treatment by the previous workers. The first one is that the passage of a single "primary" radiation particle generates a "cluster" of secondaries which can produce "hits" that damage the living cells. The second detail concerns the time scales of radiation damage and of the subsequent repair. The events of arrival of a primary particle, its generation of secondary particles and their causing "hits" on the sensitive targets within the cells, all occur for all practical purposes instantly. On the other hand the subsequent changes in the damaged cell, such as repair, etc., appear to require measurable amounts of time. While the biological and physical justifications for some of the underlying assumptions of the model were discussed in the previous paper referred to above, the present paper is concerned mainly with the mathematical details and also how the model attempts to explain some of the empirical findings available in literature.

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1. INTRODUCTION The purpose of this paper is to present certain details of and also some novel developments in the study initiated five years ago and briefly summarized in Neyman and Puri (1976). This study concerns the chance mechanism of radiation effects on single living cells. The literature on the subject is quite rich. Important surveys are due to Hutchinson (1966), Upton (1974) and Mole (1975). Stochastic models of the phenomenon were proposed by Payne and Garrett (1975a, 1975b, 1978). Our own approach incorporates certain details of the actual mechanism not included in the earlier studies.

The phenomenon of irradiation is composed of at least two different parts: The source of irradiation emits particles which we label "primary" particles. When a single primary particle crosses a living cell, it generates a cluster of particles that we label "secondary". The sizes of clusters depend very much on the kind of irradiation, namely on whether it is of low or high linear energy transfer (LET). The low LET radiation is exemplified by X-rays and by gamma rays. Examples of high LET are α -particles and neutrons. Clusters generated by low LET primaries contain few secondaries. Those generated by high LET

primaries contain many secondaries. Figure 1, reproduced from Neyman and Puri (1976), illustrates the origin of the idea of clustering. This figure is based on a photograph of a cloud chamber exposed to a certain kind of irradiation. The white lines or "stripes" mark the tracks of various primary particles. These lines consist of minute droplets formed about ions generated by particles, primaries or secondaries. The greater the width of the track, the more are the ions and thus the greater is the number of secondary radiation particles. Also the width of the visible track characterizes the distances traveled by secondary particles generated by a single primary. It is visualized that the irradiation damage to cells is mainly due to secondary particles that "hit" the sensitive parts of living cells. For details see Berendsen (1964).

Figure 1 here (for legend see p. 36)

Another detail of the phenomenon of radiation damage that attracted our particular attention is the difference in the time scales of radiation damage and of the subsequent processes developing within the damaged cell. The events of arrival of a primary particle, of its generation of a cluster of secondary particles, and of their "hits" on the sensitive targets within the cells, all occur within a minute fraction of a second, that is for all practical purposes, instantly. On the other hand, the subsequent changes in the damaged cell, such as repair, etc., appear to require measurable amounts of time. Here it is appropriate to mention that, although originally we were inspired by the experimental work on animals such as mice, particularly due to Upton, et al (1964) and Upton, et al (1967), our present work is limited to radiation effects on cells of some homogeneous tissue. The biological and

physical justification for some of the underlying assumptions were discussed earlier by the authors (1976). In the present paper, we shall be mainly concerned with the mathematical details. Also the implications of the model are qualitatively compared with some of the empirical findings available in literature. Here, some fresh mathematical work appears necessary.

2. STOCHASTIC MODEL OF RADIATION EFFECTS ON SINGLE CELLS In order to allow some further flexibility for the underlying mechanism of the phenomenon in question, we consider a stochastic model which is slightly more general than the one considered earlier in Neyman and Puri (1976).

We consider a hypothetical experiment in which a live cell is subjected to a particular single kind of irradiation, perhaps gamma rays or α -particles but not simultaneously to several such kinds. The experiment continues over T units of time, with the preassigned total dose of irradiation denoted by D . The irradiation is supposed to be administered at a constant dose-rate, denoted by ρ . Thus $D = \rho T$. The assumptions of our stochastic model are as follows.

- (A₁) Primary radiation particles arrive at the cell Poisson-wise at the rate $\lambda(t)$ per unit of time and per unit volume. Here $\lambda(t) = \lambda > 0$ for $0 \leq t \leq T$ and $\lambda(t) = 0$ for $t > T$.
- (A₂) Each primary generates a cluster of secondary particles. The letter ν designates a random variable representing the number of secondaries in the cluster. No specific assumptions regarding the distribution of ν are made except that it has a finite expectation denoted by ν_1 .

The numbers ν of secondaries generated by several primaries are independent and identically distributed. Symbol $g(\cdot)$ designates the probability generating function (p.g.f.) of ν .

- (A₃) The secondary particles of a cluster travel independently from each other and independently from all other variables of the system.
- (A₄) The contemplated cell has two disjoint "targets" denoted by letters R and K, respectively. Letter R connotes "repairable" and letter K "killing". If target R is "hit" by a radiation particle then the cell experiences a "repairable" damage. On the other hand, if target K is hit, then the cell dies or is "inactivated". The two targets R and K are located in a region A within the cell called "region of accessibility". We postulate: (i) the passage of a primary radiation particle outside of A does not affect the cell considered; on the other hand, (ii) if a primary crosses A, then each of the ν generated secondaries has the same positive probabilities π_1 and π_2 of hitting the targets R or K, respectively.

It will be convenient to use the same letter A to designate the volume of the region of accessibility A.

- (A₅) The generation of a cluster of secondaries by a single primary particle and the subsequent possible hits on R and K occur instantaneously.

The above assumptions (A₁) through (A₅) concern the physical aspect of our stochastic model. We now turn to its biological aspect. Dead cells being of no interest, we begin by considering a cell that at time t has a non-negative number k of unrepaired hits of target R. During the subsequent short period of length h , say in $[t, t+h)$, the following events may occur in the cell considered.

- (i) Some of the damages incurred may be repaired,
- (ii) The cell may become cancerous,

(iii) The cell may die.

In addition, even if the cell considered has at time t no repairable damage, it may die in $[t, t+h)$ from causes not directly connected with irradiation. Our assumptions regarding these possibilities are as follows.

(A₆) We assume that the probability of more than one of the above events happening in $[t, t+h)$ is $o(h)$.

Given k , the conditional probability of a single repair in $[t, t+h)$ is

$$\alpha kh + o(h) .$$

Given k , the conditional probability of the cell becoming cancerous in $[t, t+h)$ is

$$\beta kh + o(h) .$$

Given k , the conditional probability of the cell dying in $[t, t+h)$ is

$$[\gamma k + \delta]h + o(h) .$$

Here α , β , γ and δ designate positive, possibly time dependent quantities of which δ refers to deaths not directly connected with radiation.

The last assumption underlying our hypothetical process refers to a cell that at time t is cancerous. We assume that the only change in it occurring in $[t, t+h)$ is death. The death will occur as a result of three possible events in $[t, t+h)$. One is a hit on target K , the other, say the γ risk, of one of the unrepaired damages becoming lethal, and the third, say the δ risk, of the cell dying from causes not directly related to radiation.

The theory embodying the above assumptions refers to three random variables $X(t)$, $Y(t)$ and $Z(t)$, all referring to an irradiated cell, defined as follows.

$X(t)$ = number of unrepaired hits on R, present at time t ,

$Y(t)$ = number of hits on R, turning the cell into a cancerous cell during $(0,t)$,

$Z(t)$ = number of all the cell-killing events experienced during $(0,t)$, that is hits on target K and those due to risks γ as well as δ .

To begin with we assume that all the rates λ , α , β , γ and δ are time-dependent and derive the expression for the joint p.g.f., say

$$G(s_1, s_2, s_3; t) = E[s_1^{X(t)} s_2^{Y(t)} s_3^{Z(t)}], \quad (1)$$

defined for $|s_i| \leq 1$, $i = 1, 2, 3$. This is done in the next section.

3. DERIVATION OF THE PROBABILITY GENERATING FUNCTION (1). Let for $t \geq 0$, $k, \ell, m = 0, 1, 2, \dots$,

$$P_{k, \ell, m}(t) = P[X(t)=k, Y(t)=\ell, Z(t)=m]. \quad (2)$$

Subject to the assumptions $(A_1) - (A_6)$, since $\{X(t), Y(t), Z(t)\}$ is a Markov process, it follows in a standard manner from Kolmogorov-Chapman equations, that for small positive h , we have

$$\begin{aligned} P_{k, \ell, m}(t+h) &= \alpha(k+1)hP_{k+1, \ell, m}(t) + \beta(k+1)hP_{k+1, \ell-1, m}(t) \\ &+ \gamma(k+1)hP_{k+1, \ell, m-1}(t) + \delta hP_{k, \ell, m-1}(t) \\ &+ \lambda Ah \sum_{i=0}^k \sum_{j=0}^m P_{i, \ell, j}(t) \sum_{n=0}^{\infty} P(v=n)P(\xi=k-i, \eta=m-j | v=n) \\ &+ [1-k(\alpha+\beta+\gamma)h - \delta h - \lambda Ah]P_{k, \ell, m}(t) + o(h). \end{aligned} \quad (3)$$

Here, for the sake of simplicity, the argument t of functions α , β , γ , δ and λ is suppressed. The summation symbol appearing as the coefficient of λAh corresponds to the probability that the random number ν of secondaries generated by a primary particle, produce just enough hits ξ on target R and hits η on target K to bring the values of $X(t+h)$ and $Z(t+h)$ to the levels k and m from the possible values of i and j they could have had at time t .

Subtracting $P_{k,\ell,m}(t)$ from both sides of (3), dividing by h and taking the limit as $h \rightarrow 0$, one obtains the forward Kolmogorov system of differential equations given by

$$\begin{aligned} dP_{k,\ell,m}(t)/dt &= \alpha(k+1)P_{k+1,\ell,m}(t) + \beta(k+1)P_{k+1,\ell-1,m}(t) \\ &+ \gamma(k+1)P_{k+1,\ell,m-1}(t) + \delta P_{k,\ell,m-1}(t) \\ &+ \lambda A \sum_{i=0}^k \sum_{j=0}^m P_{i,j,\ell}(t) \sum_{n=0}^{\infty} P(\nu=n)P(\xi=k-i, \eta=m-j | \nu=n) \\ &- [(\alpha+\beta+\gamma)k + \delta + \lambda A]P_{k,\ell,m}(t) \quad , \end{aligned} \quad (4)$$

with $k, \ell, m = 0, 1, 2, \dots$. Multiplying both sides of (4) by $s_1^k s_2^\ell s_3^m$ and summing for k, ℓ , and m , one obtains the first order partial differential equation for G , given by

$$G_t + [(\alpha+\beta+\gamma)s_1 - \alpha - \beta s_2 - \gamma s_3]G_{s_1} = [\lambda A g(\pi_1 s_1 + \pi_2 s_3 + 1 - \pi_1 - \pi_2) - \lambda A - \delta(1-s_3)]G, \quad (5)$$

where we have suppressed the arguments of G and of its partial derivatives G_t and G_{s_1} . This equation is to be solved now subject to the initial condition

$$G(s_1, s_2, s_3; 0) \equiv 1. \quad (6)$$

For this the auxiliary system of equations associated with (5) is given by

$$\frac{ds_1}{(\alpha+\beta+\gamma)s_1 - \alpha - \beta s_2 - \gamma s_3} = \frac{dt}{T} = \frac{dG}{\lambda A g (\pi_1 s_1 + \pi_2 s_3 + 1 - \pi_1 - \pi_2) - \lambda A - \delta (1 - s_3)}. \quad (7)$$

The first equation leads to

$$\frac{ds_1}{dt} - (\alpha+\beta+\gamma)s_1 = -(\alpha+\beta s_2 + \gamma s_3). \quad (8)$$

Treating s_2 and s_3 as fixed, this equation yields the solution

$$s_1 = \exp\left[\int_0^t (\alpha+\beta+\gamma)d\tau\right] \left\{C_1 - \int_0^t (\alpha+\beta s_2 + \gamma s_3) \exp\left[-\int_0^\tau (\alpha+\beta+\gamma)du\right]d\tau\right\}, \quad (9)$$

or equivalently

$$C_1 = s_1 \exp\left[-\int_0^t (\alpha+\beta+\gamma)d\tau\right] + \int_0^t (\alpha+\beta s_2 + \gamma s_3) \exp\left[-\int_0^\tau (\alpha+\beta+\gamma)du\right]d\tau, \quad (10)$$

where C_1 is the constant of integration. Again the second equation of (7), after substituting the expression for s_1 from (9), yields the solution for G subject to (6), as

$$\begin{aligned} \ln G = & -(1-s_3) \int_0^t \delta d\tau - A \int_0^t \lambda(\tau) \left[1 - g \left(\pi_2 s_3 + 1 - \pi_1 - \pi_2 + \right. \right. \\ & \left. \left. \pi_1 \exp\left[\int_0^\tau (\alpha+\beta+\gamma)du\right] \left\{ C_1 - \int_0^\tau (\alpha+\beta s_2 + \gamma s_3) \exp\left[-\int_0^u (\alpha+\beta+\gamma)dv\right]du \right\} \right) \right] d\tau. \end{aligned} \quad (11)$$

Finally, substituting the expression for C_1 from (10) in (11), we have

$$\begin{aligned} G(s_1, s_2, s_3; t) = & \exp\left[-(1-s_3) \int_0^t \delta(\tau) d\tau - \right. \\ & \left. A \int_0^t \lambda(\tau) \{1 - g[\phi(s_1, s_2, s_3; \tau, t)]\} d\tau\right], \end{aligned} \quad (12)$$

where

$$\phi(s_1, s_2, s_3; \tau, t) = (1 - \pi_1 - \pi_2) + \pi_2 s_3 + \pi_1 \psi(s_1, s_2, s_3; \tau, t) \quad (13)$$

and

$$\psi(s_1, s_2, s_3; \tau, t) = s_1 \exp\left[-\int_{\tau}^t (\alpha + \beta + \gamma) du\right] + \int_{\tau}^t (\alpha + \beta s_2 + \gamma s_3) \exp\left[-\int_{\tau}^v (\alpha + \beta + \gamma) du\right] dv. \quad (14)$$

In particular, when $\lambda(\tau) = \lambda$ for $0 < \tau \leq T$, and zero otherwise, (12)

becomes

$$G(s_1, s_2, s_3; t) = \exp\left[-(1-s_3) \int_0^t \delta(\tau) d\tau - \lambda A \int_0^{\min(t, T)} \{1 - g[\phi(s_1, s_2, s_3; \tau, t)]\} d\tau\right]. \quad (15)$$

Furthermore, if α, β, γ and δ are all independent of time, then using (13), (14) and (15), we have

$$G(s_1, s_2, s_3; t) = \exp\left[-(1-s_3)\delta t - \lambda A \int_{\max(0, t-T)}^t \{1 - g[J(s_1, s_2, s_3; \tau)]\} d\tau\right], \quad (16)$$

where

$$J(s_1, s_2, s_3; \tau) = (1 - \pi_1 - \pi_2) + \pi_2 s_3 + \pi_1 h(s_1, s_2, s_3; \tau), \quad (17)$$

$$h(s_1, s_2, s_3; \tau) = s_1 \exp[-(\alpha + \beta + \gamma)\tau] + (\alpha + \beta s_2 + \gamma s_3) (\alpha + \beta + \gamma)^{-1} [1 - \exp(-[\alpha + \beta + \gamma]\tau)]. \quad (18)$$

The result (16) was reported earlier in Neyman and Puri (1976), in the present form.

As mentioned in the Introduction, the subject of this paper includes the comparison of certain empirical findings with the implications of the hypothetical stochastic model just developed. In this connection it appears expedient to modify the above formulae by altering the notation so as to conform with that customary in radio-biological studies. One

of them is the "dose" D of irradiation applied during the duration T of the experiment, and we have $D = \rho T$, where ρ stands for the dose-rate of irradiation supposed to remain constant during the experiment. Furthermore, the results of empirical studies are formulated with reference to different kinds of irradiation, each characterized by the mean size v_1 of clusters and, presumably, of varying values of δ . It is not improbable that values of δ depend on the dose-rate at which the irradiation is applied.

In order to cover all the possibilities, we set

$$A\lambda v_1 = \theta\rho ,$$

where θ is a positive constant. Furthermore, in the discussion of shapes of the so-called dose-response curves, it would be convenient to consider δ as a function of ρ .

Now, equations (15) and (16) become, respectively

$$G(s_1, s_2, s_3; t) = \exp\left[-(1-s_3) \int_0^t \delta(\rho, \tau) d\tau - \frac{\theta\rho}{v_1} \int_0^{\min(t, D/\rho)} \{1-g[\phi(s_1, s_2, s_3; \tau, t)]\} d\tau\right] , \quad (19)$$

and

$$G(s_1, s_2, s_3; t) = \exp\left[-(1-s_3)\delta(\rho)t - \frac{\theta\rho}{v_1} \int_{\max(0, t-D/\rho)}^t \{1-g[J(s_1, s_2, s_3; \tau)]\} d\tau\right] . \quad (20)$$

In the rest of the paper, using the basic formulae (19) and (20), we derive results considered to be the theoretical counterparts of the various empirical observations available in literature.

4. SURVIVAL PROBABILITIES. Motivated by certain empirical findings, the purpose of this section is to deduce a formula for the probability that the irradiated cell will survive up to T.

It is known that the behavior of the logarithm of the proportion of cells surviving immediately following the exposure of a total radiation dose D (measured in rads), when plotted against this dose varies with the type of radiation. In general, it is a decreasing function of D. However, for high LET radiation such as neutrons or α -particles, this plot is almost like a straight line, whereas for the low LET radiation this plot is nonlinear and shows what is commonly called the "shouldering effect". Essentially, this effect corresponds to a degree of concavity in the plot. The reader may refer for this to the so called dose-survival curves exhibited in Barendsen (1968), Hutchinson (1966), Hall and Bedford (1964), among others (see also figure 2). We now proceed first to obtain their theoretical counterpart, namely the survival probabilities under the present model and later shall compare them with the empirical survival curves.

Figure 2 here (for legend see p. 36)

For this we have from (19) after some simplification

$$\begin{aligned}
 P(\text{cell is 'alive' at } t) &= G(1,1,0;t) & (21) \\
 &= \exp \left[- \int_0^t \delta(\rho, \tau) d\tau - \frac{\theta \rho}{v_1} \int_0^{\min(t, D/\rho)} \{1 - g[L(\tau, t)]\} d\tau \right],
 \end{aligned}$$

where

$$L(\tau, t) = 1 - \pi_2 - \pi_1 \int_{\tau}^t \exp \left[- \int_{\tau}^u (\alpha + \beta + \gamma) dv \right] \gamma(u) du. \quad (22)$$

In particular, when all the rates are independent of time, we have from (20),

$$P(\text{cell is 'alive' at } t) = \exp\left[-\delta(\rho)t - \frac{\theta\rho}{\nu_1} \int_{\max(0, t-D/\rho)}^t \{1-g[K(\tau)]\}d\tau\right], \quad (23)$$

where

$$K(\tau) = J(1,1,0;\tau) = 1 - \pi_2 - \frac{\pi_1\gamma}{(\alpha+\beta+\gamma)} \{1 - \exp[-(\alpha+\beta+\gamma)\tau]\}. \quad (24)$$

The theoretical counterpart for the logarithm of the proportion of cells surviving immediately following the exposure to the total radiation dose D is obtained from (21) or (23) by taking its logarithm and putting $t = T = D/\rho$. For instance, for the case with constant rates, we have from (23),

$$\ln P(\text{cell is 'alive' at } T) = -\frac{\delta(\rho)D}{\rho} - \frac{\theta\rho}{\nu_1} \int_0^{D/\rho} \{1-g[K(\tau)]\}d\tau, \quad (25)$$

where $K(\tau)$ is given by (24). We shall consider this case in some detail and study the behavior of (25) as a function of dose D , specially in the light of the empirical findings mentioned in the beginning of this section. Taking first two derivatives of (25) with respect to D and using (24), we obtain

$$\frac{\partial \ln P}{\partial D} = -\frac{\delta(\rho)}{\rho} - \frac{\theta}{\nu_1} \{1-g[K(D/\rho)]\}, \quad (26)$$

$$\frac{\partial^2 \ln P}{\partial D^2} = -\frac{\theta\pi_1\gamma}{\nu_1\rho} g'[K(D/\rho)]\exp[-D(\alpha+\beta+\gamma)/\rho], \quad (27)$$

where $g'(\cdot)$ denotes the derivative of $g(\cdot)$. As expected, (26) being negative, expression (25) is a decreasing function of D . Also as long

as $\pi_1 \gamma$ is positive, and hence (27) is strictly negative, (25) is strictly a concave function. Consequently the plot of (25) may often show some shouldering effect. However, this effect may become negligible for high LET radiation characterized by very large values ν_1 of secondaries generated by a single primary. Thus, for the high LET radiation, we may take approximately.

$$g(s) \approx g(0) , \quad (28)$$

for s not close to one. Since in our case $K(t) \leq 1 - \pi_2$ for all $t \geq 0$ (see equation (24)), with $\pi_2 > 0$ the approximation (28) used for $g[K(\tau)]$ in (25) may not be unreasonable. Thus we have approximately

$$\ln P(\text{cell is 'alive' at } T) \approx - \frac{\delta(\rho)D}{\rho} - \frac{\theta D}{\nu_1} [1 - g(0)] . \quad (29)$$

This being linear in D , explains the absence of shouldering effect for the case of high LET radiation such as neutron or α -radiation, as also observed empirically (see Figure 2).

Again, the behavior of the empirical dose-survival curves also varies with the dose rate ρ , specially for a low LET radiation case; for instance for the case of gamma-radiation see Hall and Bedford (1964) and figures 3 and 4 taken from Bedford and Hall (1963). In the case of a low dose rate, a given total dose D is administered uniformly over a longer period of time compared to the case of a high dose rate. The empirical survival curves for the case of high dose rates, in general, tend to be steeper than those for the low dose rates. However, the dependence of the dose-survival curves on the dose rate appears less significant for the case of a high LET radiation. Such behavior of the

survival curves, specially for low LET radiation, can now be explained by our expression (25), while treating it also as a function of the dose rate ρ . Taking the partial derivative of (26) with respect to ρ and using (24), we have

$$\frac{\partial^2 \ln P}{\partial \rho \partial D} = - \frac{d[\delta(\rho)/\rho]}{d\rho} + \frac{\pi \gamma D}{\rho^2} g'[K(D/\rho)] \exp[-D(\alpha+\beta+\gamma)/\rho] . \quad (30)$$

The plot of $\ln P$ as a function of D will be steeper for higher dose rates provided (30) is negative. In particular, this will occur if the derivative of $[\delta(\rho)/\rho]$ and hence of $\delta(\rho)$ is sufficiently positive. It should be noted that for this, the dependence of δ on ρ is essential. Of course, for high LET radiation case, this may not be needed.

Figures 3 & 4 here (for legend see pp. 36 & 37)

5. PROBABILITY OF A CELL EVER GETTING CANCEROUS. On occasion, empirical curves of incidence of cancer plotted against total radiation dose D , show a maximum. For example, see Upton et al (1964). A roughly similar behavior has been observed for the frequency of occurrences of pink somatic mutations in stamen hairs of *Tradescantia* with varying doses of exposures to X-ray and neutrons (see figure 5 taken from Sparrow, et al (1972) and figure 6 taken from Nauman, et al (1975)). Here, according to these authors, each hair consisting of several cells resembles, in a sense, a culture of micro-organisms or cells in culture (see Nauman, et al (1975)).

As a possible theoretical counterpart of these findings, we now derive a formula giving the probability that an irradiated cell will ever become cancerous. We do so by assuming that the rates α , β , γ , etc. are time-independent. Using assumption (A_6) of our model, it is easily seen that

$$\begin{aligned}
P(\text{cell ever gets cancerous}) &= \int_0^{\infty} \sum_{k=0}^{\infty} P[X(t)=k, Y(t)=0, Z(t)=0] k \beta dt \\
&= \beta \int_0^{\infty} \frac{\partial G(s_1, 0, 0; t)}{\partial s_1} \Big|_{s_1=1} dt . \quad (31)
\end{aligned}$$

Figures 5 & 6 here (for legend see p. 37)

Using (20), (17) and (18), we have

$$\begin{aligned}
\frac{\partial G(s_1, 0, 0; t)}{\partial s_1} \Big|_{s_1=1} &= G(1, 0, 0; t) \frac{\theta \rho \pi_1}{v_1} \\
&\cdot \int_{\max(0, t-D/\rho)}^t g'[J(1, 0, 0; \tau)] \exp[-(\alpha + \beta + \gamma)\tau] d\tau . \quad (32)
\end{aligned}$$

On the other hand using (17) and (18), it easily follows that the integral on the right side of (32) simplifies to

$$(\beta + \gamma)^{-1} \left[g\{R[\max(0, t - \frac{D}{\rho})]\} - g\{R(t)\} \right] , \quad (33)$$

where

$$R(t) = J(1, 0, 0; t) = 1 - \pi_2 - \frac{\pi_1 (\beta + \gamma)}{\alpha + \beta + \gamma} \{1 - \exp[-(\alpha + \beta + \gamma)t]\} . \quad (34)$$

Thus using these in (31), we have

$$\begin{aligned}
P(\text{cell ever gets cancerous}) \\
&= \frac{\beta \theta \rho}{v_1 (\beta + \gamma)} \int_0^{\infty} G(1, 0, 0; t) \left[g\{R[\max(0, t - \frac{D}{\rho})]\} - g\{R(t)\} \right] dt . \quad (35)
\end{aligned}$$

Alternatively using (20), this can be rewritten as

$$P(\text{cell ever gets cancerous}) = \frac{\beta}{\beta + \gamma} (\mathcal{J}_1 + \mathcal{J}_2), \quad (36)$$

where

$$\begin{aligned} \mathcal{J}_1 &= \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{g[1-\pi_2] - g[R(t)]\} \\ &\quad \cdot \exp\left[-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^t \{1-g[R(\tau)]\}d\tau\right] dt \end{aligned} \quad (37)$$

and

$$\begin{aligned} \mathcal{J}_2 &= \frac{\theta\rho}{v_1} \int_{D/\rho}^{\infty} \{g[R(t-\frac{D}{\rho})] - g[R(t)]\} \\ &\quad \cdot \exp\left[-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{1-g[R(t-\tau)]\}d\tau\right] dt . \end{aligned} \quad (38)$$

However \mathcal{J}_1 and \mathcal{J}_2 can be further simplified as follows.

$$\begin{aligned} \mathcal{J}_1 &= \frac{\theta\rho}{v_1} \int_0^{D/\rho} \exp[-\delta(\rho)t] \left[\{1-g[R(t)]\} \exp\left(-\frac{\theta\rho}{v_1} \int_0^t \{1-g[R(\tau)]\}d\tau\right) \right] dt \\ &\quad - \frac{\theta\rho}{v_1} [1-g(1-\pi_2)] \cdot \int_0^{D/\rho} \exp\left[-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^t \{1-g[R(\tau)]\}d\tau\right] dt . \end{aligned} \quad (39)$$

Integrating the first integral by parts we have, after some simplification,

$$\begin{aligned} \mathcal{J}_1 &= 1 - \exp\left[-\frac{\delta(\rho)}{\rho} D - \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{1-g[R(\tau)]\}d\tau\right] - \\ &\quad \left\{ \delta(\rho) + \frac{\theta\rho}{v_1} [1-g(1-\pi_2)] \right\} \cdot \int_0^{D/\rho} \exp\left[-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^t \{1-g[R(\tau)]\}d\tau\right] dt . \end{aligned} \quad (40)$$

Similarly we can write

$$\begin{aligned} \mathcal{J}_2 &= \frac{\theta\rho}{v_1} \int_{D/\rho}^{\infty} \left[\{1-g[R(t)]\} - \{1-g[R(t-\frac{D}{\rho})]\} \right] \\ &\quad \cdot \exp\left[-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_{t-\frac{D}{\rho}}^t \{1-g[R(\tau)]\}d\tau\right] dt . \end{aligned} \quad (41)$$

Assuming that $\delta(\rho) > 0$, this yields after integrating by parts,

$$\begin{aligned} \mathcal{J}_2 = & \exp\left[-\frac{\delta(\rho)D}{\rho} - \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{1-g[R(\tau)]\}d\tau\right] \\ & - \delta(\rho) \int_{D/\rho}^{\infty} \exp\left[-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_{t-\frac{D}{\rho}}^t \{1-g[R(\tau)]\}d\tau\right] dt. \end{aligned} \quad (42)$$

Substituting these expressions in (36), we finally have for the case where $\delta(\rho) > 0$,

$$\begin{aligned} P(\text{cell ever gets cancerous}) = & \frac{\beta}{\beta+\gamma} \left[1 - \left\{ \delta(\rho) + \frac{\theta\rho}{v_1} [1-g(1-\pi_2)] \right\} \right. \\ & \cdot \int_0^{D/\rho} \exp\left(-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^t \{1-g[R(\tau)]\}d\tau\right) dt \\ & \left. - \delta(\rho) \int_{D/\rho}^{\infty} \exp\left(-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_{t-\frac{D}{\rho}}^t \{1-g[R(\tau)]\}d\tau\right) dt \right]. \end{aligned} \quad (43)$$

However when $\delta(\rho) = 0$, we need to redo the part of the above calculations following (41). This would lead to

$$\begin{aligned} P(\text{cell ever gets cancerous}) & = \frac{\beta}{\beta+\gamma} \left[1 - \frac{\theta\rho}{v_1} [1-g(1-\pi_2)] \cdot \int_0^{D/\rho} \exp\left(-\frac{\theta\rho}{v_1} \int_0^t \{1-g[R(\tau)]\}d\tau\right) dt \right. \\ & \left. - \exp\left(-\frac{\theta D}{v_1} [1-g[R(\infty)]]\right) \right], \end{aligned} \quad (44)$$

where from (34) we have

$$R(\infty) = 1 - \pi_2 - \frac{\pi_1(\beta+\gamma)}{(\alpha+\beta+\gamma)}. \quad (45)$$

In order to explain the empirical findings mentioned in the beginning of this section, using the theory developed here, we now prove the following proposition.

PROPOSITION. Let the rates α, β, γ and $\delta(\rho)$ be all independent of time. Then, under the assumptions $(A_1) - (A_6)$, $P(\text{cell ever gets cancerous})$ treated as a function of D has exactly one maximum if and only if

$$\delta(\rho) \int_0^{\infty} \exp\left(-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{g[R(u)] - g[R(u+t)]\} du\right) \cdot \{1 - g[R(t)]\} dt < 1 - g(1 - \pi_2) \quad (46)$$

whenever $\delta(\rho) > 0$, and

$$\exp\left(-\frac{\theta\rho}{v_1} \int_0^{\infty} \{g[R(u)] - g[R(\infty)]\} du\right) \{1 - g[R(\infty)]\} < 1 - g(1 - \pi_2) \quad (47)$$

whenever $\delta(\rho) = 0$. Otherwise $P(\text{cell ever gets cancerous})$ is an increasing function of D .

PROOF. Let $\delta(\rho) > 0$. Differentiating (43) with respect to D , after some algebraic simplification, we have

$$\begin{aligned} \frac{\partial P}{\partial D} = & \frac{\beta}{\beta + \gamma} \frac{\theta}{v_1} \exp\left(-\frac{\delta(\rho)D}{\rho} - \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{1 - g[R(\tau)]\} d\tau\right) \\ & \cdot \left[\delta(\rho) \int_0^{\infty} \exp\left(-\delta(\rho)t - \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{g[R(\tau)] - g[R(t+\tau)]\} d\tau\right) \right. \\ & \left. \cdot \{1 - g[R(t)]\} dt - [1 - g(1 - \pi_2)] \right] \quad (48) \end{aligned}$$

Since $R(t)$ is a decreasing function of t with $R(0) = 1 - \pi_2$, the expression in the last square brackets of (48) is positive when $D=0$ and it decreases as D increases. Furthermore, it may become negative if and only if (46) holds, the only case in which the solution D^* of $\frac{\partial P}{\partial D} = 0$ exists. That the solution D^* , whenever it exists, is indeed a point of maximum, can easily be verified by showing that $\frac{\partial^2 P}{\partial D^2} \Big|_{D=D^*} < 0$. Again in

the event (46) fails to hold, (48) always stays positive for all D , so that $P(\text{cell ever gets cancerous})$ is an increasing function of D . A similar analysis using (44) leads to (47) for the case when $\delta(\rho) = 0$. \square

It is evident that under appropriate conditions on the parameters as indicated by (46) and (47), our model is consistent with empirical findings of Upton, et al (1964) and also with those in figures 5 and 6. A rather interesting fact emerging out of the above proposition is that in our model, in order to have a point of maximum in these curves, it is necessary although not sufficient that π_2 be positive.

Before we close this section, it is interesting to make the following observation concerning the behavior of $P(\text{cell ever gets cancerous})$ as a function of the dose rate ρ . Considering first the case with $\delta(\rho) \equiv 0$, the corresponding expression (44), after routine transformations, can be rewritten as

$$\begin{aligned}
 & P(\text{cell ever gets cancerous}) \\
 &= \frac{\beta}{\beta + \gamma} \left[1 - \frac{\theta}{v_1} [1 - g(1 - \pi_2)] \int_0^D \exp\left(-\frac{\theta}{v_1} \int_0^\xi \{1 - g[R(n/\rho)]\} dn\right) d\xi \right. \\
 &\quad \left. - \exp\left(-\frac{\theta D}{v_1} \{1 - g[R(\infty)]\}\right) \right]. \tag{49}
 \end{aligned}$$

Since $R(\cdot)$ is a decreasing function of its argument, it is easily seen from (49) that $P(\text{cell ever gets cancerous})$ is a decreasing function of the rate ρ . However this does not appear compatible with what is empirically observed, at least in the case of mice [see Upton, et al (1964) and Upton, et al (1967)] and also for the case of pink somatic mutations in stamen hairs of *Tradescantia* [see Nauman, et al (1975) and figure 6], the latter case being more close to what one might expect in cells. Thus, it appears essential to assume that $\delta(\rho)$ is positive in order to fit such

empirical findings. For this one needs to study more closely the expression (43). After suitable transformations, this expression can be written as

P(cell ever gets cancerous)

$$\begin{aligned}
 &= \frac{\beta}{\beta + \gamma} \left[1 - \left\{ \frac{\delta(\rho)}{\rho} + \frac{\theta}{v_1} [1 - g(1 - \pi_2)] \right\} \right. \\
 &\quad \cdot \int_0^D \exp\left(-\frac{\delta(\rho)}{\rho} \xi - \frac{\theta}{v_1} \int_0^\xi \{1 - g[R(\eta/\rho)]\} d\eta\right) d\xi \\
 &\quad \left. - \frac{\delta(\rho)}{\rho} \int_D^\infty \exp\left(-\frac{\delta(\rho)}{\rho} \xi - \frac{\theta}{v_1} \int_{\xi-D}^\xi \{1 - g[R(\eta/\rho)]\} d\eta\right) d\xi \right]. \quad (50)
 \end{aligned}$$

The empirical findings of Nauman, et al., illustrated in figure 6, show that the dose response curves begin by increasing with D , that they may have a maximum, and that they depend strongly on the dose rate ρ : the higher the dose rate, the higher the corresponding curves. It is interesting that, in order to achieve a qualitative consistency of (50) with these findings, it is sufficient to make an appropriate assumption regarding the function $\delta(\rho)$.

6. MEDIAN LIFE-SHORTENING. Several studies on the median life-shortening due to irradiation of animals, such as mice, have been carried out. In particular, our own interest in this direction was inspired in part by papers due to Upton, et al. (1964) and Upton, et al. (1967). Looking at the median life-shortening versus dose curves (see figure 7), it appears that while the effectiveness of low LET radiation, such as gamma-rays, varies with dose-rate, those of high LET, such as neutrons, are relatively dose-rate independent for smaller doses, but for higher doses may show some dose-rate dependence. Also in general, these

curves often show a maximum before showing some drop in the median life-shortening for higher doses.

The reader will notice that the above findings of Upton, et al (1964) refer to experimental mice, while our present study deals with irradiated cells. Clearly, it is not impossible that, with some modifications, the single irradiated cells behave like irradiated mice, even though the bodies of the mice represent conglomerations of a variety of different tissues of cells. Thus, it is interesting to examine whether the present model could fit the life shortening findings relating to mice.

The life shortening experiments of Upton, et al, dealt only with mice that survived the first 30 days after the start of irradiation. Then they were observed until their death. The median life-shortening was observed for only these animals, when compared to a control group of similar animals which also survived 30 days from the start, but without receiv-

Figure 7 here (for legend see p. 37)

ing any radiation. Visualising something analogous for a single living cell, let L be the length of "life" of a cell measured from the start of irradiation. Also unless otherwise mentioned, in this section we shall restrict our study to the case where the rate δ is time-dependent while the rates α, β and γ are constants. Thus, from a modified version of (23), we have

$P(L > t) = P(\text{cell is alive at } t)$

$$= \exp \left\{ - \int_0^t \delta(\rho, \tau) d\tau - \frac{\theta \rho}{v_1} \int_{\max(0, t - \frac{D}{\rho})}^t \{1 - g[K(\tau)]\} d\tau \right\}, \quad (51)$$

where $K(\tau)$ is given by (24). However, what we need is the conditional probability of survival up to t , given that the cell survived for a fixed period ℓ (in the experiment of Upton, et al, ℓ was equal to 30 days).

Thus, for $t > \ell$ we have

$$P(L > t | L > \ell) = \exp \left[- \int_{\ell}^t \delta(\rho, \tau) d\tau - Q_{\ell}(\rho, D, t) \right], \quad (52)$$

where

$$Q_{\ell}(\rho, D, t) = \frac{\theta \rho}{v_1} \left\{ \int_{\max(0, t - \frac{D}{\rho})}^t \{1 - g[K(\tau)]\} d\tau - \int_{\max(0, \ell - \frac{D}{\rho})}^{\ell} \{1 - g[K(\tau)]\} d\tau \right\}. \quad (53)$$

The median length of life denoted by $t_{\ell}^*(\rho, D)$ (conditional on the survival up to period ℓ) is now given by the solution for $t (t > \ell)$ of the equation

$$\ln 2 = \int_{\ell}^t \delta(\rho, \tau) d\tau + Q_{\ell}(\rho, D, t). \quad (54)$$

Also for the control population without irradiation, the analogous median length of life is given by the solution t_{ℓ}^{**} of t of the equation

$$\ln 2 = \int_{\ell}^t \delta_0(\tau) d\tau, \quad (55)$$

where $\delta_0(\cdot)$ is the time-dependent risk of death in the absence of irradiation, which in general may be different from the limit of $\delta(\rho, \tau)$ as $\rho \rightarrow 0$. The curves (figure 7) of Upton, et al (1964) now correspond simply to $s_\lambda(\rho, D)$, the median life-shortening given by

$$s_\lambda(\rho, D) = t_\lambda^{**} - t_\lambda^*(\rho, D) . \quad (56)$$

In the light of an earlier remark made in the last paragraph of §5, for the case of low LET radiation, such as gamma rays, we shall assume that $\delta(\rho, \tau)$ is a nondecreasing function of ρ , whereas for the high LET radiation, we shall assume that the dependence of δ on ρ is practically negligible. In the following subsections we consider separately the two cases (a) $\lambda=0$ and (b) $\lambda > 0$, and in each case we shall attempt to see how our model holds out in comparison with the curves exhibited in figure 7.

(a). CASE WHEN $\lambda = 0$.

(A). We first consider the case of low LET radiation, where δ is assumed to be a nondecreasing function of ρ . When $\lambda = 0$, t_0^{**} and t_0^* are respectively the solutions for t of the equations

$$\ln 2 = \int_0^t \delta_0(\tau) d\tau , \quad (57)$$

and

$$\ln 2 = \int_0^t \delta(\rho, \tau) d\tau + Q_0(\rho, D, t) , \quad (58)$$

where

$$Q_0(\rho, D, t) = \frac{\theta \rho}{v_1} \int_{\max(0, t-D/\rho)}^t \{1 - g[K(\tau)]\} d\tau \quad (59)$$

Since $K(t)$ of (24) is decreasing and hence $1 - g(K(t))$ is an increasing function of t , it follows that Q_0 is an increasing function of t . Also

$$\frac{\partial Q_0}{\partial \rho} = \begin{cases} \frac{\theta}{v_1} \int_0^t \{1 - g[K(\tau)]\} d\tau & ; \quad \text{if } t < \frac{D}{\rho} \\ \frac{\theta}{v_1} \left[\int_{t-\frac{D}{\rho}}^t \{1 - g[K(\tau)]\} d\tau - \frac{D}{\rho} \{1 - g[K(t-\frac{D}{\rho})]\} \right] & , \quad \text{if } t > \frac{D}{\rho} . \end{cases} \quad (60)$$

In either case $\partial Q_0 / \partial \rho$ is positive; that it is positive also when $t > D/\rho$ follows from the fact that $1 - g[K(t)]$ is increasing in t . Thus Q_0 is an increasing function of ρ . Furthermore, it is clear from (59) that Q_0 is a nondecreasing function of D . Thus $Q_0(\rho, D, t)$ is nondecreasing in each of its three arguments. From this and that $\delta(\rho, t)$ is nondecreasing in ρ and the fact that $t_0^*(\rho, D)$ is the solution of (58), we make the following observations:

(i) For fixed dose rate ρ , the median length of life $t_0^*(\rho, D)$ is a decreasing function of D , as long as $D \leq D_0^*(\rho)$ and thereafter for all $D > D_0^*(\rho)$, we have $t_0^*(\rho, D) = D_0^*(\rho)/\rho$, where $D_0^*(\rho)$ is the solution for D of the equation

$$\ln 2 = \int_0^{D/\rho} \delta(\rho, \tau) d\tau + Q_0(\rho, D, D/\rho) \quad (61)$$

From this it follows that the median life-shortening $s_0(\rho, D) = t_0^{**} - t_0^*(\rho, D)$

is an increasing function of D as long as $D \leq D_0^*(\rho)$ and thereafter for all $D > D_0^*(\rho)$, $s_0(\rho, D) = t_0^{**} - [D^*(\rho)/\rho]$.

(ii) Again it follows that if $\rho_1 > \rho_2$, we have $t_0^*(\rho_1, D) \leq t_0^*(\rho_2, D)$, for all D , or equivalently $s_0(\rho_1, D) \geq s_0(\rho_2, D)$, for all D .

Note that the above behavior of the median life-shortening is 'approximately' compatible with the corresponding observed curves for gamma rays of Upton, et al (1964), depending upon where the solution $D_0^*(\rho)$ of (61) actually falls.

(B). In order to explain the corresponding curves (see figure 7) for neutron radiation, we assume that the dependence of δ on ρ is practically negligible. Also, as pointed out earlier, the distribution of the number ν of secondary particles caused by a neutron particle given that $\nu > 0$, is concentrated typically on much larger values as compared to those caused by a photon in the case of gamma rays. The typical value of ν may be in thousands or sometimes more. Thus as before, for the neutron radiation case $g[K(t)]$ would be close to $g(0)$, so that approximately we have from (51)

$$P(L > t) \approx \exp \left\{ - \int_0^t \delta(\tau) d\tau - \frac{\theta\rho}{\nu_1} [1 - g(0)] \min(t, \frac{D}{\rho}) \right\} . \quad (62)$$

Also, analogous to (56), our t_0^* approximately satisfies the equation

$$\ln 2 = \int_0^t \delta(\tau) d\tau + \frac{\theta\rho}{\nu_1} [1 - g(0)] \min(t, \frac{D}{\rho}) . \quad (63)$$

Clearly, for fixed ρ , the solution of (63) for t is approximately independent of the rate ρ for small doses D , whereas for larger doses it will depend on the rate ρ . In fact when δ is constant in time, we can explicitly solve (63) yielding

$$t_0^*(\rho, D) \approx \begin{cases} \frac{1}{\delta} \ln 2 - \frac{\theta}{\delta v_1} [1 - g(0)] D, & \text{if } D \leq D_0^*(\rho) \\ \frac{v_1 \ln 2}{\delta v_1 + \rho \theta [1 - g(0)]} = \frac{D_0^*(\rho)}{\rho}, & \text{if } D > D_0^*(\rho), \end{cases} \quad (64)$$

where, as before, $D_0^*(\rho)$ is the solution for D of the equation analogous to (61), and is given by

$$D_0^*(\rho) = \frac{\rho v_1 \ln 2}{\delta v_1 + \rho \theta [1 - g(0)]} . \quad (65)$$

Also, when δ_0 is constant (typically δ_0 is no greater than δ), we have from (57)

$$t_0^{**} = \frac{\ln 2}{\delta_0} , \quad (66)$$

so that the median life-shortening is approximately given by

$$s_0(\rho, D) = t_0^{**} - t_0^*(\rho, D) \approx \begin{cases} \left(\frac{1}{\delta_0} - \frac{1}{\delta}\right) \ln 2 + \frac{\theta}{\delta v_1} [1 - g(0)] D, & \text{if } D \leq D_0^*(\rho) \\ \frac{\ln 2}{\delta_0} - \frac{v_1 \ln 2}{\delta v_1 + \rho \theta [1 - g(0)]} , & \text{if } D > D_0^*(\rho) . \end{cases} \quad (67)$$

Thus for fixed ρ , the median life-shortening increases approximately linearly as long as $D \leq D_0^*(\rho)$ and then stays constant, this constant being larger for larger dose rates ρ . Note that for smaller doses i.e. for $D \leq D_0^*(\rho)$, the median life-shortening is almost independent of dose rate ρ , the boundary $D_0^*(\rho)$ being larger for larger rates.

The above theoretical conclusions are approximately compatible with the results of experiments. For instance, the present model does

explain in part the empirical observations quoted in the beginning of §6 (see also figure 7). However it does not appear to imply the occasional maxima observed in the median life-shortening curves for animals. This may partly be due to the fact that the above analysis is too approximate. Furthermore, since the present model is meant primarily for cells, it is unlikely to fit all the aspects of the behavior of the animals. Somewhat similar observations are made for the case with $\lambda > 0$. This case is dealt with below.

(b). CASE WHEN $\lambda > 0$.

(A). First we consider the case of low LET radiation, assuming that δ is a nondecreasing function of ρ . As before, we begin by studying the behavior of the function $Q_\lambda(\rho, D, t)$ given by (53). Again, since $1 - g[K(t)]$ is an increasing function of t , it follows that for fixed ρ , the function $Q_\lambda(\rho, D, t)$ is nondecreasing both in t and D . Thus for fixed dose rate ρ , the behavior of $Q_\lambda(\rho, D, t)$ and hence of $t_\lambda^*(\rho, D)$ and the median life-shortening $s_\lambda(\rho, D)$ are similar to those found earlier for the case with $\lambda = 0$. Unfortunately the behavior of $Q_\lambda(\rho, D, t)$ as a function of ρ is not quite clear. Some qualitative aspects of this are described below.

Remembering that $\lambda < t$, the following three cases arise:

$$(i) \quad T = \frac{D}{\rho} < \lambda \Leftrightarrow \rho > \frac{D}{\lambda}$$

$$(ii) \quad \lambda < \frac{D}{\rho} = T < t \Leftrightarrow \frac{D}{t} < \rho < \frac{D}{\lambda}$$

$$(iii) \quad T = \frac{D}{\rho} > t \Leftrightarrow \rho < \frac{D}{t} .$$

(i) Case with $\rho > \frac{D}{\lambda}$: Here, using (53), we have

$$\begin{aligned}
Q_{\ell}(\rho, D, t) &= \frac{\theta\rho}{v_1} \left[\int_{t-\frac{D}{\rho}}^t \{1 - g[K(\tau)]\} d\tau - \int_{\ell-\frac{D}{\rho}}^{\ell} \{1 - g[K(\tau)]\} d\tau \right] \\
&= \frac{\theta\rho}{v_1} \left[\int_{\ell-\frac{D}{\rho}}^{\ell} g[K(\tau)] d\tau - \int_{t-\frac{D}{\rho}}^t g[K(\tau)] d\tau \right] \\
&= \frac{\theta\rho}{v_1} \int_0^{D/\rho} \{g[K(\ell-\tau)] - g[K(t-\tau)]\} d\tau . \tag{68}
\end{aligned}$$

Differentiating with respect to ρ , and after some simplification, we have

$$\frac{\partial Q_{\ell}(\rho, D, t)}{\partial \rho} = \frac{\theta}{v_1} \int_0^{D/\rho} \left(\int_{\tau}^{D/\rho} \{g'[K(\ell-u)] K'(\ell-u) - g'[K(t-u)] K'(t-u)\} du \right) d\tau , \tag{69}$$

where g' and K' are the corresponding derivatives. Now, since

$$\frac{d}{dt} \{g'[K(t)] K'(t)\} = g''[K(t)] [K'(t)]^2 + g'[K(t)] K''(t), \tag{70}$$

and using (24)

$$\left. \begin{aligned}
K'(t) &= -\pi_1 \gamma \exp[-(\alpha+\beta+\gamma)t], \\
K''(t) &= -\pi_1 \gamma (\alpha+\beta+\gamma) \exp[-(\alpha+\beta+\gamma)t],
\end{aligned} \right\} \tag{71}$$

we have

$$\frac{d}{dt} \{g'[K(t)] K'(t)\} \geq 0 . \tag{72}$$

Thus $g'[K(t)] K'(t)$ is nondecreasing for all t . Consequently, for all $u < \ell < t$, we have

$$g'[K(\ell-u)] K'(\ell-u) - g'[K(t-u)] K'(t-u) \leq 0 , \tag{73}$$

so that $\partial Q_{\ell} / \partial \rho \leq 0$. Hence $Q_{\ell}(\rho, D, t)$ is a nonincreasing function of ρ for the case (i) with $\rho > \frac{D}{\ell}$.

(ii) Case with $\frac{D}{t} < \rho < \frac{D}{\ell}$: Here using (53), we have

$$Q_{\ell}(\rho, D, t) = \frac{\theta\rho}{v_1} \left[\int_{t - \frac{D}{\rho}}^t \{1 - g[K(\tau)]\} d\tau - \int_0^{\ell} \{1 - g[K(\tau)]\} d\tau \right]. \quad (74)$$

Unfortunately, it was for this case that we could not observe a clear cut behavior of $Q_{\ell}(\rho, D, t)$ as a function of ρ , since it depends very much on ℓ .

(iii) Case with $\rho < \frac{D}{t}$: Here using (53), we have

$$Q_{\ell}(\rho, D, t) = \frac{\theta\rho}{v_1} \int_{\ell}^t \{1 - g[K(\tau)]\} d\tau, \quad (75)$$

which of course is an increasing function of ρ .

Thus, qualitatively, $Q_{\ell}(\rho, D, t)$ is increasing for small values of ρ (i.e. $\rho < \frac{D}{t}$) and nonincreasing for larger values of ρ (i.e. $\rho > \frac{D}{\ell}$). Consequently for the median life-shortening $s_{\rho}(\rho, D) = t_{\ell}^{**} - t_{\ell}^*(\rho, D)$, since $t_{\ell}^*(\rho, D)$ satisfies (54), we can only say the following for its qualitative behavior as a function of rate ρ , for fixed D .

For smaller values of ρ (i.e. $\rho < \frac{D}{t}$), $s_{\ell}(\rho, D)$ increases with ρ . Also for large values of ρ (i.e. $\rho > \frac{D}{\ell}$), $s_{\ell}(\rho, D)$ decreases with ρ , assuming that for such values of ρ , the dependence of δ on ρ is weak.

This observation is not surprising, since when ρ is large, the whole dose D is administered before the time ℓ and we follow only those that survive until ℓ .

(B). Here we consider the case with $\ell > 0$, for high LET radiation where, as before, we assume that the dependence of δ on ρ is negligible. We again use the approximation $g[K(t)] \approx g(0)$, subject to which we have from (52)

$$P(L > t | L > \ell) \approx \exp\left\{-\int_{\ell}^t \delta(\tau) d\tau - \frac{\theta\rho}{v_1} [1 - g(0)] \cdot [\min(t, D/\rho) - \min(\ell, D/\rho)]\right\}. \quad (76)$$

Also, because of (54), $t_{\ell}^*(\rho, D)$ becomes approximately equal to the solution for t of the following equation

$$\ln 2 = \left[\int_{\ell}^t \delta(\tau) d\tau \right] + \frac{\theta\rho}{v_1} [1 - g(0)] [\min(t, \frac{D}{\rho}) - \min(\ell, \frac{D}{\rho})] . \quad (77)$$

If δ is constant, then equation (77) reduces to

$$\ln 2 = (t - \ell)\delta + \frac{\theta\rho}{v_1} [1 - g(0)] [\min(t, \frac{D}{\rho}) - \min(\ell, \frac{D}{\rho})] , \quad (78)$$

an equation that can be solved explicitly.

Let us denote by $D^*(\rho)$ the solution of the equation

$$\left(\frac{D^*}{\rho} - \ell\right)\delta + \frac{\theta\rho}{v_1} (1 - g(0)) \left(\frac{D^*}{\rho} - \ell\right) = \ln 2 , \quad (79)$$

which can be rewritten as

$$\frac{D^*(\rho)}{\rho} = \ell + \frac{v_1 \ln 2}{v_1 \delta + \theta\rho [1 - g(0)]} . \quad (80)$$

Further developments depend upon the relation between $D^*(\rho)$ and D .

If $D^*(\rho) < D$ then we must have $\ell < t_{\ell}^*(\rho, D) \leq D/\rho$, so that t_{ℓ}^* satisfies the equation

$$\ln 2 = (t - \ell)\delta + \frac{\theta\rho}{v_1} (1 - g(0))(t - \ell) , \quad (81)$$

Solving (81) for t , we get

$$t_{\ell}^*(\rho, D) \approx \frac{D^*(\rho)}{\rho} . \quad (82)$$

However, if $D^*(\rho) > D$, then we must have $t_{\ell}^*(\rho, D) \geq \max(\ell, D/\rho)$, so

that now t_{ℓ}^* satisfies the equation

$$\ln 2 = (t - \ell)\delta + \frac{\theta\rho}{v_1} [1 - g(0)] \left[\frac{D}{\rho} - \min(\ell, \frac{D}{\rho}) \right], \quad (83)$$

which yields

$$t_{\ell}^*(\rho, D) \approx \ell + \frac{\ln 2 - \frac{\theta\rho}{v_1} [1 - g(0)] \left[\frac{D}{\rho} - \min(\ell, \frac{D}{\rho}) \right]}{\delta}. \quad (84)$$

Putting all this together, we have

$$t_{\ell}^*(\rho, D) = \begin{cases} \ell + \frac{\ln 2}{\delta} & , \text{ if } D \leq \rho\ell \\ \ell + \frac{1}{\delta} \left\{ \ln 2 - \frac{\theta}{v_1} [1 - g(0)] (D - \rho\ell) \right\} & , \text{ if } \rho\ell \leq D \leq D^*(\rho) \\ D^*(\rho)/\rho & , \text{ if } D \geq D^*(\rho) \end{cases} \quad (85)$$

Finally, if δ_0 is a constant (typically $\delta_0 \leq \delta$), since

$$t_{\ell}^{**} = \ell + \frac{1}{\delta_0} \ln 2,$$

the median life-shortening $s_{\ell}(\rho, D)$ is given by

$$s_{\ell}(\rho, D) \approx \begin{cases} \left(\frac{1}{\delta_0} - \frac{1}{\delta} \right) \ln 2 & , \text{ if } D \leq \rho\ell \\ \left(\frac{1}{\delta_0} - \frac{1}{\delta} \right) \ln 2 + \frac{\theta}{v_1\delta} [1 - g(0)] (D - \rho\ell) & , \text{ if } \rho\ell \leq D \leq D^*(\rho) \\ \frac{\{ v_1(\delta - \delta_0) + \theta\rho[1 - g(0)] \} \ln 2}{\delta_0 \{ v_1\delta + \theta\rho[1 - g(0)] \}} & , \text{ if } D \geq D^*(\rho) \end{cases} \quad (86)$$

It is seen that, for a fixed ρ , the dependence on D of the median life-shortening varies. For small doses $D < \rho\ell$, the median life shortening is constant, and may be zero. For intermediate values of D , between limits $\rho\ell$ and $D^*(\rho)$, the median life shortening is an increasing linear function of D . Finally, after reaching its maximum value at

$D = D^*(\rho)$, the median life shortening remains constant, this constant being dependent on the dose-rate ρ .

This behavior of the median life shortening is approximately compatible with the curves exhibited in figure 7, that correspond to neutron radiation administered at moderately high dose-rate ρ . This is not so when the dose-rate ρ is really high. However, this circumstance does not necessarily imply the lack of realism of our hypothetical stochastic model. If ρ is very large, such as in the case with $\rho = 85$ rads/min in figure 7, so that D/ρ is small roughly of the order of 0.003 or less for $D \leq 300$ rads, then the approximation to (52) would be

$$P(L > t | L > \ell) \approx \exp \left\{ - \int_{\ell}^t \delta(\tau) d\tau - \frac{\theta D}{v_1} \{g[K(\ell)] - g[K(t)]\} \right\}. \quad (87)$$

Consequently the median t_{ℓ}^* becomes approximately the solution for t of the equation

$$\ln 2 = \left[\int_{\ell}^t \delta(\tau) d\tau \right] + \frac{\theta}{v_1} \{g[K(\ell)] - g[K(t)]\} D. \quad (88)$$

Clearly t_{ℓ}^* is still a decreasing function of the dose D and hence the median life-shortening $s_{\ell} = t_{\ell}^{**} - t_{\ell}^*$ is an increasing function of D .

7. CONCLUDING REMARKS. The present paper, and also the one published in 1976, have resulted from two stimuli. One was the inspiring empirical studies, primarily those of Arthur C. Upton, concerned with radiation effects on mice: carcinogenesis and life shortening. The other stimulus was the information on the two very different time scales, one

referring to the physical irradiation phenomenon and the other to the biological developments in living irradiated cells. The relevance of a mathematical model of a natural phenomenon depends on the degree of its realism. In particular, this applies to the present hypothetical stochastic model of irradiation effects occurring in single cells. As discussed in §3, the stochastic model is expressed in terms of three interrelated observable random variables: frequency of live non-cancerous cells, frequency of cancerous cells and frequency of dead (or "inactivated") cells. Because these three frequencies must add up to unity, the verification of the model may be based on empirical results referring to bivariate distribution of any two out of the three frequencies just mentioned.

Contrary to the above, the empirical data we managed to find in the literature refer to only one frequency, either of surviving cells or of cancer cells, both dependent upon the various details of the experiment, such as the dose D , the dose-rate ρ and the kind of irradiation, etc. The question is about the possibility of an experiment that could provide data on two subpopulations of irradiated cells, the subpopulation of cancerous and the subpopulation of noncancerous cells.

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LEGEND

Figure 1. Photograph of a cloud chamber. (Taken from Neyman and Puri (1976).)

left ord fraction of surviving cells

abs dose in rads x 100

Figure 2. Dose survival curves of cultured T-1_g cells in equilibrium with air, irradiated with different mono-energetic heavy charged particles in conditions where narrow distributions of dose in LET are obtained. (Taken from Barendsen (1968).)

left ord fraction of cells surviving

abs dose in rads

Figure 3. The fraction of cells surviving various doses of gamma-radiation delivered at 44.9 rad/min (closed circles) and 9.5 rad/hour (crosses). (Taken from Bedford and Hall (1963).)

left ord fraction of cells surviving

abs dose in rads

Figure 4. The fraction of cells surviving various doses of gamma-radiation delivered at 44.9 rad/min (closed circles) and 19 rad/hour (crosses). (Taken from Bedford and Hall (1963).)

left ord pink mutant events/hair (minus control)

abs dose (rads)

Figure 5. Neutron and X-ray dose-response curves for pink-mutant events in stamen hairs of *Tradescantia* clone 02. (Taken from Sparrow, et al (1972) with the kind permission of the authors and the Publisher.)

left ord pink mutant events/hair (minus control)

abs dose (rads)

Figure 6. Dose-response curve for pink mutant events/hair after X-irradiation at 0.05, 0.5, 5.0 and 30 rads/min. (Taken from Nauman, et al (1975) with the kind permission of the authors.)

left ord shortening of mean survival time (days)

abs dose (rads)

Figure 7. Life-shortening in female mice as influenced by dose and dose rate of gamma rays and neutrons. Open symbols represent gamma rays; filled symbols, neutrons. (Taken from Neyman and Puri (1976).)

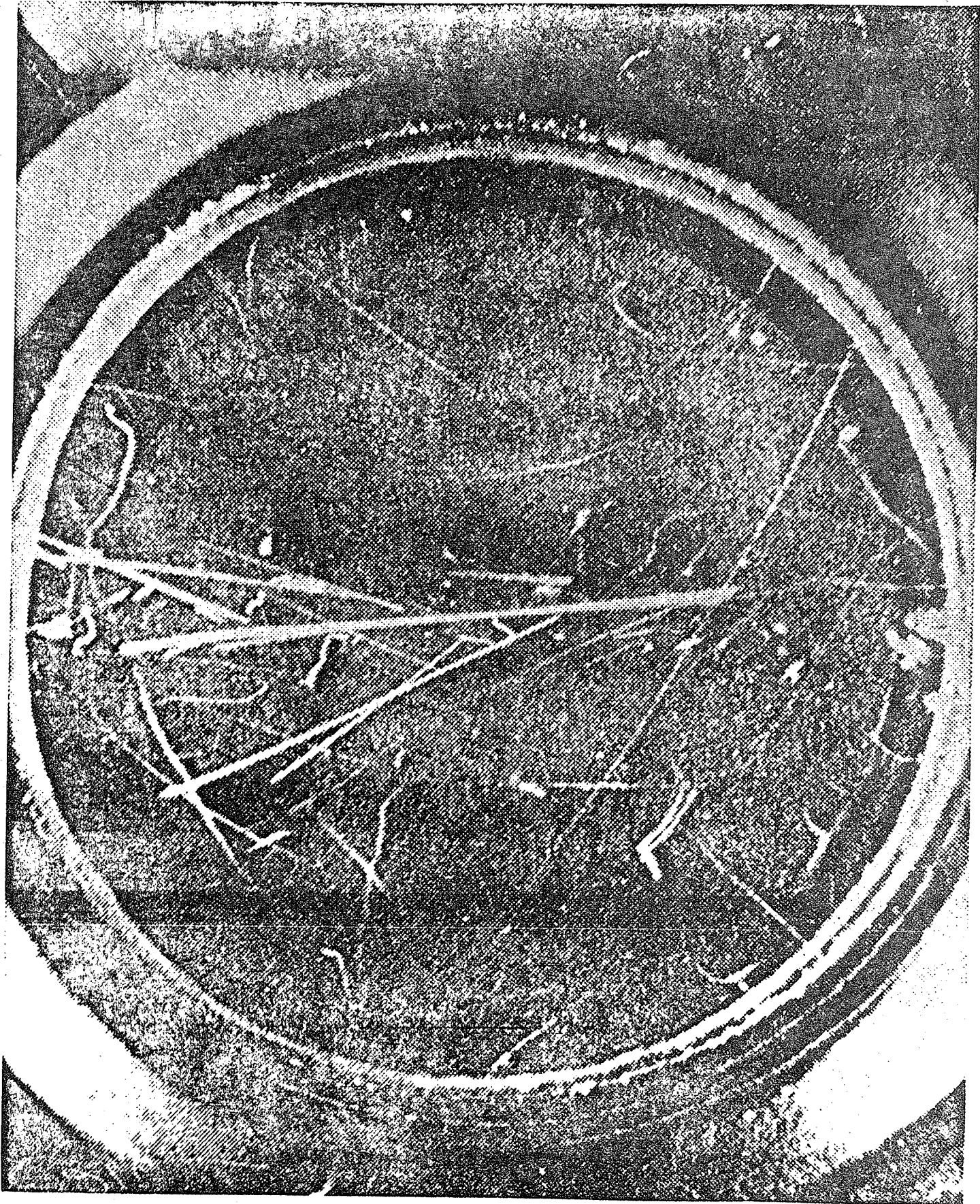


Figure 1. Photograph of a cloud chamber (Taken from Neyman and Puri (1976).)

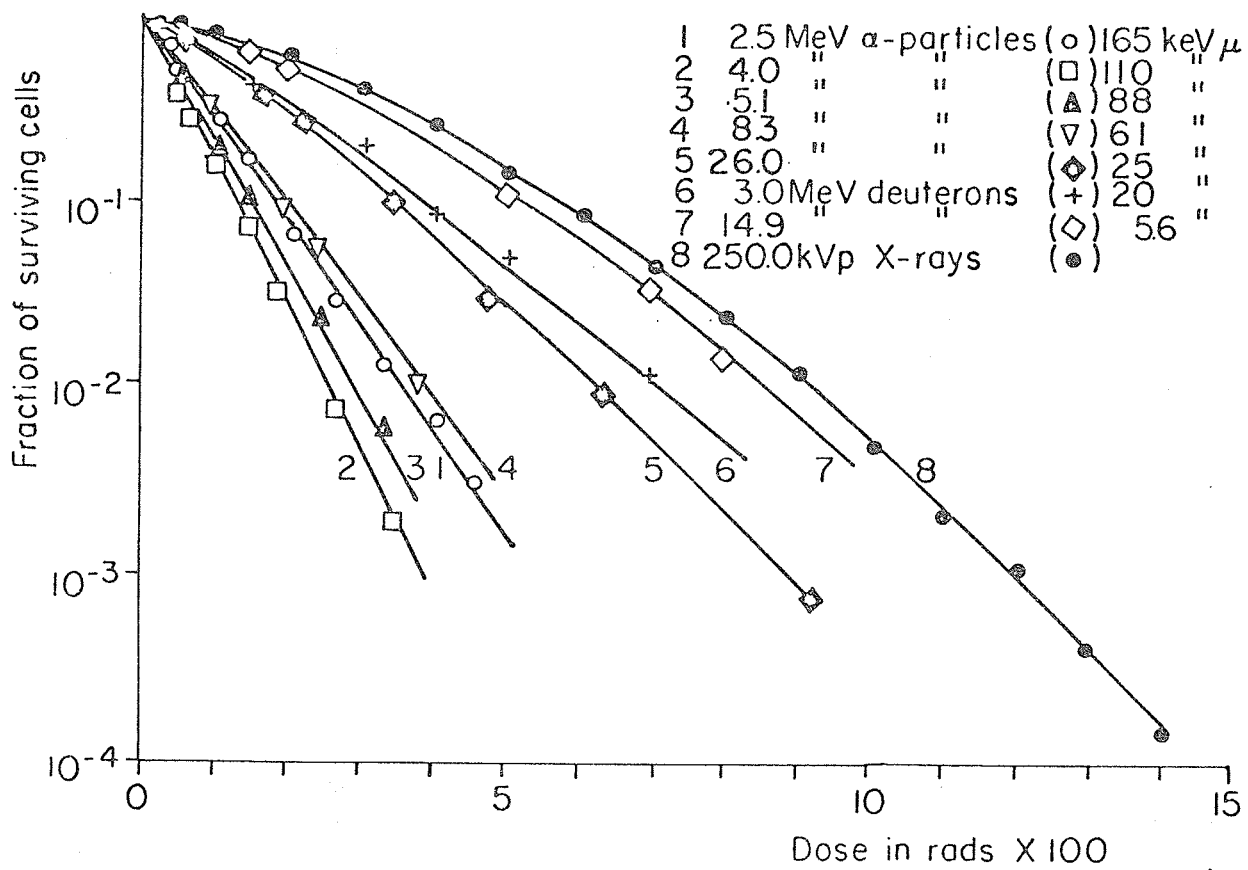


Figure 2. Dose-survival curves of cultured T-1_g cells in equilibrium with air, irradiated with different mono-energetic heavy charged particles in conditions where narrow distributions of dose in LET are obtained. (Taken from Barendsen (1968).)

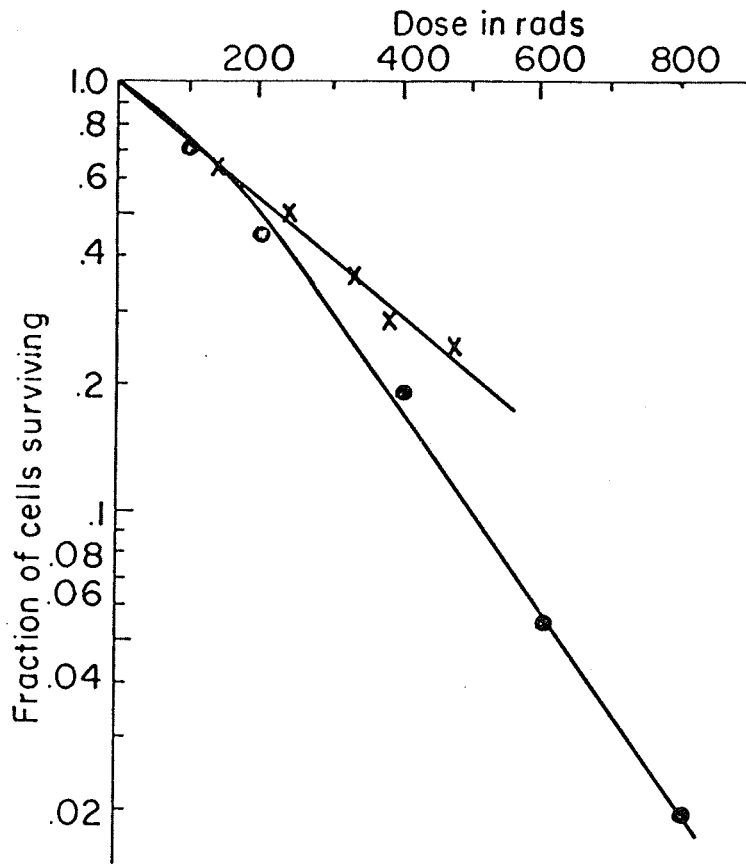


Figure 3. The fraction of cells surviving various doses of gamma-radiation delivered at 44.9 rad/min (closed circles) and 9.5 rad/hour (crosses). (Taken from Bedford and Hall (1963).)

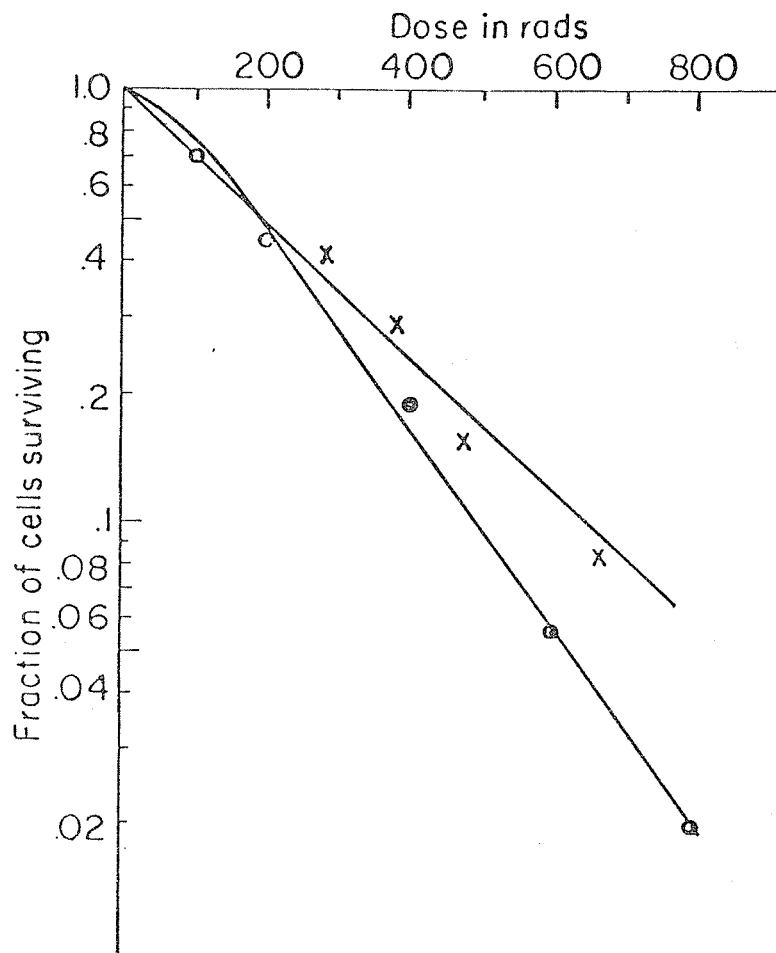


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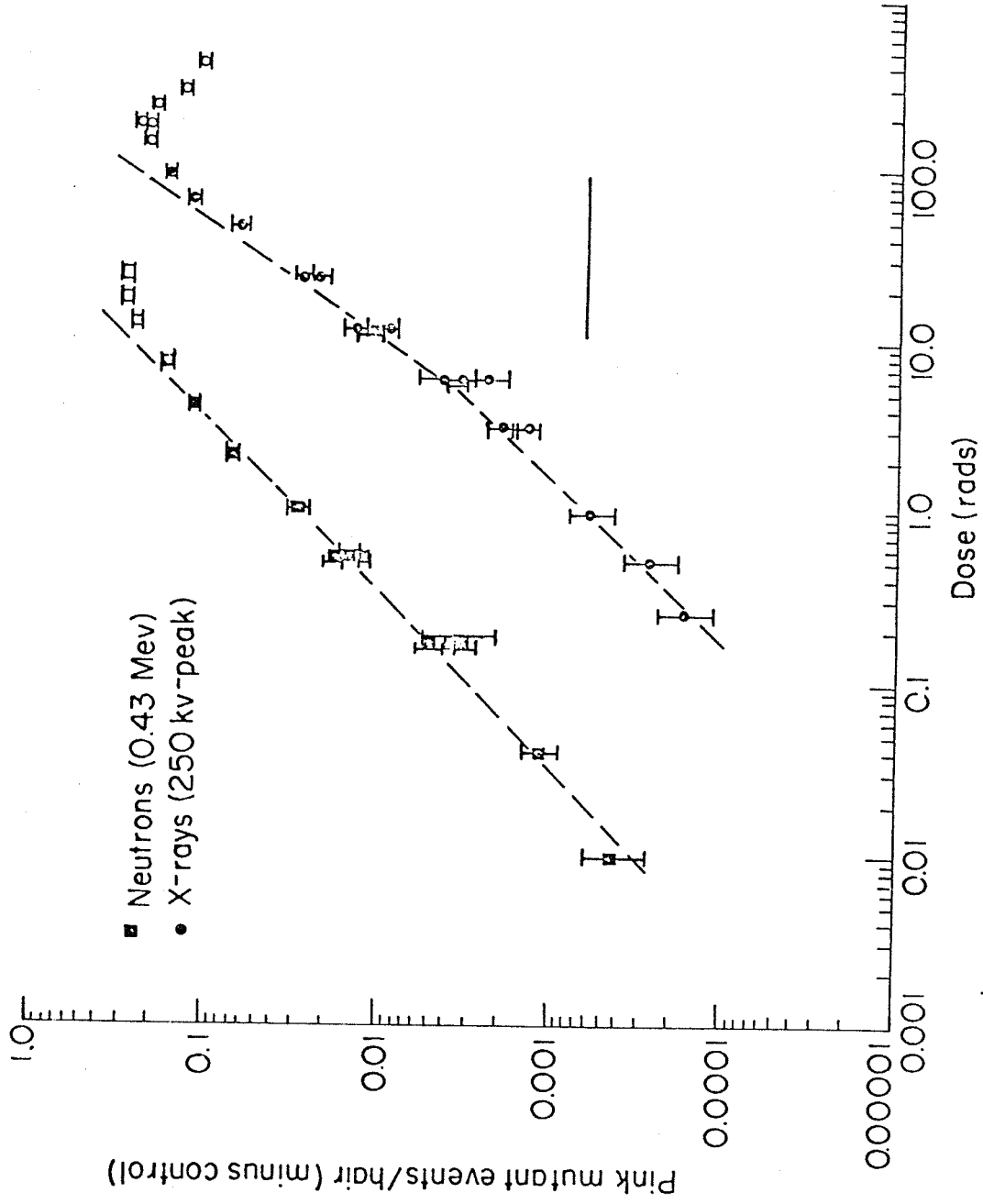


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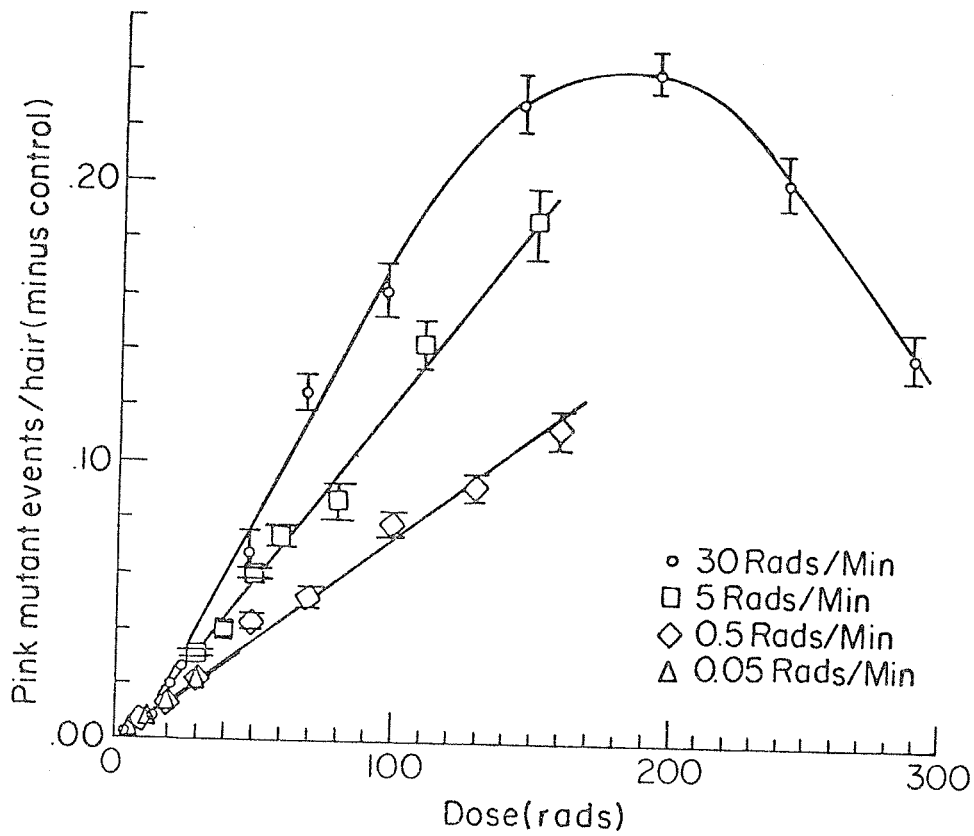


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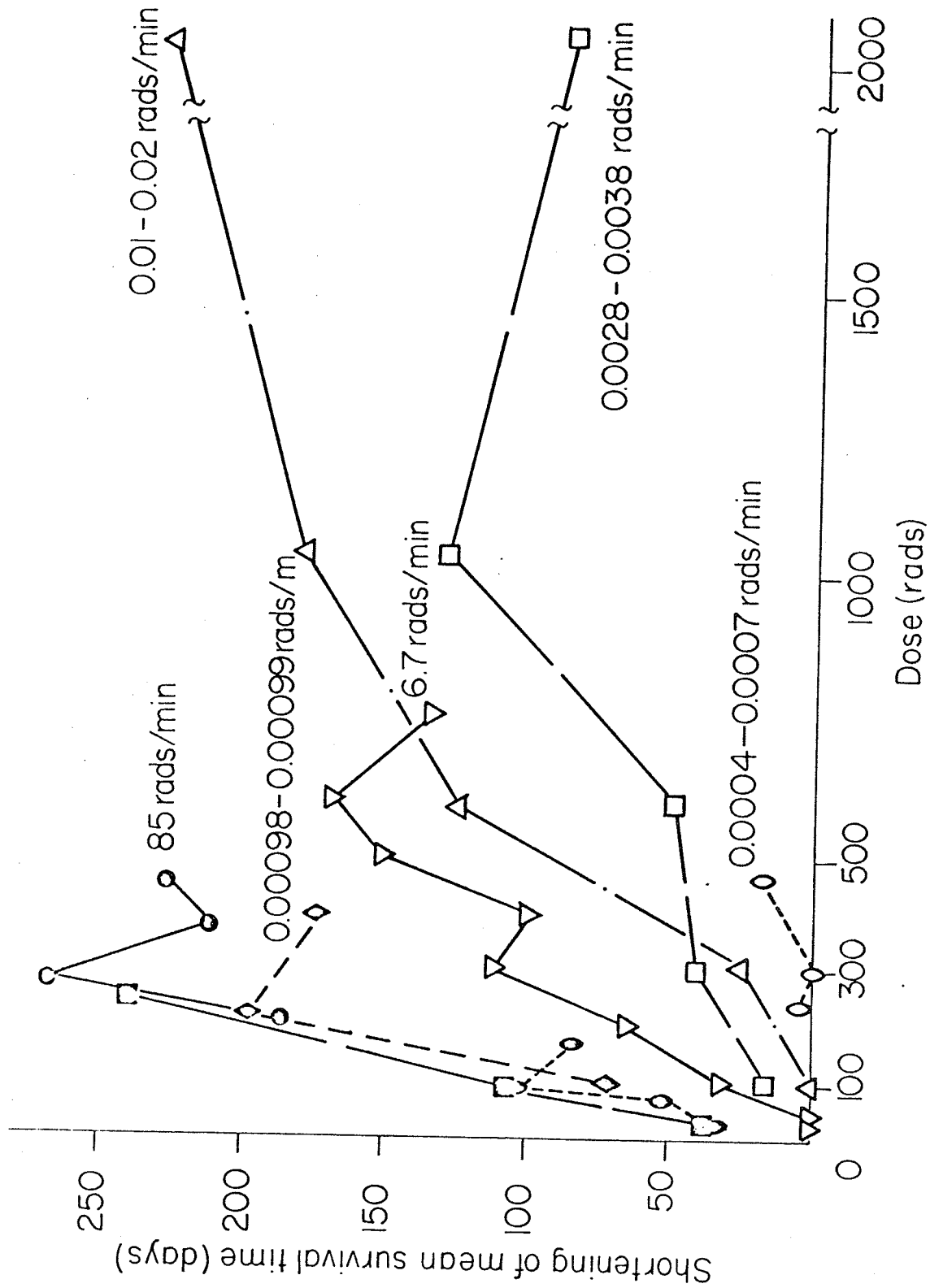


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