A HYPOTHETICAL STOCHASTIC MECHANISM OF RADIATION EFFECTS IN SINGLE CELLS: SOME FURTHER THOUGHTS AND RESULTS**

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1. INTRODUCTION. The purpose of the present paper is to briefly describe a stochastic model for radiation effects in single cells recently studied by J. Neyman and the author (see [9], [10]), discuss some results based on this model and then raise several questions which need further attention. At the outset it is appropriate to mention that originally we were inspired by the experimental work on animals such as mice, particularly that due to Upton, et al ([16],[17]). However reading through the literature we soon realised the complexity of the various mechanisms that together appear to play role in bringing about variety of responses from animals as a result of their exposure to radiation. While our ultimate goal is to develop appropriate stochastic model of phenomena arising in irradiated experimental animals, our present concern however is limited to irradiation effects on cells of some homogeneous tissue.

The literature on this subject is quite rich. The closest ancestor to our stochastic model appears in the work of Payne and Garret ([11],[12]). Our model differs from this and others in two basic details described below.

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

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clusters vary with the kind of irradiation. Clusters generated by low linear energy transfer (LET) radiation primaries (such as those of X-rays, gamma rays, etc.) contain few secondaries, while those generated by high LET primaries (such as those of α-particles and Neutrons) contain many secondaries. It is visualized that the irradiation damage to cells is mainly due to the secondary particles that "hit" the sensitive parts of living cells. The second detail of the chance mechanism is concerned with what may be called the time scales of radiation damage and of subsequent repair. The generation of a cluster of secondary particles and the possible hits occur so rapidly that for all practical purposes, they may be considered as occurring instantly. On the other hand, the subsequent changes in the damaged cells, such as repair, etc., appear to require measurable amounts of time.

We begin in the next section with the basic assumptions that underlie our stochastic model. In section 3, we qualitatively compare some of the implications of our model with the empirical findings available in literature. Section 4 deals with the case of UV-radiation, where the question of whether or not a primary particle of UV-radiation generates any secondary is touched upon. Finally we close with section 5, where we raise several questions of interest that are either under study or need further attention.

2. STOCHASTIC MODEL OF RADIATION EFFECTS ON SINGLE CELLS. We consider a hypothetical experiment in which a live cell is subjected to a particular kind of irradiation. The irradiation is assumed to be administered over T units of time at a constant dose-rate, denoted by ρ. The time T is such that by the end of this time a preassigned total dose of irradiation,

measured in rads and denoted by D, is given so that $D = \rho T$. The specific assumptions of our stochastic model are as follows.

(A_1) Primary radiation particles arrive at the cell according to a Poisson process with rate $\lambda(t)$ per unit of time and per unit volume, where $\lambda(t) = \lambda > 0$, for $0 \leq t \leq T$ and $\lambda(t) = 0$, for $t > T$.

(A_2) Each primary generates a cluster of secondary particles, the number of which, denoted by ν, is a random variable. It is assumed that the numbers ν of secondaries generated by several primaries are mutually independent with a common distribution having a finite mean ν_1.

(A_3) The secondary particles of a cluster are assumed to travel independently of each other and independently from all other variables of the system.

(A_4) Within each live cell we visualize two disjoint "targets", the biological identity of which we do not attempt to specify. Possibly they can be some particular points within a chromosome, etc. These targets are denoted by R and K, connoting "repairable" and "killing". Both targets are located in a region within the cell, denoted by A, connoting region of "accessibility". We postulate that the passage of a primary radiation particle outside the region A has no effect on the cell considered. On the other hand, if a primary particle crosses A, then each of the ν generated secondaries has the same 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.

(A_5) 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 (A_1)-(A_5) concern the physical aspects of our stochastic model. We now turn to its biological aspects.

(A_6) If the target R is hit by a secondary particle, the cell experiences a "repairable" damage. We abstain from specifying the mechanism of repair, which may involve enzymes, etc. Under the Markovian assumption, given that a cell at time t is alive and has a nonnegative number k of unrepaired hits of target R, we assume that

(i) the conditional probability of a single damage being repaired in (t,t+h) is $\alpha kh + o(h)$;

(ii) the conditional probability of a repairable damage becoming permanent (nonlethal) in (t,t+h) is $\beta kh + o(h)$;

(iii) the conditional probability of a repairable damage becoming lethal is $\gamma kh + o(h)$;

(iv) the conditional probability of the cell dying in (t,t+h) due to causes not directly connected with radiation is $\delta h + o(h)$; and

(v) the conditional probability of more than one of the above events happening in (t,t+h) is $o(h)$.

Here α, β, γ and δ designate nonnegative possibly time dependent functions of which δ may also depend on the dose rate ρ. In (ii) the biological nature of the permanent damage is not specified, but judging from relevant literature it will frequently consist in the cell's becoming the first of an initiated development of some cancer. For this reason, in [9] and [10], it was felt convenient to speak of this damage as "cancerous". However, recently we have learnt that in radiation research literature cells with such damages are more commonly referred to as "transformed" cells. This appears more appropriate since not all transformed cells are in general cancerous. Thus from hereon we shall also use this same terminology when referring to such cells.

(A_7) Regarding the target K, we assume that a single hit causes the death (or inactivation) of the cell. Similarly a single lethal damage of type (iii) above also causes its inactivation. Thus the cell could die either due to a hit on the target K, or due to the risk γ in (iii) or due to the risk δ in (iv). Finally, a live cell is considered transformed as soon as a permanent damage results due to the risk β in (ii).

In [10], we have considered the more general case, where the rates λ, α, β, γ and δ may be time dependent. However for the present, we shall consider only the case where they are constant, while keeping the risk δ of death due to other causes dependent on the dose rate ρ at which the irradiation is applied.

Again it was felt appropriate to assume that the mean number ν_1 of secondary particles produced by a single primary particle is directly proportional to the initial energy of the particle. This suggests that the dose rate ρ (radiation energy absorbed per unit time) should approximately be directly proportional to the product $\lambda\nu_1 A$, where λ is the mean number of primary particles arriving per unit time and per unit volume. Thus we may set

$$\lambda\nu_1 A = \theta\rho, \tag{1}$$

where θ is a positive constant, which typically may depend on the energy, mass of the particles, type of radiation involved, etc.

In the next section we present certain formulas derived in [10] under the assumptions (A_1)-(A_7), that are relevant to certain empirical findings against which the implications of these formulas are qualitatively compared. The reader may refer to [10] for their detailed derivation.

3.1. PROPORTION OF SURVIVING CELLS. Figure 1 (taken from Barendsen [1]) exhibits the behavior of the logarithm of the porportion of the cells surviving immediately following the exposure of a total radiation dose D (measured in rads) when plotted against this dose. In general, it is a decreasing function of D, but its behavior varies with the type of radiation. For instance, for high LET radiation such as neutrons or α-particles, this plot is almost like a straight line. On the other hand, for the low LET radiation this plot is nonlinear and shows a degree of concavity, commonly referred to as the "shouldering effect". The theoretical analog of the proportion of surviving cells at time t corresponds to the probability of a cell to be alive at time t. The logarithm of this probability, subject to the assumptions of our model and the relation (1), is given by

$$\ell n\, P(\text{cell is alive at t}) = -t\delta(\rho) - \frac{\theta\rho}{\nu_1} \int_{\max(0,t-D/\rho)}^{t} \{1-g(K(\tau))\}d\tau, \quad (2)$$

where the function $g(\cdot)$ is the probability generating function (p.g.f) of the random variable ν, the number of secondaries generated by a primary particle and

$$K(\tau) = 1 - \pi_2 - \frac{\pi_1\gamma}{\alpha+\beta+\gamma}(1-\exp[-(\alpha+\beta+\gamma)\tau]). \quad (3)$$

In order to match (2) with the curves in figure 1, we set $t = T = D/\rho$, the exposure time for the total radiation dose D, and obtain from (2)

$$\ell n\, P(\text{cell is alive at T}) = -\frac{\delta(\rho)D}{\rho} - \frac{\theta\rho}{\nu_1} \int_{0}^{D/\rho} \{1-g(K(\tau))\}d\tau. \quad (4)$$

Again to study the behavior of (4) as a function of D, we note that the derivative $\partial \ell n\, P/\partial D$ is always negative, so that $\ell n\, P$ is a decreasing function of D. Here P designates the probability P(cell is alive at T) as given in (4). Also as long as $\pi_1\gamma$ is positive, $\partial^2 \ell n P/\partial D^2$ is negative

so that $\ell n\, P$ is strictly a concave function. Consequently its plot may often show some shouldering effect consistent with some of the empirical plots of Figure 1 that correspond to low LET radiation. This effect however is negligible for high LET radiation such as neutrons, where a primary particle whenever it generates any positive number of secondaries, it does so typically in thousands. This being the case, for the high LET radiation, we may take approximately

$$g(s) \approx g(0), \tag{5}$$

for s not close to one. Since in our case $K(t) \leq 1 - \pi_2$, for all $t \geq 0$, with $\pi_2 > 0$, the approximation (5) used for $g(K(\tau))$ in (4) may not be unreasonable. Thus we have approximately

$$\ell n\, P(\text{cell is alive at } T) \approx - \frac{\delta(\rho)D}{\rho} - \frac{\theta D}{\nu_1}[1-g(0)]. \tag{6}$$

This being linear in D, explains the absence of shouldering effect for the case of high LET radiation, as observed empirically (see Figure 1).

Again the behavior of the empirical dose-survival curves is known to vary also with the dose rate ρ (see for instance, Bedford and Hall [2] and Hall and Bedford [5]). In [10], it was shown that with an appropriate choice of the function $\delta(\rho)$ the expression (4), treated as a function of ρ, remains qualitatively consistent with the corresponding behavior of empirical curves. The reader may refer to [10] for the relevant details.

3.2. PROPORTION OF CELLS EVER GETTING TRANSFORMED. To begin with we mention one of the empirical findings in animal experimentation due to Upton, et al. [16] (see Totter [15]), which stimulated our work. This refers to the so called "dose-rate effect" of gamma radiation on the induction of a particular Leukemia in mice. It is observed that for the same total dose D given at a high dose rate a substantially higher percentage of irradiated

mice acquired leukemia than those given at a low dose rate. Similar results were found by these authors for other cancers. In particular, it is observed in the case of high dose rate, that the incidence of leukemia is not a monotone function of the total dose D. It first increases with increasing dose D, reaches a maximum and then decreases. Since our model refers to cells, later we also found some published work on cells, exhibiting a similar behavior in terms of the incidence of cell transformation as a result of radiation exposure (see for instance, Sparrow et al. [13], Nauman, et al. [8], and Han, Hill and Elkind [7]) (Also see Figure 2). For the theoretical counterpart of these empirical findings, formulas giving the probability that an irradiated cell ever becomes transformed, were derived in [10] based on our stochastic model. These are reproduced below from [10].

For the case when $\delta(\rho) > 0$, we have

P(cell ever gets transformed)

$$= \frac{\beta}{\beta+\gamma}\Big[1-\{\delta(\rho)+\frac{\theta\rho}{\nu_1}[1-g(1-\pi_2)]\}$$

$$\cdot \int_0^{D/\rho} \exp\Big(-\delta(\rho)t-\frac{\theta\rho}{\nu_1}\int_0^t\{1-g[R(\tau)]\}d\tau\Big)dt \tag{7}$$

$$-\delta(\rho)\int_{D/\rho}^{\infty}\exp\Big(-\delta(\rho)t-\frac{\theta\rho}{\nu_1}\int_{t-D/\rho}^{t}\{1-g[R(\tau)]\}d\tau\Big)dt\Big].$$

However when $\delta(\rho) = 0$, we have

P(cell ever gets transformed)

$$= \frac{\beta}{\beta+\gamma}\Big[1-\frac{\theta\rho}{\nu_1}\{1-g[1-\pi_2]\}$$

$$\cdot \int_0^{D/\rho}\exp\Big(-\frac{\theta\rho}{\nu_1}\int_0^t\{1-g[R(\tau)]\}d\tau\Big)dt \tag{8}$$

$$-\exp\Big(-\frac{\theta D}{\nu_1}\{1-g[R(\infty)]\}\Big)\Big],$$

where

$$R(\tau) = 1 - \pi_2 - \frac{\pi_1(\beta+\gamma)}{\alpha+\beta+\gamma}\{1-\exp[-(\alpha+\beta+\gamma)t]\} \tag{9}$$

and

$$R(\infty) = 1 - \pi_2 - \frac{\pi_1(\beta+\gamma)}{\alpha+\beta+\gamma} \quad . \tag{10}$$

The study of the expressions (7) and (8) treated as a function of D, leads to the following proposition proved in [10].

PROPOSITION. Let the rates α, β, γ and $\delta(\rho)$ be all independent of time. Then, under the assumptions (A_1)-(A_7), P(cell ever gets transformed) treated as a function of D has exactly one maximum if and only if

$$\delta(\rho)\int_0^\infty \exp\left(-\delta(\rho)t - \frac{\theta\rho}{\nu_1}\int_0^{D/\rho}\{g[R(u)]-g[R(u+t)]\}du\right) \cdot \{1-g[R(t)]\}dt < 1 - g[1-\pi_2], \tag{11}$$

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

$$\exp\left(-\frac{\theta\rho}{\nu_1}\int_0^\infty \{g[R(u)]-g[R(\infty)]\}du\right)\{1-g[R(\infty)]\} < 1 - g[1-\pi_2], \tag{12}$$

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

As indicated in the above proposition, under appropriate conditions on the parameters exhibited by (11) and (12), our model is consistent with the empirical findings of Upton, et al. [16] and also with those in Figure 2. An 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. Evidently it is the competition between the two risks that brings about the point of maximum, one risk

being that of the death of the cell through π_2 and the other being the risk of transformation of the cell with rate β. After all, the cells having died due to the risk π_2 are no longer available for becoming transformed, a fact specially significant for high dose levels.

Before closing this section, we remark that in order that our model be consistent with the behavior of the observed dose-response curves for cell transformations for varying dose-rate ρ, it is essential that $\delta(\rho)$ be positive and have an appropriate dependence on ρ. We refer the reader to [10] for these and other details.

4. THE CASE OF UV-RADIATION. The possibility that in the case of UV-radiation a primary particle may itself act as a secondary without really generating any secondaries, was mentioned earlier in [9] and [10]. This of course is equivalent to taking $g(s) = s$ in our case. Perhaps this hypothesis may not be strictly correct. However, in this context, it is worth pointing out that in our model, we have refrained in spelling out the exact physical nature of the entities we labeled as "secondary" particles. May they be ions or free radicals or combinations thereof. Thus whether or not effectively $g(s) \equiv s$ holds in the case of UV-radiation needs further examination based on real data. With suitable data available appropriate statistical tests can be devised to test this hypothesis. For instance, to begin with, we may consider taking

$$g(s) = \frac{\exp[-\xi(1-s)]-\exp[-\xi]}{1-\exp[-\xi]}, \quad \xi \geq 0, \ |s| \leq 1. \tag{13}$$

In this case testing the above hypothesis would mean testing the hypothesis that $\xi = 0$, against the alternative that $\xi > 0$. Again the kind of data we anticipate are the following.

At time t = 0, a number N of live cells are subjected to a particular kind of radiation administered over time T at a known dose rate ρ, with total preassigned dose $D = \rho T$. At the end of time T, N_1 of these cells are observed to be alive and transformed, N_2 are observed to be alive but not transformed and the remaining $N - (N_1+N_2)$ having died. In most of the published work, the empirical behavior of the quantities such as the surviving fraction $(N_1+N_2)/N$, the transformed fraction N_1/N, number transformed per surviving cell $N_1/(N_1+N_2)$, etc., are studied as a function of D or ρ. These quantities are studied in literature one at a time. What is desired, as was pointed out in [10], is to have a joint set of data for (N,N_1,N_2) made available for varying values of D, ρ and for different types of radiation, such as UV, gamma, neutron, etc. We have pleasantly learned recently through the courtesy of Dr. E. J. Ainsworth and Dr. T. C. H. Yang, both of Lawrence Berkeley Laboratory, that such data are indeed available. In fact, Dr. Yang has kindly agreed to provide us with at least some of the needed data.

Assuming that various cells are affected by the radiation independently of each other and that each acts in a similar manner independently of each other during the time (0,T), given N, the conditional distribution of the vector $(N_1,N_2,N-N_1-N_2)$ will simply be a multinomial distribution with the needed formulas for the probabilities P(a cell is alive at T) and P(a cell is alive but not transformed at T) provided through our model. In particular, in the case of UV-radiation when the hypothesis g(s) = s is valid, using the theory developed in [10] for our model, it can be shown that

$$P(\text{a cell is alive at T}) = \exp\left[-\left(\frac{\delta}{\rho} + \frac{\pi_2\theta}{\nu_1}\right)D - \frac{\theta\rho\pi_1}{\nu_1}\,\frac{\gamma}{\alpha+\beta+\gamma}\,\psi(D,\rho)\right] \qquad (14)$$

and

$$P(\text{a cell is alive but not transformed at } T) = P(\text{a cell is alive at } T)\exp\left[-\frac{\theta\rho\pi_1}{\nu_1}\,\frac{\beta}{\alpha+\beta+\gamma}\,\psi(D,\rho)\right] \tag{15}$$

where

$$\psi(D,\rho) = \frac{D}{\rho} - \frac{1}{(\alpha+\beta+\gamma)}\left\{1-\exp\left(-[\alpha+\beta+\gamma]\,\frac{D}{\rho}\right)\right\}. \tag{16}$$

The equations (14) and (15) in turn lead to the following interesting relation valid for all D.

$$\frac{\gamma}{\beta}\,\ell n\,P(\text{cell is not transformed at } T|\text{alive at } T) = \ell n\,P(\text{cell is alive at } T) + \left[\frac{\delta}{\rho} + \frac{\theta\pi_2}{\nu_1}\right]D. \tag{17}$$

Since the probabilities P(cell is not transformed at T|alive at T) and P(cell is alive at T) correspond to the empirical quantities $N_2/(N_1+N_2)$ and $(N_1+N_2)/N$ respectively, the relation (17), at least qualitatively, can be verified empirically for some appropriate constants $\frac{\gamma}{\beta}$ and $\left(\frac{\delta}{\rho} + \frac{\theta\pi_2}{\nu_1}\right)$. The lack of support of (17), if so exhibited on the part of experimental data, would have to be interpreted as either that the hypothesis g(s) = s is not valid or that the model itself needs some scrutiny as far as UV-radiation is concerned. This will have to be a subject of our future investigation.

5. CONCLUDING REMARKS. (a) The present stochastic model is formulated in terms of hypothetical entities such as "primary" particles and clusters of "secondary" particles, each with certain hypothetical properties. The various formulas derived for the model involve two unspecified functions $g(\cdot)$ and $\delta(\rho)$ and a relatively large number of adjustable parameters namely,

λ, α, β, γ, A, π_1 and π_2. The introduction of so many parameters was motivated by the desire not to omit a detail of the modeled phenomenon which might be important. Also, it is possible that in some cases certain apriori considerations may determine some of these parameters. For instance, the rate λ may be estimable through some physical experiments with no reference to the irradiated cells. Also for example, for the UV-radiation it may be considered appropriate to take $g(s) = s$ (see section 4). Such considerations in general will help reduce nonidentifiability of parameters if there is any. This, of course, will also depend upon the kind of data that are used to test the validity of our model.

(b) Again it would be of considerable interest to study the consistency of the present model with the empirical evidence available from the experiments in which the same total dose D is split into fractions, with each fraction of the dose D given after certain gaps in time. The reader may refer to Elkind, et al. [4] and Han and Elkind [6] for such experimental studies dealing with the effects of fractionated exposures on cells (see also a recent survey paper of Yang and Tobias [18]).

(c) It is often suggested (see Yang and Tobias [18]) that certain special types of misrepairs of the radiation induced damages may ultimately lead to cell transformations. Such finer details relating to the variety of possible repair mechanisms were intentionally kept to a minimum in our model in order to keep the model simple and yet useful. In this connection, the reader may refer to a recent paper of Tobias, et al [14] that was brought to the author's attention at this conference. This paper is primarily concerned with modeling the repair-misrepair aspect of the cell survival.

(d) Again the present model does not allow multiplication of the cells during the study period (0,T). This is not unreasonable for the case of high dose-rate where T is usually small. However for the case where the dose rate is small, T is generally large. In such a case multiplications of cells are possible. Consequently the present model would need an appropriate modification in order to allow such a possibility. This possibility is currently under investigation.

(e) It was pointed out at the conference that in general not all transformations are cancerous. Thus if we were to distinguish between the transformations that are cancerous and those that are not, instead of having only one risk for transformations through the rate β, we might consider the possibility of two separate risks, one for the repairable damage to become cancerous and another one for it to become transformed without becoming cancerous.

(f) Finally, assuming that $g(s) = s$ is valid in the case of UV-radiation, one may easily obtain from (14) the approximation

$$\ell n\, P(\text{a cell is alive at T}) \approx -\left(\frac{\delta}{\rho} + \frac{\theta\pi_2}{\nu_1}\right)D - \frac{\theta\pi_1\gamma}{2\nu_1\rho}D^2, \qquad (18)$$

valid for small D and the approximation

$$\ell n\, P(\text{a cell is alive at T}) \approx \frac{\theta\rho\pi_1}{\nu_1}\,\frac{\gamma}{(\alpha+\beta+\gamma)^2} - \left(\frac{\delta}{\rho} + \frac{\theta\pi_2}{\nu_1} + \frac{\theta\pi_1}{\nu_1}\,\frac{\gamma}{(\alpha+\beta+\gamma)}\right)D, \qquad (19)$$

valid for large D. The reader may note the similarity between the expression (18) and the so called linear-quadratic dose-survival relationship based on the two-hit theory or the theory based on the double-strand breaks

familiar to radiation biologists. For details of the latter theory we refer the reader to a recent book by Chadwick and Leenhouts [3].

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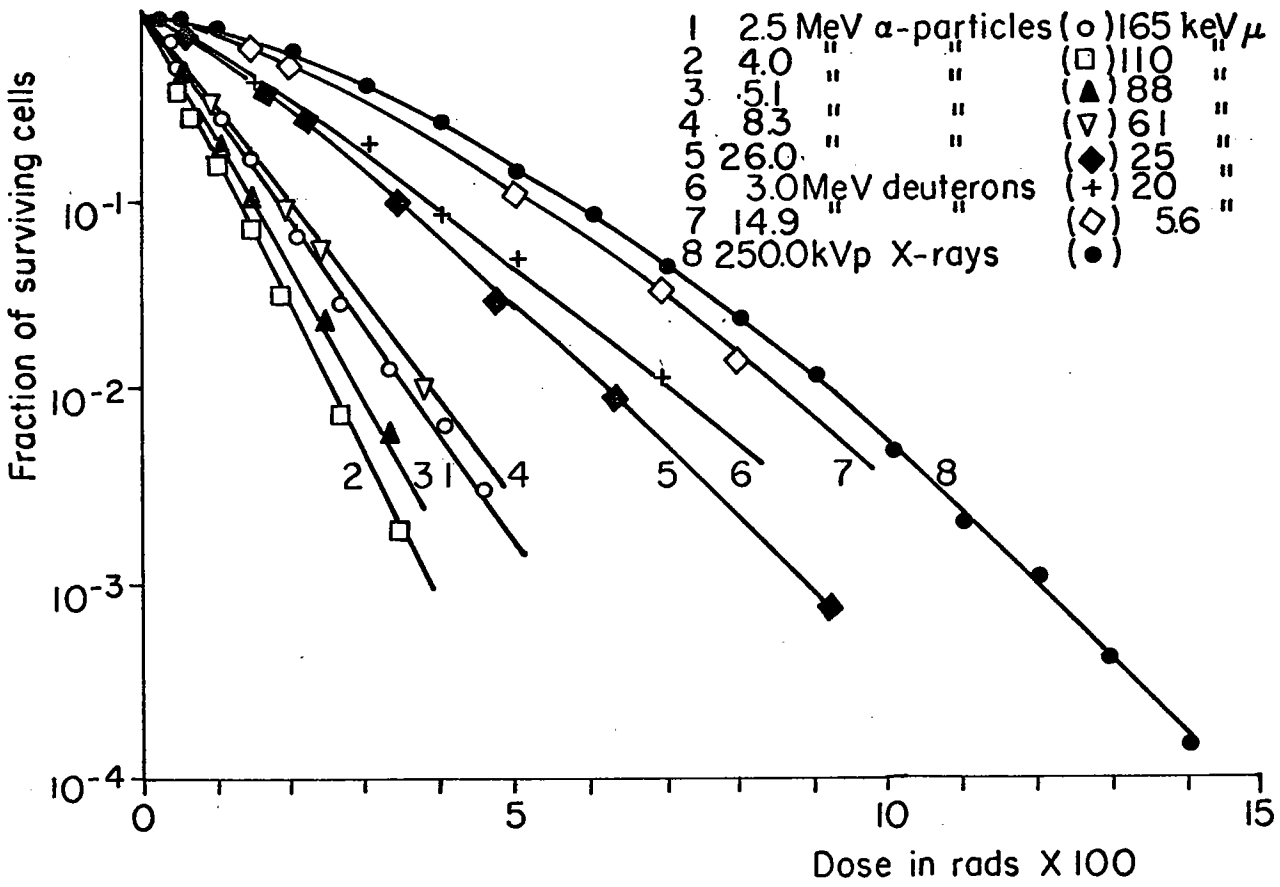

Figure 1. Dose-survival curves of cultured T-1_g cells in equilibrium with air, irradiated with different mono-energetic heavy charged particles in conditions where narrow distributions of dose in LET are obtained. (Taken from Barendsen [1].)

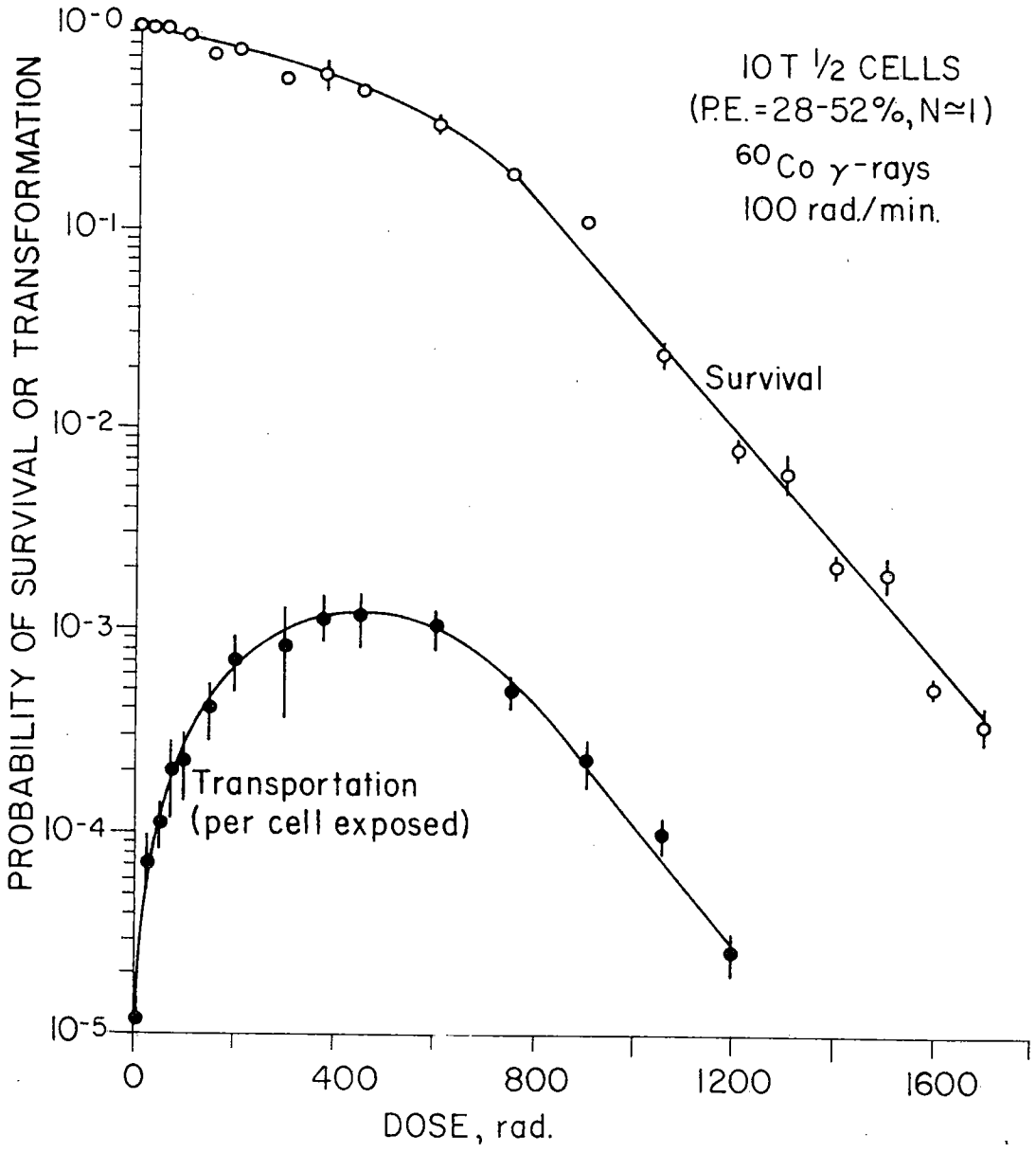

Figure 2. Survival and neoplastic transformation of C3H/10T½ cells by ^{60}Co γ-rays delivered at 100 rads/min. Transformation is expressed per exposed cell. (Taken from Han, Hill and Elkind [7].)