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BIOPHYSICAL ASPECTS OF RADIATION QUALITY

[1]

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CONTENTS

THE STOCHASTICS OF RADIATION EFFECTS*

O. HUG AND A. KELLERER
STRAHLENBIOLOGISCHES INSTITUT DER UNIVERSITÄT MÜNCHEN
FEDERAL REPUBLIC OF GERMANY

I. A KINETIC MODEL OF RADIATION EFFECTS

As the usual interpretations of dose-effect relationships are based on a static concept, the kinetics can be included only a posteriori by rather complicated corrections. The mathematical treatment of radiation effects proposed by the authors [1] and summarized in this section is an attempt to include the kinetics of radiation-induced processes as well as the dynamical character of the vital objects. As will be shown, the "hit and target" inter-

* This paper includes some points discussed by the participants of the Panel.

pretations are special cases in this scheme. The proposed treatment is, however, more than a mere generalization of target theory; it covers the different stochastic factors which determine the radiation effect whereas target theory is concerned with only one of the stochastic factors, namely the random nature of energy deposition.

For didactic reasons we start with the classical multihit model and with a description of the radiation-induced processes. As the target theory is concerned with random events (hits), it is a stochastic theory that treats the radiation-induced transitions of certain molecular or cellular units between different states. These states are characterized by the number of hits received by a unit. Therefore, the system at any moment can be described by the occupation numbers, i.e. the percentage of units in each of the possible states. The occupation numbers can be put together to a state vector $\vec{x}$. The radiation-induced time changes of the state vector are given by the transition probabilities between the different state points. The general form is:

$$\frac{d}{dt}\vec{x} = f(\vec{x},\ D,\ t) \tag{1}$$

where D is the dose, and t is the time. The treatment can be restricted to linear processes, if, as is frequently the case, the flux from one state is proportional to its occupation number. Thus Eq. (1) is converted to:

$$\frac{d}{dt}\vec{x} = A\,\vec{x} \tag{2}$$

where A is the transition matrix. The solution of this equation is:

$$\vec{x} = e^{At}\,\vec{x}_0 \tag{3}$$

where $\vec{x}_0$ is the initial value of the state vector, and e^{At} is the matrix which is defined in the usual way:

$$e^{At} = 1 + At + \frac{A^2t^2}{2} + \frac{A^3t^3}{3!} + \ldots$$

Equation (2) is equivalent to a system of linear differential equations. Matrix notation, however, facilitates the treatment considerably. A certain target theory model can be illustrated by a graph as in Fig. 1. There the initial and the radiation-induced states of damage are depicted by points arranged vertically and the transition probabilities by pointed lines connecting them. This, of course, is only the most simple model; its modificatins will be discussed in section II. Spontaneous physiological changes of a system (e.g. biochemical processes or cellular cycles) can be treated in the same way. Here the different states may be symbolized by points arranged horizontally.

The superposition of both representations leads to a two-dimensional network including radiation-induced as well as spontaneous processes (Fig. 2)

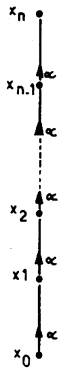

FIG. 1. Graph representing the "multihit" model (see Eq. (4))
x_i : fraction of test-objects with i hits, α : transition coefficients, I : dose rate

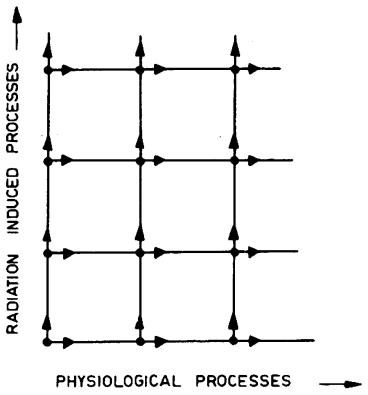

FIG. 2. Superposition of physiological and radiation-induced processes

The system can be readily simulated in an analogue computer. The advantage of this treatment becomes obvious if one has to deal with complicated systems as, for example, radiation effects on cell populations in different states of the mitotic cycle characterized by different radiation sensitivity, or the kinetics of an enzymatic system as described in Refs. [1-3].

II. THE LIMITATIONS OF THE CONVENTIONAL MODELS

The general model is also useful for illustrating the conventional models of target theory. Especially the graphical representation makes it possible to write down a certain model in a simple and well-defined way. Moreover, the treatment brings out clearly the limitations of target theory. In this section we use the general model for this purpose only.

From the different forms of dose-effect curves of low and high LET radiation, very far reaching conclusions have been drawn as to the action

mechanisms involved. They are all based on classical target models and it seems worthwhile to investigate whether this is justified or not. Let us discuss in detail the multihit mechanism of Fig. 1. The corresponding matrix equation is:

$$\frac{d}{dD}\begin{pmatrix} x_0 \\ x_1 \\ x_2 \\ \cdot \\ \cdot \\ x_{n-2} \\ x_{n-1} \end{pmatrix} = \begin{pmatrix} -\alpha & 0 & 0 & \cdot & 0 & 0 & 0 \\ \alpha & -\alpha & 0 & \cdot & 0 & 0 & 0 \\ 0 & \alpha & -\alpha & \cdot & 0 & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & \cdot & \alpha & -\alpha & 0 \\ 0 & 0 & 0 & \cdot & 0 & \alpha & -\alpha \end{pmatrix} \begin{pmatrix} x_0 \\ x_1 \\ x_2 \\ \cdot \\ \cdot \\ x_{n-2} \\ x_{n-1} \end{pmatrix} \qquad (4)$$

The solution of this equation is obtained if one inserts the explicit form of the matrix e^{AD}:

$$\vec{x} = e^{AD}\,\vec{x}_0 = e^{-\alpha D} \begin{pmatrix} 1 & 0 & 0 & \cdot & 0 & 0 \\ \alpha D & 1 & 0 & \cdot & 0 & 0 \\ \frac{(\alpha D)^2}{2!} & \alpha D & 1 & \cdot & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \frac{(\alpha D)^{n-1}}{(n-1)!} & \frac{(\alpha D)^{n-2}}{(n-2)!} & \frac{(\alpha D)^{n-3}}{(n-3)!} & \cdot & \alpha D & 1 \end{pmatrix} \qquad (5)$$

With the initial condition: $\vec{x}_0 = \begin{pmatrix} 1 \\ 0 \\ 0 \\ \cdot \\ \cdot \\ 0 \end{pmatrix}$ one obtains $\vec{x} = \begin{pmatrix} 1 \\ \alpha D \\ \frac{(\alpha D)^2}{2!} \\ \cdot \\ \cdot \\ \frac{(\alpha D)^{n-1}}{(n-1)!} \end{pmatrix}$

Thus, one arrives at the well-known dose-effect relation:

$$\frac{N}{N_0} = \sum_{\nu=0}^{n-1} x_\nu = e^{-\alpha D} \sum_{\nu=0}^{n-1} \frac{(\alpha D)^\nu}{\nu!} \tag{6}$$

Obviously there are some arbitrary implications in this scheme: firstly, recombination, i.e. backwards-directed transitions are not accounted for; secondly, only transitions between neighbouring state points are accounted for; thirdly, all transition probabilities are taken to be equal. If we complete the scheme as far as the first aspect is concerned (Fig. 3), we can include in the model certain recombination processes responsible for the dependence of biological processes on the time distribution of dose. The second aspect is of special relevance to the theme of the Panel, namely the role of radiation quality in biological effects. We can assume that certain effects are produced in low LET radiation by interaction of several absorption events, whereas at high LET radiation only a single absorption event is necessary. This latter may be represented in the graph by a transition from the ground level to higher states. This means that an effect brought about in a single step by high LET radiation requires several steps at low LET radiation. For a detailed treatment one has to consider the possibility that any kind of radiation may act by both modes but with different frequency. If one includes the whole spectrum of different hit events, the resulting graph (Fig. 4) becomes rather complicated. The corresponding matrix equation is:

$$\frac{d}{dt}\vec{x} = \begin{pmatrix} -\Sigma p_i & 0 & 0 & 0 & \cdot & \cdot & 0 \\ p_1 & -\Sigma p_i & 0 & 0 & \cdot & \cdot & 0 \\ p_2 & p_1 & -\Sigma p_i & 0 & \cdot & \cdot & 0 \\ p_3 & p_2 & p_1 & -\Sigma p_i & \cdot & \cdot & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ p_{n-1} & p_{n-2} & p_{n-3} & p_{n-4} & \cdot & \cdot & -\Sigma p_i \end{pmatrix} \tag{7}$$

The elements which are not adjacent to the main diagonal in the transition matrix correspond to the connections between non-neighbouring state points. Because in this case the form of the transition matrix is more intricate than in the simple multihit model, numerical evaluation of Eq. (7) is usually difficult. Also, in general, little is known about the spectrum of transition probabilities.

Figure 4 and Eq. (7) are therefore heuristic models rather than a basis for quantitative treatment. They have been given explicitly in the present

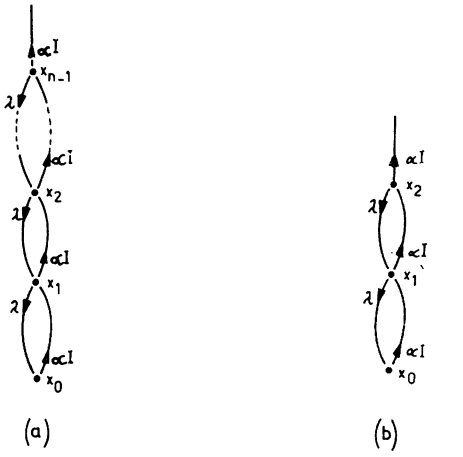

FIG. 3. Graph of the multihit model including recombination processes
(a) n-hit process (b) 3-hit process (see Eq. (8))

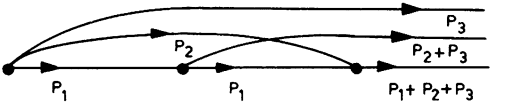

FIG. 4. Graph of the multihit model if absorption events of different kind are accounted for (see Eq. (7)). A 3-hit process is chosen as an example in this figure

context because it is necessary to show clearly the complexity of the target theory models. Naturally, one is forced to choose simplified models for practical application but to avoid incorrect use of the simplified models one must know their limitations.

Although for volumes of macromolecular size little is known about the spectra of absorption events, quantitative treatment is possible for bigger volumes with a diameter of about 1μm. Here, Rossi's concept of local energy density [4, 5] is applicable; the transition coefficients are given by the experimentally determined spectra of absorption events (see also Rossi [6]).

The considerations on the influence of the recombination processes and of the fluctuations of energy deposition show that the conventional target theory models are only very poor approximations.

Another simple example may serve to demonstrate that target theory is not quite consistent in itself inasmuch as only very arbitrary assumptions lead to the well-known distinction of multihit and multitarget curves.

Dose-effect curves with a finite extrapolation number (i.e. those curves with a final exponential part) are usually considered to indicate multitarget mechanisms. For the one-target multihit model represented by Fig. 1, target theory predicts a dose-effect curve with no finite extrapolation number. If, however, one does not assume that all transition probabilities in Fig. 1

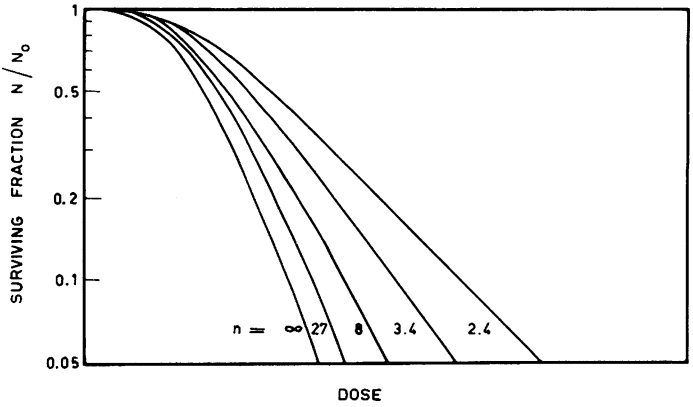

FIG. 5. Four-hit curves. The lowest curve results if all transition probabilities in Fig. 1 are equal. The other curves result if the transition probability of one step differs from the others by the factor 0.66, 0.5, 0.33 and 0.25 respectively.
n : extrapolation number

are equal – and there is no fact warranting this assumption – one gets dose-effect curves with finite extrapolation numbers. The lowest curve in Fig. 5 is a four-hit curve with equal transition probabilities. The other curves result if one of the transition probabilities differs from the others. As this difference increases, the extrapolation number decreases. This again shows clearly that the shape of the dose-effect curves allows no statement on the number of hypothetical targets and the respective number of hits to inactivate them.

We do not want to discuss the subjects related to the time factor, but one feature related to the interpretation of dose-effect curves should be mentioned. Figure 3b is equivalent to the following equation:

$$\frac{d}{dt}\begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} -\alpha I & \lambda & 0 \\ \alpha I & -\alpha I - \lambda & \lambda \\ 0 & \alpha I & -\alpha I - \lambda \end{pmatrix} \begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix} \qquad (8)$$

This equation can be evaluated on an analogue computer, and Fig. 6 presents the resulting dose-effect curves. One observes that if backwards-directed transitions are involved the dose-effect curves approximate shoulder curves with a final exponential part. If the ratio $\alpha I/\lambda$ decreases (i.e., if recovery processes become more influential), the extrapolation number decreases, and the curve more and more approximates exponential shape. This is another argument which shows that the extrapolation number is not at all to be considered as an indication of the number of hypothetical targets. Moreover, we observe that there are already two possible interpretations for the exponential part of a curve not based on a one-hit mechanism in one or

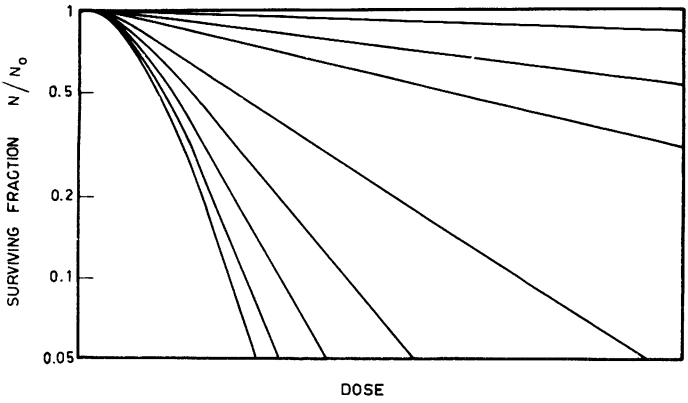

FIG. 6. Dose effect curves computed according to Fig. 3b and Eq. (8).

For the lowest curve, the ratio $\alpha I / \lambda = \infty$
For the other curves, the ratio $\alpha I / \lambda = 1$, 0.32, 0.15, 0.075, 0.032, 0.015 and 0.0075 respectively

more targets. In the first instance the inequality of the transition coefficients was responsible for the exponential part of the dose-effect curve; in the above example the exponential part of the dose-effect curve is due to recombination or recovery processes. It may be startling that exponential dose-effect dependences are brought about by such different modes of action. The common factor, however, is always a stationary state of predamage. In one-hit mechanisms it is insignificant as there is no predamage. In multihit events with recombinations, the stationary state is given by the fact that the distribution of units over the various states below the critical level becomes constant.

[This can be expressed easily by matrix calculus. An exponential part of the dose-effect curve results over the dose range where the state vector becomes an eigen-vector of the transition matrix. It is insignificant that the state vector is an eigen-value for a one-hit event because it consists of only one component; in the other cases the smallest eigen-value of the transition matrix is simple, and therefore the state vector approaches the eigen-vector belonging to the smallest eigen-value. Only in very special cases (and the multihit model is one of these special cases) are the eigen-values of the transition matrix equal; then there is no exponential part of the dose-effect relation.]

Biological variability is a factor which has not yet been mentioned; it is, however, widely discussed in the literature and is clearly of importance. This aspect can be represented in various ways in the graphs and in the corresponding matrix equations. The simplest way is to modify the multihit model by the assumption that some of the biological units need more, and some need less hits for the test effect to occur. The model then assumes the form of Fig. 1 with the additional assumption that already at the begining of the irradiation some of the units are in higher states and therefore need less hits to reach the critical level of damage. This means that the initial value of the state vector

is not taken to be: $\begin{pmatrix} 1 \\ 0 \\ 0 \\ . \\ . \\ 0 \end{pmatrix}$ but rather: $\begin{pmatrix} p_n \\ p_{n-1} \\ p_{n-2} \\ . \\ . \\ p_1 \end{pmatrix}$

where p_ν is the fraction of the biological units which need p_ν hits for the test effect to occur. With these initial conditions for Eq. (4) one obviously obtains a simple superposition of multihit curves.

This last model corresponds to the calculations done by Fowler [7 - 9]. He determines spectra p_ν which lead to dose-effect curves approximating experimental dose-effect relations. Obviously this model is equivalent to Eq. (4) and not to Eq. (7). Equation (7), which represents the influence of local energy density fluctuations, generally does not yield a simple numerical solution.

It can be concluded from section II that even for the simple multihit model there are many free parameters in the possible realisations of this model. Therefore, it is usually impossible to deduce the underlying mechanism from a dose-effect curve that is determined experimentally. As even the most simple models present such a wide spectrum of possibilities it seems pointless to construct even more complicated models, e.g. models based on the assumption of several targets in each biological unit which require different numbers of hits. Models of this kind could only be based on definite morphological and biophysical findings. The same holds true for models which include the kinetics of the physiological processes.

On the basis of this conclusion one may proceed in two different directions. Firstly, one may attempt to find relations of general validity which hold true regardless of all complicating factors in the possible target theory models. Secondly, one may try to give a very simple, and biologically more meaningful, interpretation of dose-effect curves. An attempt in this direction will be presented in section III.

III. THE BIOLOGICAL STOCHASTICS

So far we have kept the target theory assumption that the stochastic nature of biological effects reflects the random nature of energy absorption. This is obviously the most natural assumption in radiation chemistry including also the inactivation of macromolecules such as enzymes and viruses, and point mutations produced by all types of radiation. This assumption is also justified in more complicated cellular processes such as cell death if densely ionizing radiation is applied. However, its applicability to the lethal effect of low LET radiation on cells and multicellular organisms is questionable. There are several objections. Until now, attempts to relate the hypothetical targets to cytological elements have been unsuccessful except in genetic effects. Where in the cell is the centre of macromolecular size which governs life

and death? It is difficult to believe that the energy absorption in all other parts of the cell is irrelevant. General toxicology gives examples for exponential dose-effect curves where a one-hit mechanism or monomolecular reaction is impossible. Thermal inactivation of some bacteria also follows an exponential curve. Here the assumption of heat quanta is very artificial. Therefore, the principle question arises whether the dose-effect relationship can only be explained by the random nature of energy absorption. Usually, variation of the radiosensitivity is considered as the only possible alternative. The following discussion is a summary of a related paper by the authors [10] and shows a third possibility.

It must be remembered that life is characterized by its homeostasis. Vital systems possess an inherent lability, i.e. a certain probability of spontaneous breakdown. Disturbances can be compensated only up to a certain degree. Damage to such a system may increase the probability of a breakdown temporarily or permanently. The breakdown of a predamaged system is especially likely under certain additional stresses or during critical physiological processes such as mitosis. If radiation were to produce this kind of "physiological damage" (this term is used in contrast to "localized damage" like mutations) then, even if damage and individual dose of all units were approximately the same, the effect would still be distributed stochastically.

We want to emphasize that the biological stochastics of the effect have nothing to do with variability of radiosensitivity, which is a meaningless term if it cannot be referred to a certain property of the individuals. It is known that even identical individuals show certain unpredictable fluctuations in their dynamic state, and extreme fluctuations may lead to the lethal effect. We will show later that dose-effect curves of well-known forms may be explained on the basis of biological stochastics as well as, or even better than, in classical ways.

Thus, from the biological point of view as well, the usual interpretation of the dose-effect relationship appears too rigid. One would like to have a very simple description that does not presuppose any possible underlying action mechanisms.

The slope of a dose-effect curve in a semilog plot is given by the term:

$$\frac{d \ln N}{dD} = \frac{1}{N} \times \frac{dN}{dD} \tag{9}$$

It gives the percentage decrease of survivors if a certain dose element ΔD is applied. We call it "reactivity" (R).

$$R = \frac{d \ln N}{dD} = \frac{1}{N} \times \frac{dN}{dD} \quad \text{and thus} \quad \frac{\Delta N}{N} = R \, \Delta D \tag{10}$$

This term "reactivity", which is also sometimes called "inactivation constant" (though it is constant only for exponential dose-effect curves), describes the final effect only; no assumption is made on the mechanisms leading to the effect. What are the differences between the usual types of one-hit, multihit, and multitarget curves, if they are expressed in terms of reactivity?

If the reactivity is independent of dose, the dose-effect curve is exponential. If the assumption of a one-hit mechanism is, in fact, justified

by other arguments, R can be interpreted as a geometrical cross-section or as the product of a sensitive volume and an effect probability. But, if we refer to a kind of homogeneous predamage and a corresponding probability for breakdown of the damaged system, then R is merely to be taken as the factor connecting them with dose.

Which dose dependence of predamage leads to an exponential survival curve? There are different kinds of predamage which can be proportional to dose and lead to an exponential dose relationship. The following example may serve as an illustration: the stability of the cell is given by the orderly interaction of a large number of functional units. We may assume that in a certain one of these components, which we label by the index i, a dose D induces a probability p_i for malfunction. Then, p_i is a function of dose and can be expressed as the power series in D_i:

$$p_i = a_{i1} D + a_{i2} D^2 + \ldots \tag{11}$$

The total probability P for the breakdown of the system is given by

$$P = 1 - \prod_i (1 - p_i) \tag{12}$$

If the number of components is large, then even small values of p_i lead to a high value of P. With small p_i, however, we can omit the non-linear terms in the power series, and so get:

$$p_i = a_{i1} D \tag{13}$$

and

$$P = 1 - \prod_i (1 - a_{i1} D) = 1 - \exp\left(-\sum_i a_{i1} D\right) \tag{14}$$

Thus, the survival probability is an exponential function of dose. According to these assumptions, an exponential dose-effect relationship is not necessarily indicative of single-hit mechanisms; it can, on the contrary, result from the effect of many functional components. However, this is a special case. In vital systems, one can expect that any toxic agent at low doses may be compensated partially or completely. This means an increase of R with dose. R increases with dose in different ways for sigmoidal dose-effect curves. Figure 7 gives a plot of R for some typical curves. By choosing, as an example, the experimental data of Elkind and Sutton [11, 12] on irradiated cell cultures (Fig. 7), the dose-effect relationship can be explained on the assumption that R(D) approaches exponentially an asymptotical value. We call this an exponential loss of compensation ability with dose.

[This assumption can be expressed mathematically in the following way:

$$R(D) = -\frac{d \ln N}{dD} = R' - k_0 \exp(-\gamma D) \tag{15}$$

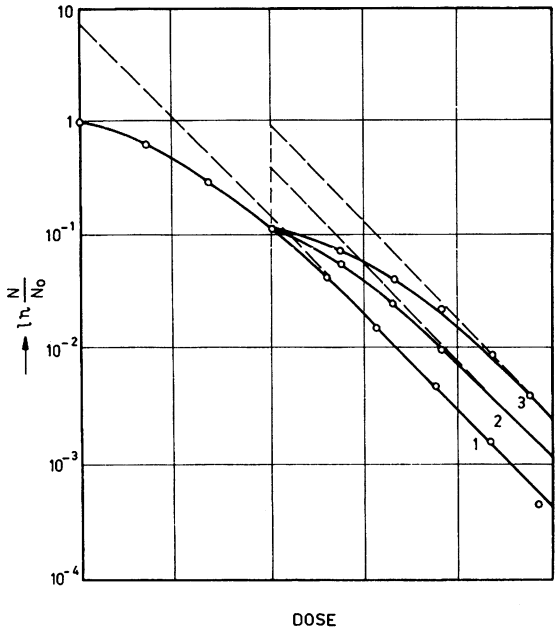

FIG. 7. Dose-effect curves for mammalian cells in vitro, according to Elkind and Sutton [11, 12].
1 : single irradiation
2 and 3 : irradiation in two fractions with different time intervals.
The curves correspond to Eq.(17)

By integration, the dose-effect relation is:

$$\ln \frac{N}{N_0} = -R'D + \frac{k_0}{\gamma} [1 - \exp(-\gamma D)] \tag{16}$$

or

$$\frac{N}{N_0} = \exp \left\{ -R'D + \frac{k_0}{\gamma} [1 - \exp(-\gamma D)] \right\} \tag{17}$$

The curve corresponding to this equation is given in Fig. 7. It is apparently in accordance with the experimental data.

It may be mentioned that the deduction of Eq.(17) was given independently by Haynes [13], who used a somewhat similar argumentation, and spoke of reactivation mechanisms where we prefer the term compensation ability. Obviously linear increase of the reactivity, i.e. inactivation constant, with dose is a limiting case of the model discussed above (see Sinclair Ref. [14])

An exponential dose-effect curve or an exponential part of a dose-effect curve is attained whenever R becomes independent of dose. This is true if there is no compensation ability at all (static system, single-hit mechanism), or if an equilibrium of predamage is reached (stationary state). The latter possibility is already illustrated in Figs. 5 and 6.

This interpretation is not committed to one certain mode of compensation. In some cases we know factors by which shoulder curves may be converted into exponential curves and vice versa, showing certain modes of compensation. Alexander [15] showed that the size of the shoulder depends on the concentration or amount of chemical protectives. Dose-effect curves of Escherichia coli are exponential if the bacteria are cultivated aerobically, and sigmoid-like when cultivated anaerobically in the same medium containing glucose (Hollaender [16]). Other examples of the change in dose-effect curves by metabolic and environmental conditions are given by Alper [17].

A certain compensation is already given by the fact that even damaged cells undergo a few divisions, especially with low LET radiation. Even if we assume that according to our above considerations the probability for a successful mitosis decreases exponentially with dose, one may get a shoulder curve. This is because the experimental criterion is not the fraction of successful mitosis but the ability of a cell to form a macrocolony.

To show this, we choose a very simplified model. We assume that the first division after irradiation is undisturbed; the second division is taken to be the critical phase. The probability for breakdown in this phase is equal to $q = 1 - e^{-\alpha D}$. Both cells originating from the first mitosis have to fail if no colony is to be formed. Thus, the probability that no colony is formed is equal to $(1 - e^{-\alpha D})^2$. This means one obtains a so-called two-target curve as the dose-effect relation. Analogous to this, multitarget curves of higher order result if the critical phase lies in a later mitosis. This, of course, is a very unrealistic model, but one may assume that the breakdown probability after irradiation is increased for a certain number of cell generations, and still in this more general case the dose-effect curve for cell colony formation can be shown to be more sigmoid than the dose dependence of q. One could say that at high survival rates the breakdown of a cell in a later mitosis is "compensated" by the continued division of the sister cells which are already present.

Although this interpretation may appear to renounce the explanation of fundamental mechanisms – an interpretation fitting so closely for target hit models – the terminology used in this paper does not contradict the validity of the target theory treatment when it is based on the special case of physical and cytological findings. The authors feel it is better to avoid "pseudo-exactness" if it has limited value for interpretation, and especially if it enforces a restricted viewpoint.

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