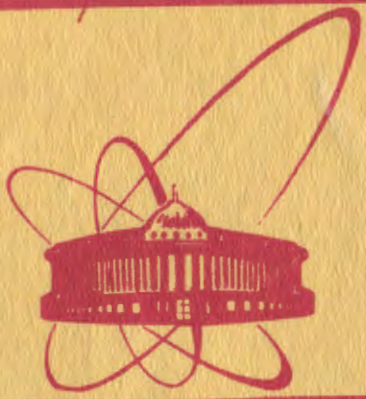

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A MATHEMATICAL MODEL OF CUMULATIVE BIOLOGICAL EFFECT

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1. INTRODUCTION

In establishing the laws of cumulative radiation effect it is necessary to take into account two basic aims. One of them consists in a detailed understanding of the whole mechanism and the possibilities of influencing the resulting effect in different phases of the whole process. The other equally important problem is represented by a presentation of these laws in a form that would give a sufficiently simple possibility of applying these pieces of knowledge in practical radiotherapy.

The latter goal has been fully solved by introducting the Ellis formula [1]

$$NSD = D \cdot N^{-0.24} T^{-0.11} ,$$

which characterizes a cumulative effect by a very simple function of the quantities defining a corresponding course of irradiation. This formula is tightly connected with the knowledge of early sixties when Cohen [2] has presented more exact fractionation data than those published much earlier by Strandquist [3]. It was shown on the example of human skin and tumour tissue that the isoeffect curves expressing the T-dependence of an applied total dose D (at a constant time interval t) were represented in a logarithmic scale in a wide T-interval by straight lines (the so-called Strandquist lines) being parallel for the same tissue and radiation types.

Some difficulties are, however, related to the given formula: first, it is the fact that NSD factor cannot be brought into any relation with a number of surviving cells which are generally regarded as a measure of a corresponding macroscopic effect. Further, it is the problem of interpreting individual factors in the NSD formula; it will be seen in the following that, e.g., proliferation is not given by the T-factor and destruction by the N-factor only, as is often accepted. And finally, there are still growing experimental data which show that linear Strandquist graphs represent a global characteristic only and some deviations from linearity should be taken into account.

The series of authors have tried, therefore, to describe the cummulative effect in another way (see, e.g., ref. [4,5]);

they combine the destruction effect of each fraction dose with the proliferation of tissue cells running between the fractions. There does not exist, however, till now any resonable idea, how to describe such a combined process. Thus in formulating basic assumption of such an approach one can make some mistakes not removable in further steps.

We shall, therefore, attempt to perform a global analysis of all characteristics of the cumulative effect. We shall start with a detailed analysis of all assumptions the NSD formula is based on. By relaxing some of them, which are most limiting, we shall obtain a more general formula, which not only describes better the corresponding experimental data but can also help in solving the problem how to combine the description of destruction and proliferation processes.

2. BASIC ASSUMPTIONS OF THE NSD CONCEPT

The NSD concept has started from experimental characteristics as well as from some additional assumptions. We shall now summarize all the points this concept is based on.

A. The basic experimental features already mentioned can be characterized in the following manner:

a) The T dependence of the total dose D at a constant $t = T/N$ can be in a relatively broad interval of the quantity T expressed by the relation

$$\lg D = \lg D_1 + \kappa \lg T, \tag{1}$$

where the quantity κ represents the slope of the corresponding straight line in a logarithmic graphs.

b) The parameter t in Eq. (1) depends only on the types of tissue and radiation and not on a tested biological reaction.

As the interval t between individual dose fractions is constant the quantities T and N are mutually proportional, which means that Eq. (1) should be written in a more general form

$$\lg D = \lg R + r \lg T + \nu \lg N, \tag{2}$$

or

$$D = R N^{\nu} T^{r}, \tag{3}$$

where

$$\nu + r = \kappa \tag{4}$$

and the corresponding biological reaction can be characterized by the quantity R.

B. The experimental data give a possibility of determining the value of κ only. When trying to specify the values of both the parameters ν and r Ellis has been forced to add some other assumptions which can be expressed in the following way:

i) For given types of tissue and radiation the parameters ν and r are assumed to be constant and independent of a biological reaction.

ii) The slope differences for skin and tumour tissue are fully given by a greater proliferation ability of the normal tissue.

iii) The parameter ν is fully related to a destruction effect of radiation; while r, to a proliferation ability of a given tissue.

Even if some attempts have been made to reason these assumptions they have never been proved and must be regarded as a-priori statements. Thus, it is quite justified to generalize the NSD concept in such a way that one starts from the basic experimental facts only without any additional assumptions. A comparison of this new more general model with experimental data will allow us to give also an answer to the question which of the mentioned assumptions can be valid and which not.

3. DIFFERENT SCALES OF RADIATION EFFECT

As has been already mentioned the radiation effect can be defined by

$$R = D N^{-\nu} T^{-r}. \tag{5}$$

In analogy with TDF factor introduced by Orton and Ellis [6] another scale of the radiation effect can be given by a quantity

$$F = R^{\gamma}, \tag{6}$$

where γ can possess a quite arbitrary value. If one puts

$$\gamma = \frac{1}{1 - \nu - r + \mu} \tag{7}$$

then for $\mu = 0$ the factor F is identical to the known TDF factor; for $\mu = \kappa$ one obtains $\gamma = 1$ and F will be identical to R.

Similarly to the TDF factor the general factor F can be expressed as a sum of contributions from individual dose fractions. One can write [7]

$$F = \sum_{i=1}^{N} F_i, \tag{8}$$

where

$$F_i = y_i d^{\gamma} t^{-\beta-\epsilon} \tag{9}$$

and

$$y_i = i^{1-\epsilon} - (i-1)^{1-\epsilon} ; \qquad d = D/N , \quad t = T/N . \tag{10}$$

In the definition of the new more general factor we have three free parameters, which can depend on tissue and radiation types. For the original parameters ν and r it holds then

$$\nu = 1 - \frac{1+\epsilon}{\gamma} , \quad r = \frac{\beta+\epsilon}{\gamma} \tag{11}$$

and the slope is given by

$$\kappa = \frac{\gamma-1}{\gamma} + \frac{\epsilon}{\gamma} . \tag{12}$$

The cumulative radiation effect at the end of a fractionation course is determined by

$$F = N d^{\gamma} t^{-\beta} T^{-\epsilon} . \tag{13}$$

The free parameters γ, β and ϵ should possess special numerical values in each concrete case. However, they cannot be determined from fractionation data only, as one of them can always be chosen quite arbitrarily. One must take further data into account. But before, it is necessary to clarify the deeper meaning of individual parameters.

Any of the unlimited set of F factors determines a macroscopic biological effect in a special scale. All such scales are in mutual non-linear relations. And one must ask which of these scales (if any) corresponds to a scale of a biological effect expressed in radiobiological terms (e.g., as a number of destroyed cells at the end of a fraction course). If such a scale among the F factors was determined one would obtain also a corresponding interpretation of all free parameters. It will be shown in the following section that such a correlation can be really found (see also refs. [8,7]).

4. CELL SURVIAL AT THE END OF FRACTIONATED IRRADIATION

The biological effect in a radiobiological scale is usually determined as a ratio of surviving cells. Let us denote such a ratio at the end of fractionated irradiation by $S(N, D, T)$; then it is possible to write quite generally

$$S(N, D, T) = \prod_{i=1}^{N} s_i(d, t) , \tag{14}$$

where s_i is the ratio of the cell number surviving at the end of the i-th interval to that surviving just before the application of the i-th dose fraction (i.e., at the end of the $(i-1)$-th interval). Eq. (14) can be rewritten as

$$\lg S(N, D, T) = \sum_{i=1}^{N} \lg s_i(d, t) . \tag{15}$$

Eq. (15) represents the same system of linear equations as Eq. (9). And if the quantities F and lgS should be equivalent for any N, D and T it must hold

$$\lg s_i(d, t) = -\chi F_i$$

or

$$\lg s_i(d, t) = -\chi y_i d^{\gamma} t^{-(\beta+\epsilon)} , \tag{16}$$

where χ is a positive constant of proportionality.

The survival at the end of the whole fractionation course is then given by

$$S(N, D, T) = \exp(-C) , \tag{17}$$

where

$$C = N h(d) f(t, T) \tag{18}$$

with

$$h(d) = \alpha d^{\gamma} \tag{19}$$

$$f(t, T) = \eta t^{-\beta} T^{-\epsilon} . \tag{20}$$

The constant parameter χ has been divided into two independent factors ($\alpha\eta = \chi$) so as to introduce two dimensionless functions $h(d)$ and $f(t, T)$.

Factor $h(d)$ in Eq. (18) determines the destruction effect of each fraction dose. It can be defined as

$$h(d) = -\lg s(d) , \tag{21}$$

where $s(d)$ is the survival curve under given conditions. In our case it can be expressed as

$$s(d) = \exp(-\alpha d^{\gamma}) , \tag{22}$$

which is the parametrization proposed earlier by Hugget [9], who has also shown that it describes survival curves of mammalian cells quite well.

The function $f(t, T)$ containing the parameters η, β, ϵ describes then the influence of proliferation processes. And

one can see at once from Eq. (11) that the quantities ν and r are represented by special combinations of destruction and proliferation parameters, or that the assumption iii) of Sec.2 cannot be valid.

5. ANALYSIS OF EXPERIMENTAL DATA

The C factor defined by Eq. (18) has been derived under the assumption that the corresponding Strandquist graphs are linear and parallel. Their slope is given by Eq. (12); it depends only on the parameters γ and ϵ and is fully independent of other parameters. Thus the basic features of Strandquist graphs would remain unchanged if, e.g., the parameters η and β were reaction-dependent. The parameter α should be constant as it describes the destruction effect of radiation.

The numerical values of free parameters can be determined from fractionation data for different biological reactions if at least one reaction is compared with the effect of one single dose. We must, however, take into account that at least some of the given data could lie already outside the linearity region. In such a case the slope κ cannot be a constant any more; it should depend on T. As the parameter γ in Eq. (12) is related to the destruction effect and should be constant this T dependence will be given by the parameter ϵ; we will assume it in the form

$$\epsilon(T) = \epsilon_1 + \epsilon_2 T + \epsilon_3 T^2 . \qquad (23)$$

Now it is possible to compare our model with experimental data. We will make use of the data from /10/ which concern the radiation effect on rat skin and represent probably the greatest available set of fractionation data. The set contains data for five different levels of biological effect with approximately 15 different fraction schemes in each group; for each group the given effect is compared with that given by a single dose, too.

We have obtained the following numerical values of our parameters (if doses are in Gy and time in days).

$$\epsilon_1 = 0.65 \cdot 10^{-1}, \quad \epsilon_2 = 0.61 \cdot 10^{-2}, \quad \epsilon_3 = -0.22 \cdot 10^{-4}, \quad \gamma = 1.4$$
$$\beta = -0.15.$$

We have had to admit a reaction dependence of the parameter η; the numerical values obtained for each level of biological effect have been

η = 0.64; 0.70; 0.86; 0.98; 1.18.

As to the parameters C and α it is possible to determine only the values of $\xi = C/\alpha$ for each reaction; we have obtained

ξ = 46.5; 69.1; 104.2; 139.4; 197.4.

The reaction dependence of η can, however, be admitted only as a consequence of the fact that η does not influence the value of the slope κ; it is hardly admissible in the frame of the whole model where η should be a reaction-independent constant. A way out of this dilemma will be shown in the next section.

6. CUMULATIVE EFFECT AND A SINGLE-DOSE SURVIVAL CURVE

In the analysis of experimental data presented in the preceding section we have assumed that the survial curve in the whole dose region (including the single doses necessary for reaching the highest levels of biological effect) is given by Eq. (22) with the same values of the parameters α and γ. One must expect, however, that the irradiated tissue is not represented by a homogeneous cell population; cells with different radiosensibility (in different parts of the cell cycle) will be surely present. Thus, if α and γ describe quite well the part of a survival curve being involved in fractionated irradiation they no longer need a correspondence to the part playing a role in irradiation by a single dose.

It is, therefore, necessary to generalize the function $h(d)$ in Eq. (18). We will define it again by Eq. (21) where the survival curve is described now by

$$s(d) = (1-\rho)\exp(-\alpha(d^{\gamma} + \delta d)) + \rho \exp(-\alpha_r d). \qquad (24)$$

Beside the second term in Eq. (24) we have added the linear term δd in the first expression, as it is known that such a term plays a great role in fractionation data with small fraction doses (see e.g. /11,12/).

However, another problem is related to Eq. (24). In the analysis performed in the preceding section we could not determine the value of the parameter α; we were able to determine the values of ξ only. Now the situation is not so simple and we should specify the values of the parameters α and α_r (or at least one of them), before looking for the values of other free parameters. We cannot, however, determine the mentioned parameters beforehand as it would be necessary to know a corresponding survival curve "in vivo" in a sufficient dose region; and such a curve is not available.

In our optimization procedure it is, however, sufficient to know one point on the given survival curve only. To illustrate the whole approach we have chosen the survival at 30 Gy

equal to $S_{30} = 5 \cdot 10^{-8}$ (in a similar way as in [13]). Having added this value to the other fractionation data we have obtained

$$\gamma = 1.2, \quad \alpha = 0.12, \quad \delta = 4.5, \quad \alpha_r = 0.27, \quad \rho = 1.6 \cdot 10^{-4},$$
$$\eta = 0.67, \quad \beta = -0.31, \quad \epsilon_1 = 0.12, \quad \epsilon_2 = 0.42 \cdot 10^{-2}.$$

We have put $\epsilon_3 = 0$ in Eq. (23) as this term represents a negligible correction only (at least in the T-interval concerned).

The actual value of S_{30} has no influence on the shape of the function $f(t, T)$. When changing this value from 10^{-8} to 10^{-6} the parameters η, β, ϵ_1 and ϵ_2 have been practically unchanged. They are the parameters ρ, α_r and α only which have exhibited a stronger dependence.

We have been also able to show that instead of an absolute value in one point it is possible to take a ratio of survival values in two different points. If we have taken, e.g., $S_{30}/S_{10} = 10^{-4}$ and $S_{30}/S_{20} = 10^{-1}$ (see [14]) we have obtained practically the same values of all free parameters as in the case with $S_{30} = 10^{-7}$.

Together with the values of all free parameters we have determined also the C-values (or better the values of $C' = C \log e$) corresponding to individual levels of biological reaction. For $S_{30} = 5 \cdot 10^{-8}$ we have obtained

$$C' = 5.0; \quad 6.1; \quad 7.0; \quad 7.8; \quad 8.9.$$

The ratio of cell survival at the end of irradiation is then given by $S = 10^{-C'}$.

If higher and lower bounds of confidence intervals given in [10] are taken to correspond to two standard deviations and if we assume the relative errors of D and lgS to be equal (due to an approximate mutual linear dependence) the χ^2-value of all mentioned fits is less than

$$\chi^2 \doteq 80.$$

The resulting survival curve given by Eq. (24) is shown in Fig.1 together with experimental data from [13] (see Fig.4); the coincidence of both the scales has been done by hand. It is evident that the parameters ρ and α_r do not play any role in proper fractionation data; they are important for single-dose points only. The fractionation region is, however, significantly influenced by introducing the parameter δ; a better agreement with all experimental data has been reached with the help of this parameter.

On the other hand it is necessary to mention that the χ^2-value is not very sensitive to the numerical value of the parameter γ; there exists a mutual competition between the values of γ and ϵ. The fit with $\chi^2 \lesssim 80$ can be obtained with γ lying in the interval from 1.1 to 1.3. A greater set of fractionation data is necessary to obtain a more reliable value of the γ-parameter.

7. DISCUSSION

First, we would like to mention the problem of survival curve "in vivo". To normalize our survival curve we have used some data on cell survival determined for another (even if similar) biological system; it is very probable that an actual survival curve will differ to some extent from that shown in Fig.1. The values of other parameters do not seem, however, to be very dependent on such a change.

This form of survival curve differs rather significantly from the "in vivo" survival curve determined recently in [15], although a similar dose range has been involved. It is necessary to realize that the approach used in [15] is not unique; it can strongly depend on the parametrization chosen. The polynoms of very low orders, which were used in that analysis, can never give a survival curve to that in Fig.1.

The relations between the parameters describing a corresponding survival curve and the C factor can be immediately made use of in an orientation analysis of that how different radiation-effect modifying agents or different radiation types can influence the main characteristics of cumulative effect represented, e.g., by D-T dependences (or Strandquist graphs). In our earlier papers we have supposed that the value of ϵ does not play a very important role. The new more detailed analysis has shown, however, that in some systems the value of ϵ can hardly be neglected, and also that its time dependence can cause some deviations of Strandquist graphs from linearity. It is also very probable that the ϵ factor will depend on the radiation type used.

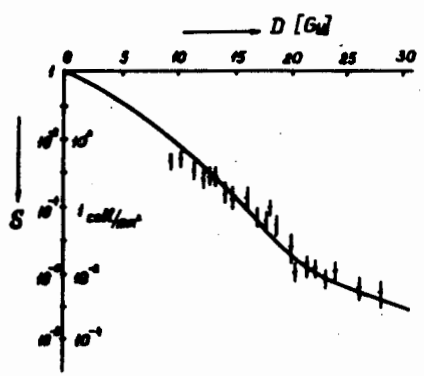

Fig.1. The single-dose survival curve s(d); the data from [13] are given, too.

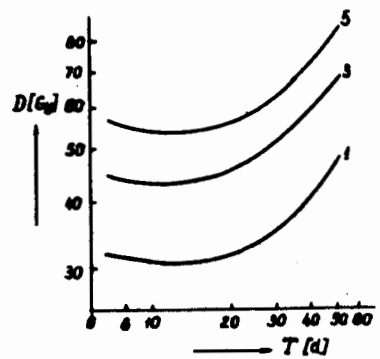

Fig.2. Iso-effect curves (D-T dependences) at constant N for different biological reactions (N=7).

All these new features in our model description of cumulative effect open a new way to searches for some optimal courses in radiotherapy. It may be seen, e.g., in Fig.2, where a dependence between D and T at a constant N for all biological levels involved is shown, that some extremum can exist. The corresponding nonlinear Strandquist graphs (at $t = 1$ day) are then represented in Fig.3.

As to the basic assumptions the Ellis formula is based on it is necessary to conclude that even in a linear part of Strandquist graphs (i.e., in a region where the T-dependence of ϵ could be fully neglected) the assumptions ii) and iii) of Sec. 2 are surely not valid. As to the assumption i) both the parameters ν and r can be regarded as reaction-independent; they may depend on T through ϵ (see Eqs. (11)).

All calculations have been performed with the help of the computer programs MINUIT and JOLOPLOT.

8. CONCLUSION

The presented mathematical model of cumulative biological effect describes the experimental data used with a sufficient statistical reliability. It should be now tested on all fractionation data available.

There are, however, still two points which need some more clarification. First, it is the already mentioned problem of finding a suitable norm for the corresponding survival curve; an absolute value in one point of a ratio for two different points must be always added to fractionation data. The other concerns the values of the parameters ρ and α_r. In our optimization approach it is not possible to determine an exact form of the second part of the survival curve. We cannot exclude that some other term with a higher power of d should be added. The numerical value obtained for ρ must, therefore, be regarded rather as a higher bound of this parameter.

We have already mentioned that the parameters α_r and ρ do not play any practical role

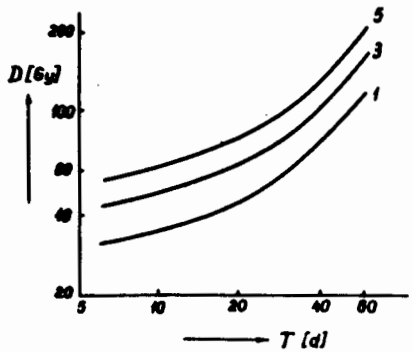

Fig.3. Iso-effect curves (D-T dependences) at constant t for different biological reactions ($t = 1$ day).

in the description of the cumulative effect. The factor

$$C = N\chi(d^{\gamma} + \delta d)\, t^{-\beta}\, T^{-(\epsilon_1 + \epsilon_2 T)}$$

with the numerical values of individual parameters given above can be used for determining the cummulative effect in any fractionated irradiation of rat skin by electrons or gamma-rays if $N \geq 3$, $T \leq 60$ days and the interval between fractions is at least ℓ day (internal cell repair should be finished). The corresponding cell-survival ratio is given by Eq. (17).

The presented approach can be then used in determining the values of free parameters corresponding to any other kinds of tissue and radiation.

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