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EVALUATION OF EXPERIMENTAL IRRADIATION FRACTIONATION WITH THE SINGLE-HIT, MULTI-TARGET MODEL

by

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All theoretical models developed for indicating the dose response curve in irradiation of cells are based upon the interaction of ionizating radiation with the cells (FORSSELL 1924, WARREN 1957, HIGGINS 1958). The one most commonly used is the single-hit, multi-target model (ZIMMER 1961). This model, as represented by formula (1), is often referred to as a multi-hit model, although the equation does in fact correspond to a multi-target model in which it is assumed that the cells have several targets, each requiring one hit for inactivation. This particular model was employed in this study. The multi-hit, single-target model (OLIVER & SHEPSTONE 1964), and the 'kinetic' model (DIENES 1966) are also of value. Some kind of treatment fractionation is usually applied in radiotherapy, and consequently the function describing the total dose producing a certain effect for different numbers of fractions is of importance to radiotherapists. Surveys of experimental findings, concerned with the change in the total dose with fractionated treatment have been published (see FOWLER & STERN 1963, WOOTTON 1966). These findings were obtained in animal in vivo and in vitro experiments.

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FOWLER (1965) presented two ways of considering the change in the total dose with the overall time used. One way (A) was derived by replotting clinical data and results from normal tissues of experimental animals; it corresponded to a high extrapolation number and a survival curve slope that continued to increase with dose. The other way (B) was by calculation from a simple cell survival model, assuming a single-hit, multi-target model with an extrapolation number of 2.8, and a 37 % dose slope $D_0 = 140$ rad. He concluded that the two predictions may be regarded as limiting values between which the empirical answers might be expected to lie, although he preferred experimental results derived from (A).

If a start is made from the assumption that different types of 'radiosensitive' and 'radioresistant' cells exist at the beginning of the irradiation, or from the assumption that the cells change to more 'radioresistant' cells after several irradiations, a change is to be expected in the extrapolation number and in the 37 % dose slope during fractionation treatment. The findings reported in this paper do not include cell repopulation during the time of treatment.

The purpose of this study was to compare the results determined experimentally and reported by FOWLER (1965), and indicating the change in the total dose taken against the number of fractions, with corresponding results derived by means of the single-hit, multi-target model. It was hoped that the use of a criterion in respect of the closeness of the fit of the experimental and theoretical results, together with a suitable assumption concerning a variation of the values of the extrapolation number and the 37 % dose slope, would permit a better description of the experimental results.

The single-hit, multi-target model. The fact that on the absorption of radiation, the events (hits) are statistically distributed and mutually independent means that Poisson's law is relevant. If it is assumed that the cells consist of m targets, each of which must receive one hit to make the cell react, i.e. lose its reproductive integrity, the following formula is valid:

$$S = 1 - (1 - e^{-D/D_0})^m \qquad (1)$$

This formula gives the cell survival curve in dealing with the single-hit, multi-target model.

S is the proportion of the cell population which survives the dose D (rad). D_0 (rad) is the 37 % dose slope, i.e. the dose required to reduce the survival proportion to 37 % of its initial value on the straight region of the logarithmic survival curve. The extrapolation number m may be thought of as the average number of targets (sensitive sites) in the cell but should rather be regarded as a mathematical parameter with no morphologic or biochemical significance.

It has been found that this formula provides a good description of the survival of a cell population given a single radiation dose. Usually, m lies between 2 and 10, and D_0 between 100 and 180 rad for oxygenated cells. For anoxic cells, D_0 increases to about 400 rad.

Fractionation. For small values of D, the shoulder of the survival curve plays an important role. In fractionation radiotherapy, accordingly, the total dose has to be increased for attainment of the same survival proportion as in one treatment; this depends upon the reduction in the efficiency of irradiation with small doses. The final surviving proportion S_N, after N treatments, may be calculated from the following formula:

$$S_N = \left\{1 - (1 - e^{-D/ND_0})^m\right\}^N \tag{2}$$

assuming that parameters D_0 and m do not change during the fractionated treatment. N is the number of fractions, and consequently D/N the dose per fraction.

The experimental values considered by FOWLER (1965) give the total doses D for different numbers of fractions, 1, 2, . . . N. If the doses given are used, then the same survival proportion S_N will be derived, regardless of the number of fractions, i.e. $S_1 = S_2 = \ldots = S_N$, respectively. If the experimentally determined values of D, corresponding to different numbers of fractions, are introduced into formula (2), a series of S_N are obtained, all of which should be equal if the model describes the process perfectly, and the proper values for m and D_0 have been chosen. This is not the case in practice, where a set of different S_N values results. The values for these that best fit the experimental results are determinable by varying m and D_0. A general criterion, called 'the relative closeness of fit' has been employed; this is indicated by Ω, and defined as follows:

$$\Omega = \hat{S}^{-1}\left\{\Sigma(S_N - \hat{S})^2\right\}^{1/2}(k-2)^{-1/2} \tag{3}$$

$\hat{S}$ is the mean value of the S_N values obtained, S_N the survival proportion corresponding to N fractions, and $(k-2)$ the degree of freedom, where k is the number of experimental values.

The smallest value of Ω exhibits the best fit between the experimental and theoretical results. The results of calculation are presented below.

Cell population with two different cell types. A model of a cell population comprising two different types of cells, 'radiosensitive' and 'radioresistant', was also employed. The following formula was used:

$$S_N = x\left\{1-(1-e^{-D/ND_1})^{m_1}\right\}^N + (1-x)\left\{1-(1-e^{-D/ND_2})^{m_2}\right\}^N \quad (4)$$

x is the proportion of 'radiosensitive' cells at the beginning of the irradiation. Thus, $(1-x)$ is the proportion of the 'radioresistant' cells, D the total dose, N the number of fractions and D/N the dose per fraction as defined earlier. D_1 and D_2 are the 37 % dose slopes, and m_1 and m_2 the extrapolation numbers of the 'radiosensitive' and 'radioresistant' cells, respectively.

The criterion for closeness of fit given in formula (3) was also applied in the calculation with formula (4).

Cell population with varying parameters. A further model, in which parameters m and D_0 change during the fractionated treatment, was also studied. The formula corresponds to a cell population which changes to a more 'radioresistant' one with an increasing number of fractions:

$$S_N = \left\{1-(1-e^{-D/NA})^B\right\}^N \quad (5)$$

where

$$A = A_1-(A_1-150)N^{-c}$$

$$B = (\varepsilon-1.5)N^{-c}+1.5$$

A represents the 37 % dose slope which varies in accordance with the formula presented above. It is assumed that the 37 % dose slope is 150 rad at the first irradiation. This value holds good, at least approximately, in most cases where cells have been irradiated. During the fractionated irradiation, the value changes towards A_1, which has been assumed to lie between 250 and 450 rad. Exponent c determines the speed of the change, and if this is varied it might be possible to determine the speed. B represents the extrapolation number, defined by the formula presented above. Also here, c determines the speed of the change. ε is the extrapolation number at the first irradiation, and changes towards 1.5. The value 1.5 was arrived at from the calculations in the next section.

The relative closeness of fit was also determined by means of formula (3).

Results and Discussion

In all the calculations, use was made of the experimental results published by FOWLER (1965), as shown in Fig. 6 and in the Table. The numerical calculations were effected with the Elliot 803 Computer at the Department of Theoretical Physics, University of Helsinki.

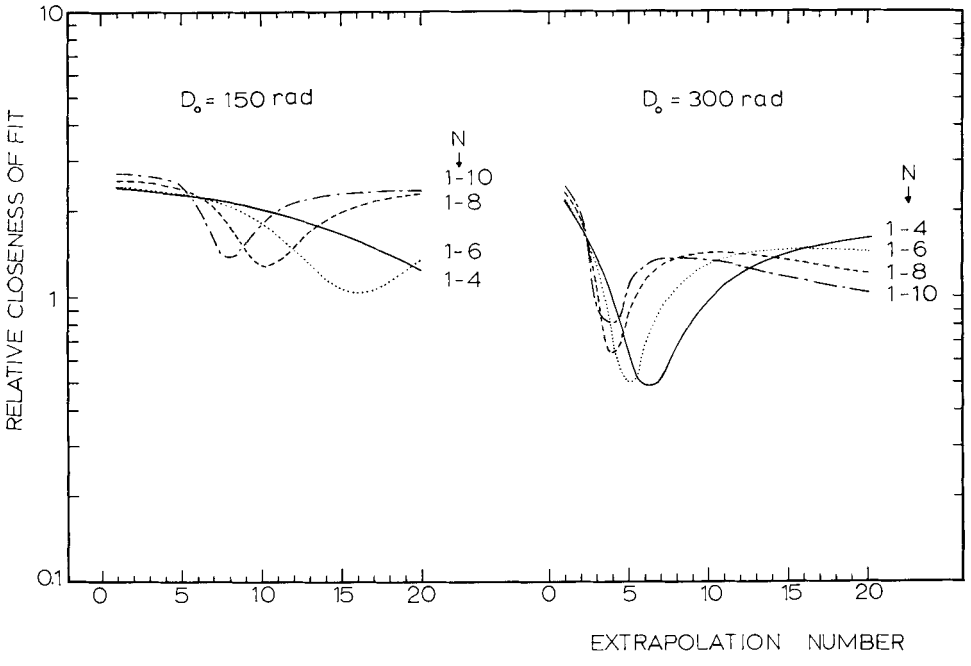

Fig. 1. Results of calculations with formulas (2) and (3). N indicates the interval of fractions included in the calculations. The curves depict results of the study of fractions from 1 to 10.

As has been demonstrated by WOOTTON (1966), the change in the total dose D for five irradiations, or more, can be expressed by the formula

$$D = D_1 N^a \tag{6}$$

where N is the number of fractions, and D the total dose needed in N fractions to arrive at the same survival proportion as for another irradiation number exceeding four. D_1 is the extrapolated iso-effect dose in one fraction, and a is a constant characteristic of the tissue system.

These facts led to the assumption that the theory would provide a better fit for the experimental results if account were taken only of the results between the eighth and the last irradiation. Initially, however, all the experimental results were included in the calculations but subsequently the initial and subsequent parts of the fractionation results were examined separately.

Formulas (2) and (3) were used. At first, D_0 was varied from 50 to 500 rad in steps of 50 rad, and m from 1 to 20 in steps of 1. When Ω was near minimum, it was examined more carefully by changing D_0 and m, in small steps, in the

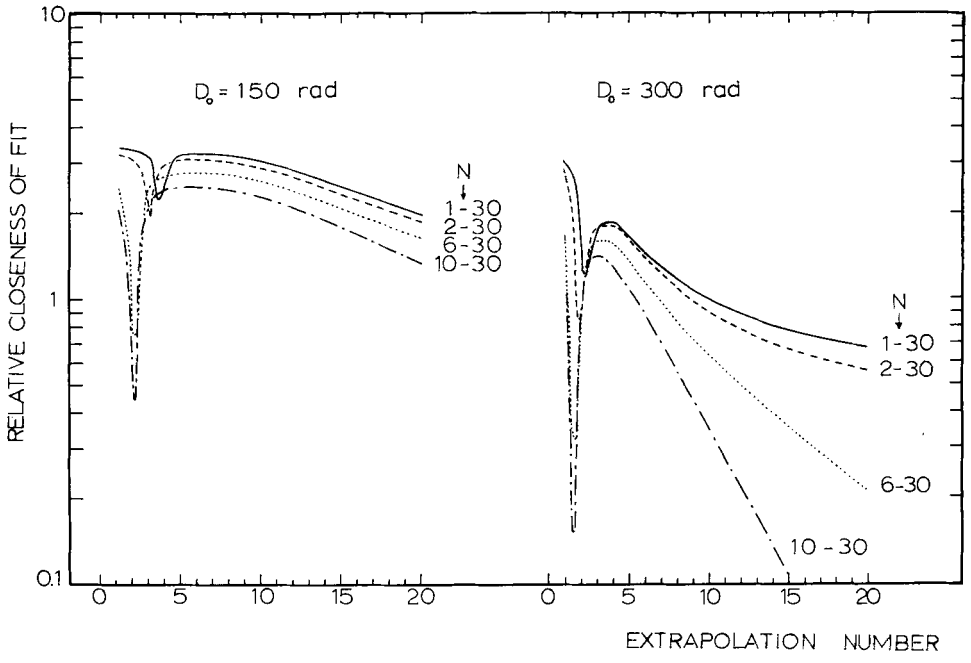

Fig. 2. Results of calculations, with formulas (2) and (3), on the study of fractions from 1 to 30. (Compare legend to fig. 1.)

region near the minimum. The experimental dose D should produce the same S_N, regardless of the number of fractions. The obtained quantity of Ω should accordingly at its minimum give the values of D_0 and m that best describe the experimental results. The results for $D_0=150$ rad and $D_0=300$ rad appear in Figs 1 and 2.

It may be observed that, independently of D_0, the value of m moves towards a value of about 1.6 if the total doses D for small numbers of N are neglected. This means that during the fractionation, m falls from its initial value, probably between 2 and 10, to about 1.6. This is discernible from the curves in which the calculations include N from 1 to 30 and from 10 to 30. Moreover, the curves based on N-values from 1 to 10 indicate that at the beginning of the treatment m is higher than 3.5 for $D_0=150$ rad, and higher than 2 for higher D_0-values. The agreement between experiment and theory is usually better on an increase in D_0. It has been assumed that the minima at low m-values are the realistic ones, until experimental evidence in support of higher extrapolation numbers may be brought forward. The final conclusion is that the extrapolation number

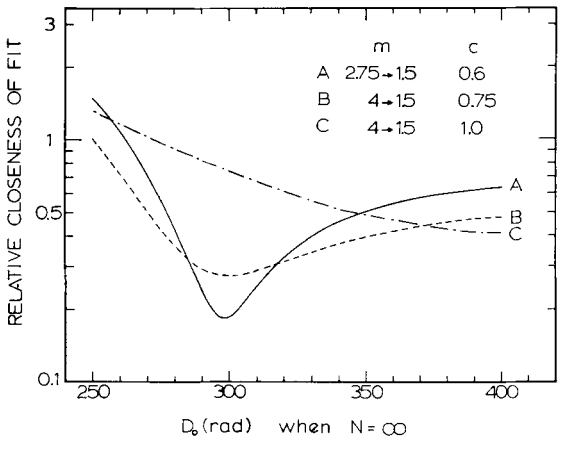

Fig. 3. Results of calculations with formula (5). The minima at 300 rad show that the 37 % dose slope changes from its initial value of 150 rad to about 300 rad. The value of m and c are indicated in the figure.

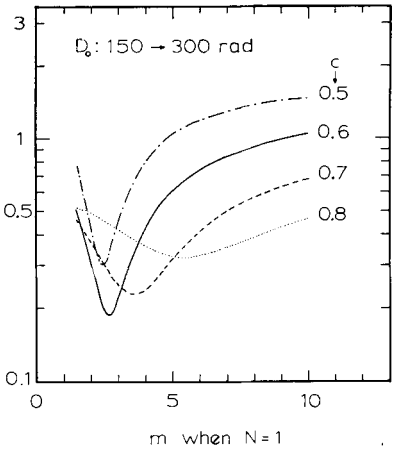

Fig. 4. Calculations illustrating how the extrapolation number m changes between 2 and 4 to 1.5 when formula (5) is applied. The value of D_0 is indicated in the figure.

m exceeds 2 at the beginning of irradiation, and diminishes towards 1.6 during fractionation. Nothing can be said about the dose slope D_0 from the results of calculations.

If we start from the assumption that at the first irradiation $D_0=150$ rad, m is between 2 and 10, and the total dose is 2 000 rad (FOWLER), then after this irradiation the survival proportion will be $S=0.3 \ldots 1.6 \times 10^{-5}$. If it is assumed that $N=30$, i.e. 30 irradiations, $m=1.6$ and $D=200$ rad per irradiation (FOWLER), there must be $D_0=280$ to 310 rad to arrive at the same survival proportion. This involves a change in D_0 from 150 to about 300 rad.

The calculations with application of formula (3), a mixture of two cell types, did not provide any acceptable results. In these calculations, the 'radiosensitive' cells were assumed to have the 37 % dose slope $D_1=150$ rad and the extrapolation number $m_1=2$ to 15; the 'radioresistant' cells had $D_2=150$ to 450 rad and $m_2=1.6$, respectively. The best results were obtained for $m_1=5$ to 8 and $D_2=300$ to 400 rad, but the smallest value of Ω was about 1.8. (This type of cell population does not seem useful in the application of the single-hit, multi-target model.)

Finally, we employed formula (4) for a cell population in which the parameters change during the fractionated irradiation. The starting assumption was that D_0 is 150 rad at the first irradiation and changes towards a higher value, 250 to 400 rad, with an increasing number of irradiations. The values

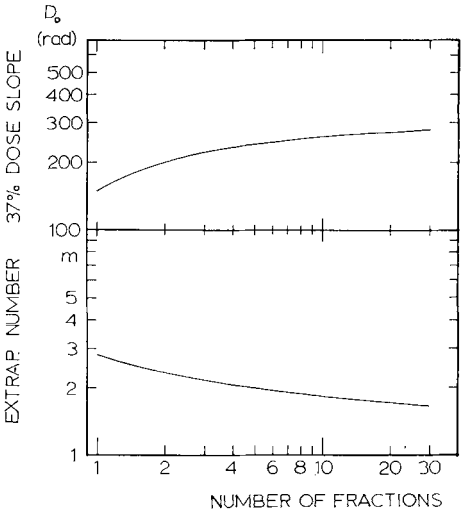

Fig. 5. Curves showing the change in D_0 and m for the best fit obtained with formula (5).

used for m were from 1.5 to 15 at the first irradiation; these were allowed to change towards 1.5. The variation in both parameters was determined by the formula presented in the preceding section. The results of calculations, some of them presented in Figs 3 and 4, indicate that the best agreement between theory and experiment, i.e. the smallest values of Ω, was arrived at on a change in D_0 from 150 to 300 rad, in m from 2.75 to 1.5, and to have $c=0.6$. The value of c is sharply determined, which means that the change in D_0 and m becomes apparent. Fig. 5 indicates the change in D_0 and m when $c=0.6$. The results should be so understood that for a definite number of fractions the values of D_0 and m are average values which correspond to that particular number of fractions. In fact, the value of D_0 is less than that of the average value at the beginning of the fractionated irradiation, and larger in the later part. Similarly when N irradiations are made, the value of m exceeds its average at the beginning, and is smaller at the end of the irradiations.

In conclusion, the last model seems the best one for describing the change in the total dose during fractionated irradiations of cells. It was assumed that during the irradiations the 37 % dose slope changes from its initial value o 150 rad to about 300 rad. The extrapolation number has a value between 2 and 4 at the beginning, and changes towards about 1.5 at the end of the fractionated treatment.

The results now arrived at seem to confirm the view that the radioresistance of irradiated cell populations may change during fractionated treatment.

Table

Comparison of experimental and theoretical results

Number of fractions N	Experimental results FOWLER (1965) D_{total} (rad)	Theoretical results based upon the single-hit, multi-target model				
		$D_0=150$ rad $m=3.5$ $S=4.50\times10^{-7}$	$D_0=300$ rad $m=1.6$ $S=1.12\times10^{-5}$	Formula (5) $c=0.6$ $S=5.44\times10^{-6}$		
		D_{total} (rad)	D_{total} (rad)	D_{total} (rad)	D_0 (rad)	m
30	6 000	6 240	6 000	6 030	281	1.66
20	5 460±50	5 140	5 360	5 500	275	1.71
15	5 070±70	4 500	5 025	5 100	270	1.75
12	4 810±70	4 100	4 800	4 780	266	1.78
10	4 560±70	3 800	4 620	4 500	262	1.81
8	4 300±80	3 500	4 410	4 280	257	1.86
6	4 010±80	3 170	4 220	3 940	249	1.93
4	3 490±120	2 830	3 920	3 500	235	2.04
2	2 730±160	2 475	3 690	2 780	201	2.33
1	2 000±250	2 265	3 555	1 970	150	2.75

The changes in the parameters are rather rapid, and they may be considerable even after four irradiations, as can be seen from the Table and Fig. 6, in which the results of calculations are compared with the experimental findings of FOWLER. Close agreement may be attained if the last model, proposed in the form of formula (5), is applied.

It would seem that the present findings should be taken into consideration in connection with fractionated irradiation of cell populations or in connection with fractionated radiotherapy.

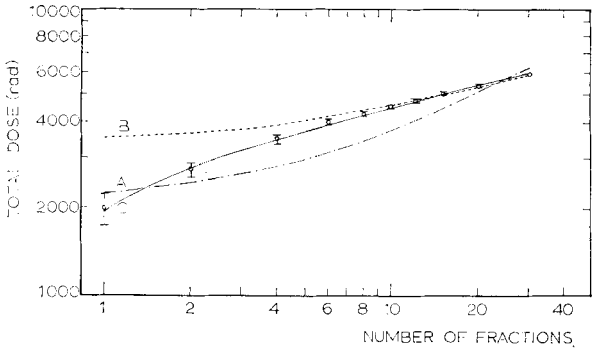

Fig. 6. A comparison of experimental results (FOWLER 1965) with theoretical calculations. Curve A is derived from formula (2) with $D_0=150$ rad and $m=3.5$. Curve B gives similar results with $D_0=300$ rad and $m=1.6$. Curve C is the best fit on application of formula (5). The values of the parameters D_0, m, and c are contained in the Table presented.

SUMMARY

The experimental results of FOWLER (1965) of the change in the total dose with an increasing number of irradiations of cells have been compared with theoretical calculations based upon the single-hit, multi-target model.

ZUSAMMENFASSUNG

Die experimentellen Untersuchungen von FOWLER (1965) über die Veränderung der Totaldosis mit zunehmender Anzahl fraktionierter Bestrahlungen von Zellen wurden mit theoretischen Berechnungen verglichen, die auf Basis der Treffertheorie mit einem 'single-hit, multi-target' Modell durchgeführt wurden. B

RÉSUMÉ

Les résultats expérimentaux de FOWLER (1965) sur la modification de la dose totale quand on augmente le nombre des irradiations des cellules ont été comparés avec les calculs théoriques basés sur le modèle du coup unique à cible multiple.

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