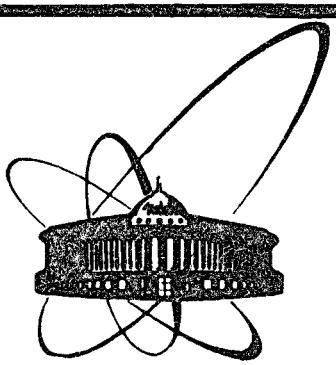

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ANALYTICAL FORMULAE IN FRACTIONATED IRRADIATION OF NORMAL TISSUE

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The choice of single number to represent the expected effect of a fractionated regime of radiotherapy is obviously not possible if one expects a full accounting of all the factors included [16]. Nevertheless the existence of dominating factors is likely to manifest itself in observable regularities and, vice versa, in spite of complex situation.

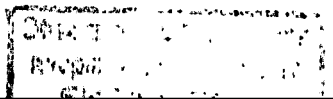
Such regularities have been found. Strandqvist [39] observed the linear dependence of the logarithm of dose producing the given effect on the logarithm of the overall time for human skin reaction and epidermoid skincancer. Similar dependences were determined by other authors, too [37,24]. The dependences were statistically evaluated by Cohen [2].

Later on a semiempirical concept of NSD (nominal standard dose) based on these observed regularities was introduced. The NSD conception was in common use for more than a decade. When published by Ellis [11,12], the NSD was being developed by many authors. The CRE (cumulative radiation effect) was proposed by Kirk et al. [25] and the TDF (time - dose - fraction) factor was established by Orton and Ellis [36]. Attempts were made to develop both CRE [38,47] and TDF [18]. Most recently some works have appeared relating these formulae to cell survival at the end of fractionated irradiation [31,32,33].

The NSD conception has been criticized from the very beginning [30]. The summary of critical comments is given recently by Withers and Peters [46]. Each approach mentioned above has some of these disadvantages. It is concluded finally that the use of the NSD formula is dangerous. Fischer [15] gave similar criticism, where he pointed out that the power functions used in the NSD or similar formulae do not correspond to the physiology of tissues.

In spite of the criticism, the NSD formula was one of the important steps toward the quantitative evaluation of the observed regularities concerning the fractionated irradiation of cell tissues. In the light of today's knowledge the use of NSD should be considered as very restricted.

Besides, the Cohen cell tissue kinetic model based on radiobiological considerations enabled us to analyse the dose-time factors using a computer program [5]. A number of analyses have been performed [3,4]. Although some authors confirmed Cohen's results [10], the question arises as to wherher the complex formulae of such a model could really describe all tissues and whether they really correspond to the nature of the proces-



ses being described. In fact these two questions should be verified experimentally and recent experimental data are precise enough to give negative answers to our questions [26]. The model describes experimental data better than NSD owing to fitting the set of parameters for each reaction to the observed values. The set of parameters may, however, be sometimes superfluous or cannot be determined unambiguously. If several reactions are evaluated, we obtain different values of the parameters for each reaction. Therefore one may conclude that the formulae do not fully correspond to the underlying mechanisms of tissue kinetics.

Nevertheless the Cohen model showed that the gross reactions can be explained in terms of cell survival and its basic assumptions are kept in this work, too.

During the last years new techniqes have been developed connected with the effect of fractionated irradiation of cell tissue and very precise results have been gained on tissue level. Many endpoints for damage to normal tissues have been established [14]. So an attempt is made in this work to establish also new conception of modeling the tissue kinetics after fractionated irradiation for practical purposes.

BASIC IDEAS OF CURRENT MODEL

It is widely accepted that the early as well as late effects of radiation on individual tissues can be traced to the killing of cells whose normal function is to proliferate [1]. The evidence exists for haemopoietic tissue and mouse intestine [20].

The most important problem at the tissue level of the biological effect of radiation is the separation of the destructive action of radiation and the restitution of damaged tissue. The destructive action itself, when expressed in terms of cell killing, is the result of radiation induced damage of some vital intracellular structures and its restitution at the cellular level. So the process of restitution can be mostly divided into two waves (Figure 1). The first wave is completed in several hours after each fraction of dose and is due to the intracellular repair. The second wave lasting usually for a longer period is attributed to the repopulation of surviving cells.

The cell inactivation is mostly attributed to DNA lessions at present time [19]. So far, however, no consistent theory of the lethal effect of radiation exists. The formulae in current use (multitarget, multitarget - single hit, exponential - quadratic) should be considered phenomenological only, in spite of their theoretical origin, as too many factors are included and the picture has not been cleared yet. These formulae are used as it is difficult to discuss radiobiological phenomena relating

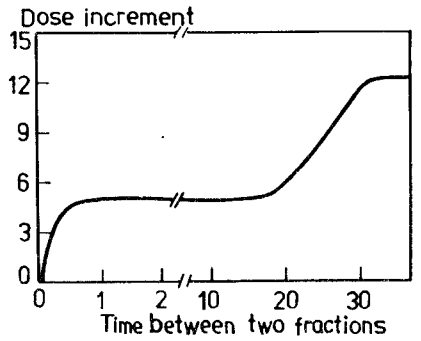


Fig. 1. The two waves of the restitution of irradiated tissue. When divided into two fractions, the total dose must be increased (dose increment) in order to produce the same effect as single exposure. The increment depends on the total time between the fractions. The ordinate: dose increment in Gy, the abscissa: time in days.

to cell killing without referring to survival curve parameters [1]. On the other hand there is evidence against the validity of exponential - quadratic equation as a model [1] and the extrapolation number of the multitarget or multitarget - single hit formula can have various meanings [1]. So any other convenient formula should be considered as valid as the formulae mentioned above at present time, particularly at the tissue level.

To choose some phenomenological formula for the description of cell killing one must consider the accuracy, mathematical properties and the possibilities of interpretation of the parameters in terms of experimentally determined dependences. In these respects the formula suggested by Huggett [23] seems to be advantageous:

$$S = e^{-\alpha d^{\gamma}}, \qquad (1)$$

where d is the dose, S is the surviving fraction and α, γ are the parameters. The formula has the most convenient properties at the shoulder region (the region of doses of fractionated irradiation) and can be generalized for very low or very high doses [26,27].

The effect of repopulation will be discussed further; it was described as simple autogeneses after some lag (T_0) in previous works [26,28]:

$$S = S_0 \cdot e^{\beta (T - T_0)} \quad \text{for} \quad T \geq T_0. \qquad (2)$$

It was shown that an exponential growth fits well the data of rat myelopathy and rat skin. Further evidence for this assumption is given in this paper.

Combining eq. (1) and eq. (2) we obtain the invariant of time and fractionation

$$DFT = DF - \beta_0 (T - T_0) \quad \text{for} \quad T > T_0,$$
$$DFT = DF \quad \text{for} \quad T \leq T_0 . \tag{3}$$

where

$$DFT = -\ln(S)/\alpha, \quad DF = N \cdot d^{\gamma}, \quad \beta_0 = \beta/\alpha .$$

The data on rat myelopathy and rat skin were analysed by means of these simple formulae. The results are summarized in Table 1. Similar values of T_0 and γ for reactions 2-5 (various degrees of skin desquamation) enabled us to develope reaction independent formulation /26/.

Table 1

The results of rat skin and rat myelopathy data analyses. Various levels of skin reaction correspond to threshold of erythema (1), dry desquamation (2) and three degrees of moist desquamation (3,4,5). Myelopathy was determined after 1 year in 50% of animals. Model parameters are described in text. s^2 has Chi-square distribution with DF degrees of freedom

QUANTITY	RAT MYELOPATHY	RAT SKIN LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 5
γ	1.550	1.506	1.307	1.359	1.344	1.295
β_0	0.42	2.47	2.53	3.29	3.36	3.16
T_0	22.5	15.0	19.1	19.5	20.1	21.2
DFT	163.4	56.1	63.7	83.4	95.4	105.5
s^2	8.66	24.0	23.4	25.2	9.0	12.8
DF	5	10	11	11	11	10

The dimensions are: β_0 = Gy·day^{-1}, T_0 = day, DFT = Gy.

LOW DOSE REGION OF SURVIVAL CURVE

The doses per fraction in the analysed tissues were rather high and the simple Huggett formula was a good approximation. In order to allow for the bending of Strandquist's graph while the number of fractions becomes larger and the dose per fraction smaller /10,13,44/ two possible improvements of the survival curve can be made:

1) Introduction of further - low dose region parameter /27/. The formulae for survival then read:

$$S = e^{-\alpha_0 \cdot d} \quad \text{for} \quad d \leq \frac{d_0}{\gamma - 1},$$
$$S = e^{-\alpha (d + d_0)^{\gamma}} \quad \text{for} \quad d \geq \frac{d_0}{\gamma - 1}, \tag{4}$$

where

$$\alpha_0 = \alpha \frac{d_0^{\gamma - 1}}{\gamma - 1} \gamma^{\gamma},$$

and so

$$DF = N \cdot (d + d_0)^{\gamma} \quad \text{for} \quad d \geq \frac{d_0}{\gamma - 1},$$
$$DF = \left(\frac{d_0}{\gamma - 1}\right)^{\gamma - 1} \gamma^{\gamma} \cdot N \cdot d \quad \text{for} \quad d \leq \frac{d_0}{\gamma - 1}. \tag{5}$$

The additional parameter d_0 describes the initial exponential part of the survival curve. The other parameters α, γ were introduced earlier.

This combined formula is in direct relation to the Dutreix graphs /10,27/ and is more convenient than the other formulae in current use. The correction can be seen as the expression of the presence of inhomogeneous population of cells having different sensitivities or single hit mechanism of killing.

The formula (further "generalized Huggett's formula") is represented by a straight line in Dutreix's graph and the parameters d_0 and γ can be calculated directly from it having determined the slope κ_D and intercept Δ_D on horizontal axis:

$$\gamma = \frac{\ln 2}{\ln(1/(1 + \kappa_D))}, \quad d_0 = \frac{\kappa_D}{1 - \kappa_D} \cdot \Delta_D . \tag{6}$$

The values of d_0 and γ have been determined for various experiments and are shown in Table 2. The comparison of the new for-

Table 2

The slopes $\varkappa_D$ and intercepts Δ_D of the graphs of Dutreix's type and corresponding parameters of the generalized Huggett's formula calculated for various tissues. There is direct relation between the slope and corresponding exponent γ of survival curve; the second survival curve parameter d_0 can be calculated from the slope and the intercept-eqs. 6

TISSUE /AUTHOR/	SLOPE $\varkappa_D$	INTERCEPT Δ_D	γ	d_o
WHT/Ht mice skin /DOUGLAS and FOWLER 1976/	0.365 ±0.017	2.61 ±0.35	1.816 ±0.06	1.5 ±0.2
C57 BL/6B x C3B/HeB F1 mice /DOUGLAS et coll. 79/				
7 day scorign:	0.323	1.90	1.677	0.91
22 day scoring:	0.328	1.88	1.692	0.92
Human skin /DUTREIX et coll. 1973/	0.35 ÷ ÷ 0.25	2.0 ÷ ÷ 3.2	1.45 ÷ ÷ 1.75	0.6 ÷ ÷ 1.7
Mouse intestine /WAMBERSIE et coll. 1974/	0.595	3.48	3.06	5.11
Mouse jejunum /WITHERS 1974/				
3 hour intervals:	0.314	1.31	1.65	0.6
1 hour intervals:	0.240	1.27	1.45	0.4
Mouse colon /WITHERS and MASON 1974/	0.342	2.31	1.736	1.20
Mouse lung /FIELD and HORNSEY 1975/	0.415	2.0	2.00	1.4

Δ_D and d_0 in Gy.

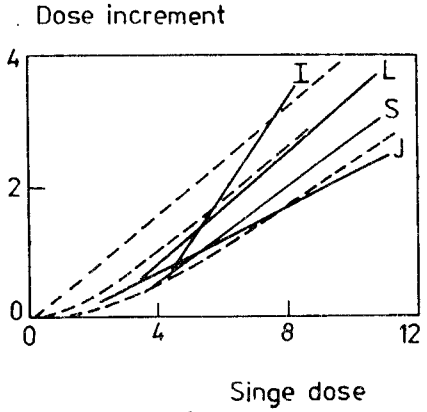


Fig. 2. The Dutreix graphs for mouse intestine (I), mouse lung (L), skin (S) and mouse jejunum irradiated with 1 hour intervals (J). The best fits to the generalized Huggett formula are shown - full lines. The series of dashed lines is produced by the exponential - quadratic equation. The latter is incompatible with experimental data following full lines. The ordinate: dose increment in Gy, the abscissa: single dose in Gy.

mula with exponential quadratic is performed in Figure 2. The exponential - quadratic formula is not able to give all the measured curves.

2) The introduction of the parameter describing the accumulation of irreparable sublethal injury. The effect is well known in yeast cells and was shown to take place in mammalian cells, too [34].

LAG IN REPOPULATION PROCESS

The repopulation was studied by many authors and the most common picture showed initial lag or even opposite dependence (decreasing recovery for increasing time) after the first dose fractions.

Denekamp et al. [7] didn't observe any repopulation for seven days (there was even some small fall of total dose for given effect) and only four Gy could be added at fourteen days after the first dose. The effect was attributed to residual synchrony.

Douglas and Fowler [9] didn't observe repopulation until sixteen days during fractionated irradiation of WHT/Ht mice. Similarly Denekamp [8] didn't observe repopulation until approximately two weeks for WHT/Ht mice and ten days for SAS/TO mice.

Moulder and Fischer [35] estimated the beginning of repopulation during fractionated irradiation of rat skin to seventeen days. The model analysis led to similar conclusions [26].

Dutreix et al. [10] having determined the shape of the survival curve for human early skin reaction and comparing their results with Strandquist's graphs concluded that the increase in dose up to fifteen fractions is due mainly to fractionation (not to repopulation).

Withers and Elkind [43] observed the beginning of a very fast repopulation of jejunum stem cells at 64 hours. The delay was attributed to the migration of cells, survivors and non survivors alike, out of the proliferative compartment. This reduces the number of surviving cells in the crypt, causing a fall in survival ratios at fractionation intervals of about 2-2.5 days.

White and Hornsey [40] observed delay in the second wave of restitution for rat spinal cord lasting for about three weeks (see also the analysis by Kozubek and Černý [28]).

Withers et al. [45] didn't find repopulation in testis stem cells for two weeks. To explain the dependence of total dose necessary for the given effect, he suggested biphasic survival curve for given system.

It seems likely that the lag in repopulation is connected with cell turnover rate in the tissue [46]. Normal turnover rate should be kept during this time, together with corresponding cell loss factor. So the repopulation coefficient β_0 represents the increase of the turnover rate.

During the latent period the changes of the sensitivity of cell population may take place. The changes are cyclic during the first hours [7,22], but no cyclic changes were found during the prolonged fractionated irradiation. Cyclic changes can be observed after great doses that lead to partial synchronization of the population. The description of such changes is rather complicated [29]. The magnitude of cyclic changes decreases with decreasing doses in fractionated irradiation, and so, one should rather suppose continual change of survival curve during the schedule.

REPOPULATION AS SIMPLE AUTOGENESIS

The parametrization of the survival curve was chosen arbitrarily; the formula (4) is only appropriate one. It is not a model, but a convenient and general enough description. One of the possible forms of survival curves (independently of parametrization) gives consistent behaviour of calculated surviving fractions in relation to reaction level and overall time. The clearance of the picture is shown in Figure 3. The initial latent period does not depend on reaction level (or slightly only) and the dependence of DF factor on overall time T is linear with very good correlation. The rate of repopulation (the repopulation parameter β_0) depends slightly on reaction level. This dependence can be monitored by the final survival (this assumption is not fully consistent, but provides sufficient accuracy if the repopulation parameters differ slightly only):

$$\beta_0 = a \cdot DFT + b, \qquad (7)$$

Table 3

The analyses of mouse colonic mucosa and rat skin data in terms of eqs. 9. In the case of rat skin single exposures were excluded (doses are beyond the region of eq. 1 validity)

QUANTITY	MOUSE COLON	RAT SKIN
Survival curve parameters	$\gamma = 1.736 \pm 0.005$ $d_0 = 1.20 \pm 0.03$	$\gamma = 1.33 \pm 0.02$ without d_0
Repopulation parameters	$T_0 = 39.8 \pm 0.3$ $a = 0.00456 \pm 0.00005$ $b = 0.0875 \pm 0.004$	$T_0 = 19.8 \pm 0.5$ $a = 0.0141 \pm 0.0035$ $b = 1.84 \pm 0.37$

DFT factors	Cells per circumf.	DFT	Skin reaction	
	100	103.96 ± 0.37	Dry desquamation	65.2 ±5.9
	50	116.18 ± 0.84	Slight moist desquamation	80.8 ±6.5
	20	131.76 ± 0.47	Modest moist desquamation	92.7 ±7.2
	10	142.94 ± 0.45	Severe moist desquamation	109.8 ±9.3
	5	155.41 ± 0.82		
Sums of squares		51.5		74.5
Degrees of freedom		57		51

The units are: Gy, hour for mouse colon,
Gy, day for rat skin.

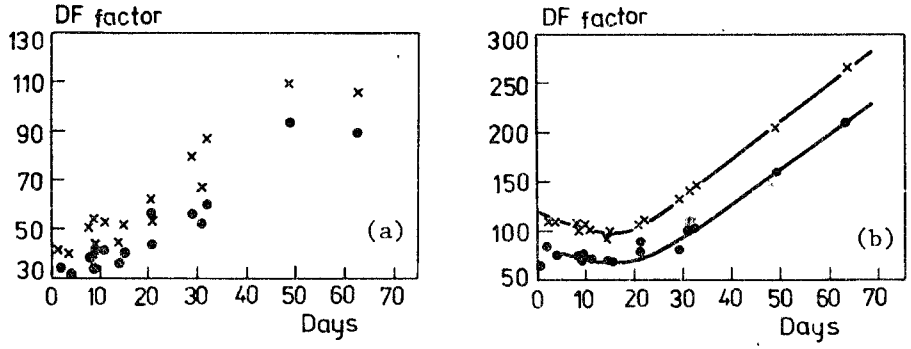


Fig.3. The dependence of the DF factor on the overall time for dry desquamation (circles) and moderate moist desquamation (crosses) of rat skin. The three pictures show the experimental data for various shapes of the survival curve represented by the parameter γ. Fairly dispersed points for γ=1.0 (a), the points settled on the line quite consistently for γ = =1.4 (b), and the points dispersed again for γ =2.0 (c). This shows that an appropriate average shape of the survival curve does exist; the repopulation exhibits exponential pattern after some initial time. The ordinate: DF factor in Gy^{γ}, the abscissa: overall treatment time in days.

where $DFT = -\ln(S)/\alpha$ and a, b are the free parameters. So, we have four parameters γ, d_0, β_0, T_0 for all reactions. From equations 3, 5 and 7 we can easily express the dose:

$$D = (((DFT' + (a \cdot DFT + b)(T - T_0))/N)^{1/\gamma} - d_0) \cdot N \qquad (8a)$$

for $d \geq d_0/(\gamma - 1)$ and for $T \geq T_0$,

$$D = ((DFT/N)^{1/\gamma} - d_0) \cdot N \qquad (8b)$$

for $d \geq d_0/(\gamma - 1)$ and for $T \leq T_0$,

$$D = (DFT + (a \cdot DFT + b)(T - T_0))/((\frac{d_0}{\gamma - 1})^{\gamma - 1} \cdot \gamma^{\gamma}) \qquad (8c)$$

for $d \leq d_0/(\gamma - 1)$ and for $T \geq T_0$

$$D = DFT / ((\frac{d_0}{\gamma - 1})^{\gamma - 1} \cdot \gamma^{\gamma}) . \qquad (8d)$$

For the doses great enough (above 3 Gy) the parameter d_0 can be omitted in the analysis; if the analysis were performed with this parameter, it cannot be omitted in equations for calculations thereafter. For d_0=0 the fractionation dependence is represented by a straight line in the Strandquist graph and by a straight line in Dutreix's graph, too [27].

ANALYSES OF LARGE DATA SETS (MOUSE COLON, RAT SKIN)

These extensive data sets provide sufficient information for full analyses. The data on mouse colon were obtained by clones counting technique [44] for variety of fractionation schedules. The results were reanalysed. Doses gained by quadratic interpolation were used. The simultaneous analyses have been performed, optimum parameters of eqs.8 have been determined together with their standard deviations. They are shown in Table 3 as well as the sum of squares which corresponds to the error of dose ±0.5 Gy and is on the level of experimental error. The good agreement can be seen in Fig. 4 where the DF factors are drawn in time dependence together with theoretical curves. It is clear that no simple formula like NSD can fit the data. This conclusion was reached by Withers and Mason [44], too.

The DFT factors are in direct relation to cell survival DFT= $= -\ln(S)/\alpha$. Since we known the numbers of cells per circumference for given reactions, we can calculate the values of α and the initial number of cells N_0; $S = N/N_0$:

$$DFT = a_0 \cdot \ln N + b_0 , \qquad (9)$$

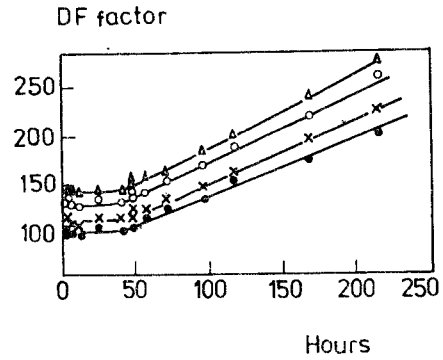


Fig. 4. The dependence of the DF factor on the overall time for colonic mucosa. Experimental points are compared with the theoretical curves. The endpoints: 10 cells per circumference (Δ), 20 cells per circumference (o), 50 cells per cirs. (×), and 100 cells per circumference (•). The standard errors are less than the symbols. The ordinate: DF factor in Gy^{γ}, the abscissa: overall treatment time in hours.

where

$$a_0 = -1/\alpha, \qquad b_0 = 1/\alpha \cdot \ln N_0,$$

The correlation coefficient of linear regressing $r = 0.9999$, which means nearly exact correlation; $a_0 = -17.06$ and $\alpha = 0.0586\ Gy^{-\gamma}$ $b_0 = 182.7$ and $N_0 = 4.4 \times 10^4\ (\pm 1.10^4)$ cells. From the values of β_0 the doubling times can be calculated directly: they are in the range 16.3-21.1 hours and are at lower limit of Withers' values. It is however, quite understandable as Withers calculated these values without regard to latent period - so he determined initial doubling times higher. The value of N_0 is in good agreement with the estimation of Withers and Elkind [48] and Withers et al. [42] of about 2.10^4 cells per circumference for mouse jejunum. According to eq. (4) the initial slope of survival curve can be calculated: $D_0 = 4.57$ Gy; which is in very good agreement with lower approximation of about 4 Gy given by Withers [41].

Rat skin data from experiments by Moulder and Fischer [35] have been already analysed [26]. The parameters of the original analysis (only doses in Gy) are shown in Table 1. Simple original Huggett's formula was used as doses were fairly great. In order to compare repopulation characteristics the value of parameter α should be known. Assuming (very roughly) similar sensitivity as for mice skin we can determine from the work by Douglas and Fowler [9] $\alpha = 0.15$. Average doubling times are then 33--44 hours. These values could be slightly higher than actual ones as repopulation delay after each fraction was not included.

DISCUSSION

There is an essential need for mathematical expressions concerned the biological effect of radiation on the tissue level, owing to the possibilities of utilizing such expressions in radiation therapy of human beings. The complexity of real situation is such that every formula should be, however, considered as a limited approximation. The principles to be kept while constructing some model approaches are not unambiguous under these circumstances, but several remarks can be done.

The formulae should describe experimental data as accurately as possible, although it is questionable, if the chi square test could be used. Great discrepancies should make us discard or modify the current models or methods of phenomenological description.

The models based on tissue kinetics and offering the possibility to be checked by independent way should be preferred to phenomenological formulae.

The formulae (model or descriptive) should be as simple as possible. Every additional parameter should be weighted carefully and have some interpretation. Many parameters make the model descriptive only without understanding the underlying mechanisms. Such a model fitted to the observation - with parameters derived specifically for the system analysed - provides estimates for endpoints of the tissue concerned. The accuracy of predictions, especially, if some interpolation or even extrapolation is made, however, strongly depends on the quality of the model - how successfully the underlying mechanisms were reflected by the formulae. The comparison of Ellis', Cohen's and present approaches is given in Fig. 5.

The formulae used in this paper should not be considered universal. The region of their validity can be checked on the basis of experiment only as well as the validity of basic assumptions *.

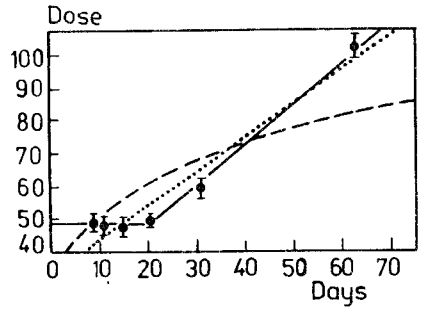


Fig. 5. The comparison of various theoretical approaches. The full line - present model, the dotted line - Cohen's model, the dashed line - NSD conception. The number of parameters is 4 for the new model, 5 for the Cohen's model and 3 for the NSD formula. All parameters were optimized (see Kozubek [26]). Slight moist desquamation of rat skin was used as endpoint for 14 different fractionation schedules. The points are shown with 95% confidence intervals (it means that statistically 1 point of 20 may be out of theoretical curve). The ordinate: dose in Gy, the abscissa: treatment time in days.

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*Further analyses are given in the full text.

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Козубек С. Аналитические формулы для фракционированного облучения нормальной ткани E19-82-579

Предлагается новый подход для описания кинетики лучевой реакции ткани после фракционированного облучения. Предполагается, что восстановительные процессы на уровне ткани обусловливаются путем простого автогенеза после некоторого латентного периода. Показано, что эти предположения находятся в количественном согласии с большим набором экспериментальных данных, касающихся реакции кожи и кишечника на облучение. Показано, что эти данные резко противоречат как НСД концепции, так и известной модели Когена.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

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Kozubek S. Analytical Formulae in Fractionated Irradiation of Normal Tissue E19-82-579

The new conception of the modeling of the cell tissue kinetics after fractionated irradiation is proposed. The formulae given earlier are compared with experimental data on various normal tissues and further adjustments are considered. The tissues are shown to exhibit several general patterns of behaviour. The repopulation, if it takes place, seems to start after some time, independently of fractionation in first approximation and can be treated as simple autogenesis. The results are compared with the commonly used NSD conception and the well-known Cohen cell tissue kinetic model.

The investigation has been performed at the Laboratory of Nuclear Problem, JINR.

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