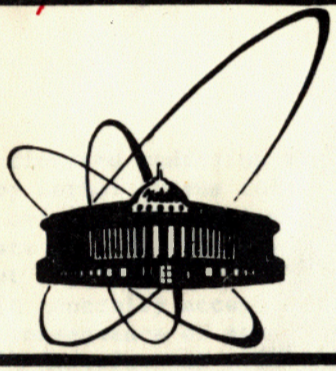

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LATE EFFECTS OF FRACTIONATED IRRADIATION OF NORMAL TISSUE

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Fractionated radiation therapy of malignant diseases is limited by normal tissue tolerance. Both early and late effects can be critical. Early damages can be controlled easier than the late ones in clinical practice. So the late effects are of great importance.

It is generally accepted that macroscopic tissue reaction is the consequence of stem cell depletition to some critical level/1/. Experimental evidence exists for haemopoietic and intestinal tissues. Theoretical analyses, however, showed that the macroscopic reaction can be interpreted in terms of cell survival in many other cases /2,3/. The nature of both early and late effects of radiation is probably the same in many cases/4/.

A lot of experimental animal data on early effects are available. The data on late effects are much less extensive. Experimental animal data can be utilized for the derivation of quantitative laws of cell tissue kinetics during and after fractionated irradiation. The corresponding formulae, if valid for several mammalian systems, are likely to be valid for the tissues of man, too.

The late effects of fractionated irradiation will be evaluated in terms of the formulae given earlier/2,3/. Human tissue late reactions will be interpreted in terms of tissue specific formulae which differ both from Ellis' NSD and Wara's ED conceptions. An attempt is made to explain the relation between early and late effects and to discuss corresponding RBE for fast neutrons.

MODEL EQUATIONS

Assuming the existence of an average survival curve during the course of fractionated radiation treatment, we can obtain dose - fractionation (DF) invariants for various schedules:

$$DF = N.d^{\gamma}, \qquad (1)$$

where N is the number of fractions, d is the dose per fraction, γ is the survival curve parameter. For low dose region a more general formula can be written/5/:

$$DF = \begin{cases} N.(d+d_0)^{\gamma} & \text{for } d > \frac{d_0}{\gamma-1} \quad (2a) \\ N.d.\gamma^{\gamma}\left(\frac{d_0}{\gamma-1}\right)^{\gamma-1} & \text{for } d \leq \frac{d_0}{\gamma-1}, \quad (2b) \end{cases}$$

where d_0 is further-low dose region parameter. DF factor should be constant for different schedules providing the repopulation can be neglected. The total dose can be calculated from given parameters and fraction number.

Two types of time-dependent recovery have been established recently: repopulation by simple autogenesis after some latent period /6/, and "slow repair" /8/. The formulae including repopulation with doubling time $T_0 = \ln 2/\beta$ after the latent period T_0 read:

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

$$DFT = DF \quad \text{for } T \leq T_0. \quad (3b)$$

The DFT factor is the invariant of dose-time-fractionation for given tissue and given reaction.

"Slow repair" has been fitted well by power function:

$$DFT = DF.\, T^{-\kappa}, \quad (4)$$

There are several assumptions inherent in the formulae above. The discussion of these assumptions is given elsewhere /6,7/. The hypothesis concerning repopulation agrees very well both with experimental animal data on fractionated irradiation of normal tissue and independent experiments on mitotic activity measurements in irradiated tissue. The value of T_0 is probably the time of stem cell maturation (in the case of skin T_0 = = 20 days).

SPINAL CORD AND BRAIN

The analysis of experimental data by Hornsey and White /9/ and White and Hornsey /10,11/ in terms of the cell kinetic model has been already performed /2/. It was shown that the macroscopic response can be interpreted in terms of cell survival. The survival curve was described by Huggett's formula which gives linear Strandquist graphs. The slope of Strandquist's graph in the region 4-60 fractions was determined to $\kappa = 0.355$, which corresponds to the survival curve parameter $\gamma = 1.55$. The repopulation parameters were $T_0 = 22.5$ days and $\beta_0 = 0.42$ (the rate of repopulation). DFT for 50% probability of rat myelopathy in 1 year corresponded to DFT = 163.4.

The same interpretation could be applied to the data of Van der Kogel and Barendsen /12/. The parameters somewhat differ from those given above. The slope of Strandquist's graph is $\kappa = 0.43$ in the region 1-30 fractions for both lumbar and cervical spinal cord. The repopulation started after ~60 days and was somewhat faster than in the experiments of White and Hornsey.

White and Hornsey /11/ estimated an average slope of Strandquist's graph in the region 1-30 fractions to $\kappa = 0.40$, which gives $\gamma = 1.67$ for the survival curve parameter. This value is in good agreement with clinical data (Fig.1). Two modes of repopulation have been considered in the region of fractionated radiotherapy. The first mode includes repopulation in the region >20 days (15 fractions) with the speed $\beta_0 = 0.6$ ($\beta_0 = 0.4$ corresponds to $\gamma = 1.55$, $\beta_0 = 0.6$ corresponds to $\gamma = 1.67$) in accordance with the data by White and Hornsey /9-11/. The second mode does not include repopulation (dotted lines in Fig.1). Clinical data /13/ support the first hypothesis where isoeffect is given by the equation:

$$DFT = N.(D/N)^{1.67 - 0.6\,(T-20)} \quad \text{for } T > 20 \text{ days}, \quad (5a)$$

$$DFT = N.(D/N)^{1.67} \quad \text{for } T \leq 20 \text{ days}. \quad (5b)$$

Tolerance doses for the thoracic cord correspond to DFT = 65-70.

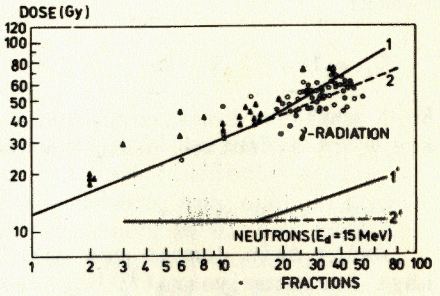

Fig.1. Radiation myelopathy in man. ▲ - patients with myelopathy, o - patients without myelopathy (one centre only). 1 - isoeffect line (Eq.5) with repopulation, 2 - isoeffect line without repopulation. 1',2' - isoeffect lines for neutrons with and without repopulation. The treatment time is proportional to the number of fractions.

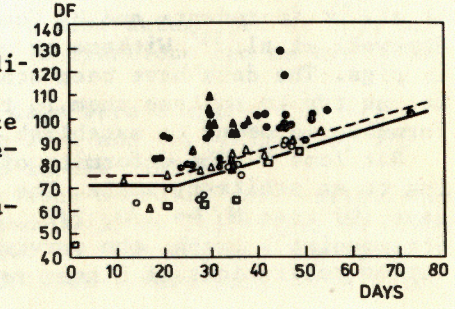

Fig.2. Human brain necrosis. The DF(T) dependence is shown. ● - brain necrosis (whole brain irradiated), ▲ - brain necrosis (large volumes irradiated), Δ - tolerance doses for large volumes, o - tolerance doses for whole brain irradiation. Data taken from literature. Isoeffect lines (Eq.5) are shown for DFT = 70 (whole brain irradiation) and DFT = 75 (large volumes).

Similar regularities have been noticed in the case of brain, damage, too. The slope of Strandquist's graph has been determined to $\kappa = 0.37 \pm 0.07$ for X-rays induced death within one year following irradiation of the rat brain[14]. Fig.2 shows some cases of brain damage together with regimes of "save treatment"[15,16]. The lines were calculated by means of Eq.5; the values of DFT for the treatment with low risk are DFT = 70 for the whole brain and DFT = 75 for large volumes.

The average value of the slope $\kappa = 0.40$ for N = 2-30 fractions cannot be extrapolated to large fraction numbers. The slope in the region 4-60 fractions was determined to $\kappa = 0.355$, which suggests that Strandquist's graph with the number of fractions as independent variable is not given by a straight line. Such a behaviour needs further-low dose region parameter d_0[5]. It is difficult to establish it from the available experimental material. This correction influences the graphs with constant time between fractions in the opposite way than repopulation so as it may look more like a straight line[5].

The treatment of the rat spinal cord with fast neutrons has shown no recovery between fractions for N = 2. In spite of it the long term recovery took place[11]. The parameters for $N \geq 2$ have been estimated: $\gamma = 1$, $T_0 = 20$ days, $\beta_0 = 0.1$, DFT = 18.5 for 50% myelopathy during one year in rat. The tolerance of human cord (if the animal data can be extrapolated to man) should correspond to DFT = 11 and equation for the total dose reads:

$$D_0 = 11 + 0.1\,(T - 20) \qquad \text{for } T > 20 \text{ days.} \qquad (6)$$

Even smaller doses correspond to brain damage where the neutrons are very effective owing to the high lipid contents.

LATE SKIN DAMAGE

Early skin damage was considered to be an index for late damage for many years[17,18]. Recent experiments have shown that the two reactions may be quite different[19] Late effects of fractionated irradiation have been investigated by Field[20], Masuda et al.[21] in rodents and by Fowler et al.[22], Berry et al.[23], Hopewell et al[24], Withers et al[19], and Turesson and Notter[25] in pigs. The data have been scanty and contradictory so far. Let us try to analyse them in terms of our new mathematical formulae in order to establish some parameters.

Rat foot[20]. The deformity of the foot was classified according to an arbitrary scale. The number of fractions (N) and days (T) was: N/T = 1/0, 2/2, 5/5. The slope of corresponding Strandquist's graph, the survival curve parameter γ and correlation coefficient of linear regression is given in the Table.

Table

Late skin reactions in pig and rodent skin. The slope of Strandquist's graph and survival curve parameter γ are given. The correlation coefficient was obtained from linear regression

ANIMAL /AUTHORS/	α	γ	r
Pig /Berry et al., 1974/	0.389	1.636	0.997
Pig /Fowler et al., 1963/	0.410	1.696	0.999
Pig /Hopewell et al., 1979/	0.393	1.649	0.993
Pig /Withers et al., 1978/	0.375	1.600	-
Pig /Turesson, Notter, 1979/	0.419	1.721	-
Average values	0.397	1.660	
Rat /Field et al., 1969/	0.359	1.56	0.996
Mouse /Masuda et al., 1981/	0.320	1.47	0.990
Mouse /Suit, Howard, 1967/	0.454	1.83	-
Average values /all data/	0.390	1.645	

Mouse spin contraction[21] was measured as late effect. The phenomenon of "slow repair" has been noticed similarly as in the case of mouse lung but the time dependence was much faster. The repair was completed during one day. Such an effect cannot be excluded in the case of pig or human skin and could have great therapeutical importance. The slope κ varied with the time between fractions and approached the value $\kappa = 0.32$ for one day interval.

Late reactions in mouse skin were also determined by Suit and Howard[26]. Only single exposure and 10 fractions can be evaluated (Table).

Pig skin reactions[22] in 60-90 days were compared for N/T = = 1/0, 5/5, 9/28, and 21/28 in pig 2166 and for N/T = 1/0, 5/5 in pig 2154. The results are shown in the Table.

The doses which just fail to produce necrosis were established in pigs[23] for N/T = 1/0, 6/18, and 30/39 to 24, 49, and 90 Grays. If the repopulation can be neglected in that region, the value of γ can be calculated to $\gamma = 1.636$ with a very good correlation.

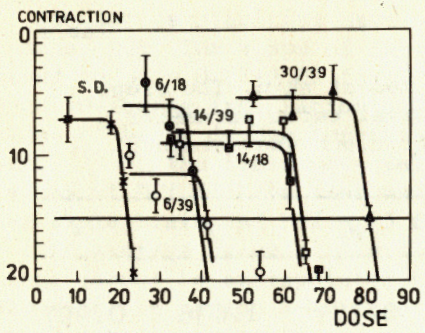

Fig.3. Pig skin contraction (%). The initial value of spin contraction does not depend on the dose (Gy). Quite consistent doses can be determined for 15% contraction. The number of fractions and overall time are shown as N/T.

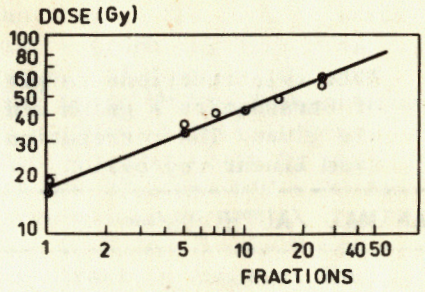

Fig.4. Human skin tolerance. The data from great therapeutical centres have been taken and plotted in Strandquist's graph. The slope of isoeffect line is $\kappa = 0.40$. The dependence includes fractionation only. DF = 114 and $\gamma = 1.67$ (Eq.1).

The doses which correspond to 12% skin contraction in pigs /24/ were determined for N/T = 1/0, 6/18, 6/39, 14/18, 14/39, and 30/39. The schedule 6/39 was found to be very effective and so no dependence on N or T could be established. The unexpected result is, however, clearly the consequence of two component behaviour of the dose - response curve. There is some schedule dependent but dose-independent damage for low doses (Fig.3) and the reaction increases with dose only above some threshold. The dose dependent damage should be established from the region above the threshold. For example, the contraction to 85% gives quite consistent doses:

N/T	1/0	6/18	6/39	14/18	14/39	30/39
D(Gy)	22.0	39.5	41.5	62.0	64.0	80.0

The slope of Strandquist's graph (neglecting repopulation) is given in the Table.

The slope can be determined also for late effects in pig skin scored according to an arbitrary scale in /19/.

SCORE	5.5	6	7
D_1 (Gy)	50	56.5	59.0
D_2 (Gy)	74	75.5	80.5

D_1 corresponds to N/T = 13/45, D_2 to N/T = 32/45. The average value of γ is 1.60.

Medium term skin reaction after single exposure and seven or eight fractions have been studied in pigs /25/. The parameters are given in the Table.

Rodent skin late damage may be the consequence of early effects /27/ and so the values of the parameters may differ from that of pigs. In spite of this fact the average values are similar and quite close to that of spinal cord. We can take the slope $\kappa = 0.40$ and consequently $\gamma = 1.67$.

Figure 4 shows the comparison of isoeffect line taken from animals and tolerance skin doses from great therapeutical centers (according to Berry et al. /23/) in Strandquist's graphs. It can be noticed that the line is markedly steeper than that of NSD and that there is only fractionation dependence in it. DFT factor is DFT = 114. Similarly stronger dependence on the number of fractions was found by Bates et al. /28/.

On the other hand there exists some time-related recovery. It was found that the tolerance of heavily irradiated human skin approaches normal values after many years (Hunter and Stewart /29/). The second course of radiotherapy with fast neutrons after late recurrences could be delivered after 10 months with mostly moderate late reactions /30/. Some studies have been done with animals /31/. The "tolerance" of rat tails heavily irradiated approached normal after 6 months. Residual damage was 10-15%. The speed of restitution in the case of human skin as well as the residual damage are unknown. It seems, however, reasonable to assume linear function similar to Eq.1.

The neutron DF is probably again fractionation independent and equal to DF = D = 19.5 Gy for E_p = 66 MeV + Be /30/, DF = D = = 16 Gy for E_d = 16 MeV + Be /32/.

LUNG DAMAGE

The response of mouse lung to fractionated irradiation has been extensively investigated /33-36/. The lung tissue repairs radiation damage by means of Elking type repair; in addition to it a much slower repair process has been discovered and called "slow repair". The $\ell n(D)$ vs $\ell n(N)$ graph has been shown to be non-linear with the slope of about $\kappa = 0.39$ for 1-8 fractions and $\kappa = 0.25$ for 8-30 fractions. The slope of Dutreix's graph κ_D = = 0.415 with the intercept $\Delta_D = 2.0$ Gy /33/. This behaviour can be explained by the accumulation of irreparable sublethal damage, by the presence of sensitive cell compartment or by single-hit killing.

Correct mathematical description of the lung tissue reaction to fractionated irradiation needs a good model of the effect of

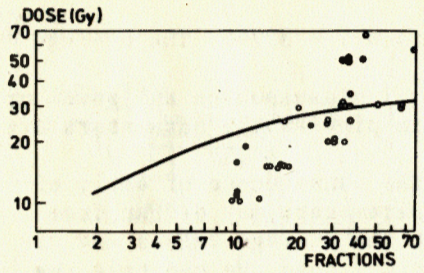

Fig.5. Radiation pneumonitis in man. • - patients with radiation pneumonitis after whole lung irradiation, o - patients without pneumonitis. Isoeffect line calculated according to Eq.7, DFT = 96.

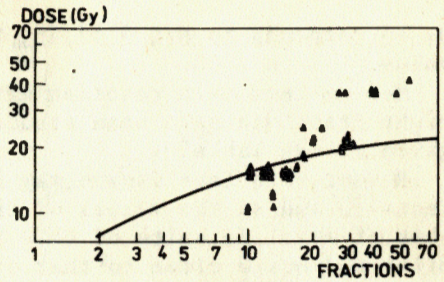

Fig.6. Radiation pneumonitis in man after dactinomycin. Data taken from Wara et al./35/. Isoeffect line calculated according to Eq.7.

radiation on cells in vitro. Such a model does not exist at present time. We can derive some descriptive equations.

The parameters of the generalized Huggett's formula are/6/ $\gamma = 2.0$, $d_0 = 1.4$ Gy. The correction for slow repair can be done by power function similar to that of Ellis' formula. Final equations then read:

$$DFT = N.(\bar{d} + d_0)^2 \cdot T^{-0.14} \qquad \text{for } d > 1.4 \text{ Gy}, \qquad (7a)$$

$$DFT = 5.6 \,.\, D \,.\, T^{-0.14} \qquad \text{for } d \leq 1.4 \text{ Gy}. \qquad (7b)$$

The value of DFT is connected with cell survival and should be constant for given reaction. Figures 5 and 6 show this dependence fitted to the data of Wara et al./36/. The value of DFT for isoeffect line separating the cases with radiation pneumonitis corresponds to DFT = 96. The initial slope of the graph consists of two components including both fractionation and "slow repair". The final slope is determined by "slow repair" only. The average slope in the region 20-40 fractions is much lower than that of Wara et al./36/ determined from clinical data using the multiprobit method. The analysis combined the data with and without dactinomycin and it can be easily seen that the value of the slope $\kappa' = 0.41$ can be an artefact. On the other hand, the value of the slope in the region 20-30 fractions can be greater than that of our graph owing to the fact that formulae 7 are derived from the assumption of the existence of initial exponential region on the survival curve. If the accumulation of sublethal damage takes place, the slope will be somewhat greater.

There is neither Elkind's repair nor "slow repair" after fractionated irradiation with fast neutrons/34/. The dose corresponding to DFT = 96 is $D_n = 6.7$ Gy.

EARLY AND LATE EFFECTS OF RADIATION AND RBE

A great effort has been expensed to decide whether late reactions are determined by acute ones or not. Experimentation with animals seemed to show that there existed a relation between early and late effects in the case of rodent skin even for various fractionated schedules, for neutrons and X rays/32/. The discrepancies, however, appeared for a great number of fractions or great overall treatment time. Recent work of Withers et al./19/ showed that late effects do not correspond to early ones in the case of pig skin. The value of RBE was shown to be greater for late effects than for early ones.

How we can explain these contradictory findings? We shall try to discuss the question. The consideration will be restricted to the region of values of N where the low dose region parameter d_0 is not important (for example, up to 15-20 fractions). So Eqs.1 and 3 will be used.

The tissue, if irradiated by single dose, responds by some early and some late reaction. There is unambiguous dependence between the two reaction in arbitrary scales. The dose producing given acute reaction (D) changes under some other modelity to D_M^A for late reaction to D_M^L. The ratio of the two doses will be denoted LAR (late - acute ratio):

$$LAR = D_M^L / D_M^A. \qquad (8)$$

What values of LAR could be expected for fractionated irradiation if $T < T_0$? Let the survival curves be described by Huggett's equation. The acute (late) reaction is produced by reducing the cell population to $S_A (S_L)$ by the dose D

$$D^{\gamma_A} = -\ln (S_A)/a_A = K_A/a_A, \qquad (9a)$$

$$D^{\gamma_L} = -\ln (S_L)/a_L = K_L/a_L \qquad (9b)$$

and so

$$(K_A/a_A)^{1/\gamma_A} = (K_L/a_L)^{1/\gamma_L}. \qquad (10)$$

For fractionated irradiation we can write:

$$N.(D_M^A/N)^{\gamma_A} = K_A/a_A, \qquad (11a)$$

$$N.(D_M^L/N)^{\gamma_L} = K_L/a_L, \qquad (11b)$$

where the indexes refer to acute and late damage. Then

$$LAR = N^{(\gamma_L - \gamma_A)/(\gamma_L \gamma_A)}. \qquad (12)$$

Owing to the fact that the values of γ differ but slightly for various tissues, LAR = 1 for a small number of fractions, If, e.g., γ_L = 1.6 and γ_A = 1.5 and N = 5 fractions then LAR = 1.07; if $\gamma_L = \gamma_A$ LAR = 1 for all regimes, where $T < T_0$.

If repopulation is considered then LAR < 1 for $\gamma_L = \gamma_A$ as

$$LAR = \left[1 + \frac{\beta}{K_A}(T - T_0)\right]^{-1/\gamma_x}, \qquad \text{where } \gamma_x = \gamma_L = \gamma_A. \tag{13}$$

In the case of neutrons the value of LAR = 1 for rat skin and single exposure [20]. It can be, however, expected that LAR < 1 for $T > T_0$:

$$LAR = \left[1 + \frac{\beta}{K_A}(T - T_0)\right]^{-1/\gamma_n}, \qquad \text{where } \gamma_n = \gamma_L = \gamma_A. \tag{14}$$

The indexes x and n refer to X rays and neutrons respectively. The ratio of RBEs for late and acute reactions is

$$\frac{RBE_L}{RBE_A} = \frac{LAR_x}{LAR_n} = \left[1 + \frac{\beta}{K_A}(T - T_0)\right]^{(\gamma_x - \gamma_n)/(\gamma_x \gamma_n)}. \tag{15}$$

The value of γ_x is mostly greater than γ_n and consequently $RBE_L > RBE_A$ if $T > T_0$. $RBE_L = RBE_A$ for $T \leq T_0$. This model analysis shows that the repopulation diminishes RBE. Late effects are caused by damage to slowly repopulating or non-repopulating tissues and so their RBE should be greater. The situation is, however, more complicated as the sensitive fraction of stem cells probably arises in the repopulation phase, which may affect to RBEs. Recent experiments by Withers et al. [19] showed that RBEs for late effects are greater both for 13 fractions in 43 days and for 32 fractions in 43 days.

DISCUSSION

The model equations can be derived as general laws for animals and fitted to available clinical data in order to be valid for practical purposes. The analyses of animal data have been formerly done for acute skin reaction [3], spinal cord [2], and colon [6]. Some general regularities have been established, cell lethality and repopulation parameters have been introduced. This paper is the first attempt to relate such analyses to clinical data. Figure 7 shows the role of radiobiological models in the radiation treatment planning.

The utilization of tissue kinetic models depends on the quality of the underlying cell survival model. A good cell survival model should provide dose limits in the case of high-LET therapy,

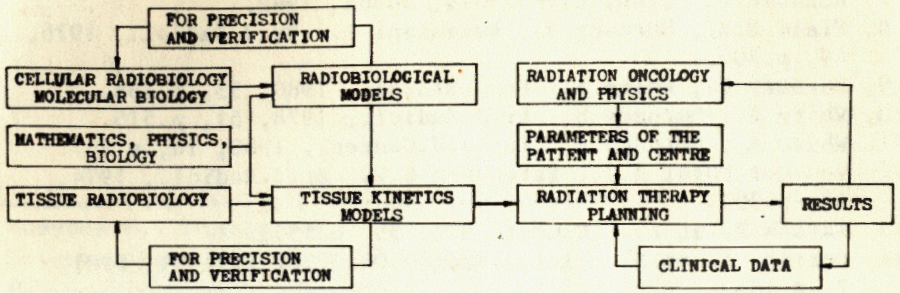

Fig.7. The role of radiobiological models in radiation therapy planning.

combined therapy or chemo-radiotherapy. The advantages of various treatment possibilities could be evaluated and optimum radiation regimes chosen. Such a model should be based on cellular and molecular biology and physics of ionizing radiation. At attempt to derive the model for bacteria has been already done [37].

The significance of the biological interpretation can be shown in the following example. The knowledge of the repopulation parameters β and T_0 of irradiated tissues from target volume help to choose treatment strategy. Owing to the real biological interpretation of the two parameters, there should exist the ways of independent determination of them (this problem could be solved on animals). On the contrary, the values of NSD exponents are fully empirical and they do not correspond to some biological quantities. The knowledge of β and T_0 for an individual patient (established without radiation) could be of a great importance in the prediction of the macroscopic tissue reaction and its modification. It could be a step to more effective individual treatment planning utilizing all available modes of therapy with increased survival or local control rates.

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Козубек С., Водварка П. E19-83-151

Поздние реакции нормальной ткани
после фракционного облучения

На основе новой концепции моделирования действия излучения на клеточную ткань рассматриваются дальнейшие данные по поздним реакциям на облучение. Показано, что макроскопические реакции ткани человека на облучение можно анализировать в рамках уравнений, специфических для данной ткани. Параметры, полученные для разных тканей человека, нужно уточнить перед использованием в клинике.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

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Late Effects of Fractionated Irradiation
of Normal Tissue

The formulae derived in previous papers for cell tissue kinetics have been fitted to further animal data on late reactions. Equations for some human tissue late reactions after X-rays and neutrons have been derived and discussed. The relation between early and late effects is considered. The presented analyses of clinical data have preliminary character and the suggested formulae should be further checked and precised before using in clinical radiotherapy.

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

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