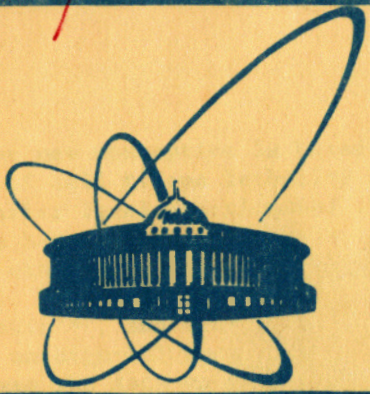

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ACUTE SKIN REACTION AFTER FRACTIONATED IRRADIATION

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The new conception is based on simple radiobiological modelling of cell tissue lethality and restitution processes during and after local fractionated irradiation. Several simple assumptions have been tested against some animal data and compared with other theoretical treatments (Cohen's model, NSD conception). The analyses have been performed for rat spinal cord [1], rat skin [2], and mouse colon [3]. Some considerations have been done on high-LET radiations [4]. An attempt has been made to analyse the data on multicelluar spheroids in terms of the new formulae [5]. Some remarks have been published on human skin acute reaction [6] as well as on late reactions of several human tissues [7]. Further experimental data on mouse and pig skin will be discussed in this paper.

SURVIVAL CURVE ACUTE SKIN REACTION

Many experiments have been performed on mouse skin. The experiments were so accomplished that the full survival curve could be established [8]. In the case of mouse skin the derived survival curve was well fitted by an exponential quadratic equation and it led to the analysis in terms of the "Fe" concept [8]. It is possible to use a quadratic equation for the calculation of DFT, too:

$$DFT = N \cdot (d + \omega d^2) - \beta_0 (T - T_0), \qquad (1)$$

where ω is the survival curve parameter. There are, however, several reasons for which we shall take rather generalized Huggett's formula through further analyses:

The exponential-quadratic formula is not general enough to describe all experimental results for various tissues [3]. The survival curve determined by Douglas and Fowler [8] is the initial one. The survival curve during repopulation differs from that of initial days and so the survival curve parameters are the average ones. The presence of more sensitive compartment should be expressed in the existence of a pronounced initial slope of the survival curve, which is in contradiction with exponential-quadratic formula.

Table 1 shows the data by Doglas and Fowler [8] on fractionated irradiation together with the results of analyses in terms of generalized Huggett's and exponential-quadratic formulae. It is obvious that the first formula describes experimental data

Table 1

The analyses of mouse skin fractionated irradiation experiments in terms of generalized Huggett's and exponential-quadratic formulae. $D_E \pm R_E$ ... experimental dose with standard deviation, D_1 ... theoretical dose obtained from exponential-quadratic equation with optimal $\beta/\alpha = 0.096$ and $DF = D + \beta/\alpha D^2 = 76.0$, D_2 ... theoretical dose obtained from generalized Huggett's formu formula with optimal parameters $\gamma = 1.816$, $d_0 = 1.5$ Gy, $DF = N \cdot (d + d_0)^{\gamma} = 325$. The squares SQ_1 and SQ_2 determined as $((D_E - D_{1,2})/R_E)^2$.

SCHEDULE	$D_E \pm R_E$	D_1	SQ_1	D_2	SQ_2
Single exposure	22.6±0.5	23.4	2.56	22.7	0.04
4 fr. in 3 days	38.5±0.7	39.2	1.00	39.1	0.73
5 fr. in 4 days	42.7±0.6	42.1	1.00	42.3	0.44
8 fr. in 7 days	49.4±0.5	48.2	5.76	49.5	0.04
16 fr. in 8 days	60.0±1.3	56.7	6.44	60.0	0.00
17 fr. in 8 days	$58.0^{+4.0}_{-2.0}$	57.4	0.09	60.8	0.49
32 fr. in 8 days	$65.1^{+2.0}_{-1.3}$	63.8	1.00	66.7	0.64
64 fr. in 8 days	67.6±0.8	68.9	2.64	66.9	0.77
14 x 2.00 Gy in week + D_E	16.5±0.5	16.5	0.00	16.4	0.04
28 x 1.00 Gy in week + D_E	16.0±0.5	17.1	4.84	16.4	0.64
64 x 0.45 Gy in week + D_E	16.5±0.5	17.3	2.56	16.2	0.36
Sum of squares S^2			27.89		4.19
Degrees of freedom DF			9		8
S^2/DF			3.10		0.52

much better. The difference in sums of squares is significant at 1% level ($P < 0.01$). So if using the two formulae as descriptive ones we should prefer generalized Huggett's formula in spite of its additional parameter.

The "Fe" plot (the dependence of log - survival over total dose vs dose per fraction) has been suggested as particularly useful way of plotting the cell survival curve for skin response data which appeared to fit a quadratic survival equation as this gave a straight line on such a plot[8]. More exact experiments, however, showed a slight curvature[9] just corresponding to the curve of generalized Huggett's formula.

Dutreix's graph (or "D_r" plot) was recently found to be linear in the broad region of doses (from 4 to 20-25 Gy), which is further evidence for the superoirity of the new formula as it gives linear D_r plot (experiments by Douglas et al.[9]).

Generalized Huggett's formula has been fitted to the cubic equations given as the best fits of survival curves by Lam et al.[10] for 7-day scoring and 22-day scoring systems for mouse skin reaction. The correlations were nearly exact (differencies in dose between 4-25 Gy were less than 1% with average difference of 0.6%).

Furthermore, generalized Huggett's formula is easy to handle in respect to experimental data. Its parameters can be interpreted in terms of Dutreix's and Strandquist's graphs and orientational values can be determined from such graphs.

The additional parameter may be sometimes superfluous or may have approximate value only, of course.

The parameters can be derived from Douglas' survival curve, too. The linearization of generalized Huggett's formula gives:

$$\ln(-\ln(S)) = \ln\alpha + \gamma \ln(d + d_0). \qquad (2)$$

Good agreement can be achieved with $d_0 = 1.5$, $\gamma = 1.82$, $\alpha = 0.034$. The value of α could be determined from the full survival curve, of course; but it is usually impossible. Douglas and Fowler[8] used the data of Emery et al.[11] on clone counting in order to achieve the absolute scale. The absolute scale can be determined with some uncertainty only $\alpha = 0.034 \pm 0.010$.

The least squares fitting assumes in this case constant dispersion of the quantity $\ln(-\ln(S))$. Such a method differs somewhat from usually used assumption that $\ln(S)$ has the same dispersion but in such cases it is an advantage[6].

The determined survival curve formula describes well the results of Field et al.[12] with the irradiation during 43 days. The computed DF factor for 8, 16 and 32 fractions is DF = 500.5± ± 3% (for 4 fractions the computed value was somewhat greater but the authors confirmed less precision in that case and they themselves did not use the point for their analyses). This fact suggests that there could be small changes of the parameters d_0 and γ during the schedule only (the parameter α may very). The mice used by Field et al.[12] and Field and Hornsey[13] were of SAS/TO strain; Douglas and Fowler[8] used WHT/Ht mice. The survival characteristics seemed to be the same for the two strains[12], although the dose corresponding to given reaction somewhat differs, and so the parameter α may differ, too.

The determined survival curve describes also the results of Fowler et al.[14] with fractionated irradiation up to 18 days. Fowler obtained a straight line with a slope of $\kappa = 0.33$ in

Table 2

Doses and DF factors for various levels of mouse skin reaction $\gamma = 1.816$, $d_0 = 1.5$, $T = 43$ days.

SCHEDULE FRAC/DAYS	REACTION 0.5 D/Gy/	DF	REACTION 0.6 D/Gy/	DF	REACTION 0.7 D/Gy/	DF	REACTION 1.0 D/Gy/	DF
Single dose							18.7	234.7
8/43	50.7	336.4	56.5	395.1	61.5	449.0	67.2	514.2
16/43	60.8	330.7	70.2	400.2	75.8	444.5	82.8	502.7
32/43			74.1	364.1	83.0	413.8	94.9	484.5
Mean values of DF ± S.D.		333.6 ± 1%		386.5 ± 5%		435.8 ± 4%		500.5 ± 3%

Strandquist's graph, which corresponds to $\gamma = 1.49$ of original Huggatt's formula. The doses per fraction were, however, rather great (≥ 4 Gy), and so we have further evidence that in these cases original Huggett's formula gives a fairly good approximation. It can be easily shown, that the original and generalized formulae coincide in the region 3-15 Gy. The values of γ differ, of course.

The value $\gamma = 1.49$ for mouse skin is quite near to the value $\gamma = 1.40$ determined for rat skin [2,3], which suggests that there is one common survival curve for acute skin reaction.

REPOPULATION OF SKIN STEM CELLS

Repopulation during fractionated irradiation has been investigated in the case of rat skin [2]. The model parameters have been estimated. The latent period is about 20 days, doubling times 33-44 hours [3]. The process of repopulation in mouse skin has been studied by many authors [12, 14, 15, 16]. Denekamp has shown that the repopulation does not start until approximately 10 days after the beginning of irradiation in fractionated irradiation by 3 Gy fractions. Douglas and Fowler [8] did not observe repopulation until 16 days. Denekamp used SAS/TO mice and WHT/Ht mice, Douglas and Fowler used WHT/Ht mice. SAS/TO mice were used also in further experiments by Field et al. [12]. The numerical values of doses from his work were determined for early reactions and are given in Table 2 together with the values of DF factor. Small errors of mean values suggest that the survival curve formula describes these data well. The difference in DF values between a single dose and fractionated irradiation should

Table 3

Schedules, doses, and DF factors for SAS/TO mice [15]. The values of DF are not shown where the dose is beyond model applicability; in parentheses are rough estimations

SCHEDULE Daily frac./days	Reaction 1.0 D_T	DF	Reaction 1.5 D_T	DF	Reaction 2.0 D_T	DF
Single dose	20.0	262.9	24.8	-	31.3	-
8x3 Gy + D_T /10	11.5	228.3	15.4	292.6	18.6	355.4
9x3 Gy + D_T /11	11.0	236.4	15.7	313.5	18.3	374.5
9x3 Gy + D_T /15	13.7	278.2	18.2	362.4	21.3	/430.6/
9x3 Gy + D_T /19	16.5	328.5	20.3	/407.7/	23.7	-
9x3 Gy + D_T /26	18.2	362.4	22.1	-	27.1	-

be given by repopulation. The estimation of β_0 can be calculated: $\Delta DF = 268$, $T_0 = 10$-15 days and so $\beta_0 = 8$-10 ($Gy^{\gamma} day^{-1}$).

Further experiments were performed with irregular schedules and it should be noted that the predictions of the model for fairly irregular regimes from parameters derived from regular ones may be rough only. The basic interpretation should be, however, valid for irregular schedules, too.

Denekamp et al. [15] irradiated SAS/TO mice with 9 fractions per 3 Gy daily. Then a test dose was delivered at different times. The schedules, doses, times, and DF factors are enlisted in Table 3. The values of β_0 can be determined by the simple least squares fit to the equation

$$DF = \beta_0 \cdot T + DFT - \beta_0 \cdot T_0 \qquad (3)$$

providing only schedules with $T \geq T_0$ are used for the analysis and T is less than the time of full restoration of tissue cell level. The values of β_0, $DFT - \beta_0 \cdot T_0$ and DFT values are given in Table 4. The values of correlation coefficients are near to 1.0 and it is the evidence for the exponential pattern of growth. See also Fig.1. It should be emphasized that this conclusion does not depend on precise form of the survival curve formula. The repopulation coefficients β_0 quite correspond to those of Field's experiment owing to the fact that our survival curve formula should be considered as rough approximation for such different schedules and the speed of repopulation itself may depend on fractionation, too. Somewhat greater value for β_0 of reaction 2.0 is probably due to a greater test dose which is

Table 4

The analysis of the data given in Table 3. The least square fit has been used to Eq.3. The values in parentheses are rough estimations. DFT values are calculate for T_0 = 9 days (DFT_1) and T_0 = 10 days (DFT_2). Correlation coefficient r is shown.

REACTION	β_0	DFT-$\beta_0 \cdot T_0$	DFT_1	DFT_2	r
1.0	11.2	114.5	214.9	226.0	0.998
1.5	12.5	172.3	284.7	296.2	0.997
2.0	/15.2/	/201.3/	/337.8/	/353.0/	0.999

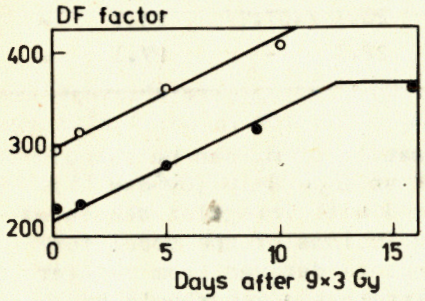

Fig.1. DF factor as a function of the time between 9x3 Gy delivered daily and the test dose for SAS/TO mice skin. Reactions 1.0 (●) and 1.5 (○) are shown. The linear dependence reflects an exponential growth of the stem cell population. The optimal parameters from Table 1 have been used for the calculations.

beyond the region of the validity of model equations. It seems that after the doses exceed 20 Gy, the population exchibits more resistant response - perhaps due to some small resistant component. Average value of β_0 for reactions 1.0 and 1.5 is β_0 = = 11.85.

Similarly the results with split dose (10 Gy + test dose) experiments by Denekamp et al. [16] for SAS/TO mice can be analysed. The corresponding quantities are given in Table 5. This data suggest the repopulation does not start before the 8th day. The repopulation coefficient can be estimated to β_0 = 12.9-15.6 (T_0 = = 9-10 days). The two experiments mentioned above give further evidence for the hypothesis that T_0 - the latent period - does not depend on fractionation (in the first approximation).

NORMAL TURNOVER RATE AND REPOPULATION

Plucked mouse skin exhibits somewhat different pattern of behaviour [17]. After single doses of X-rays the peak of skin reaction appears in 10-12 days for plucked skin and in 20-

Table 5

Split dose experiments for SAS/TO mice skin [16]. Doses and DF factors are calculated;
$DF = (d_1 + 1.5)^{1.82} + (d_2 + 1.5)^{1.82}$.

First dose	Second dose	Time	DF
25.7	-	0	-
10.0	20.8	1	365.3
10.0	20.8	8	365.3
10.0	24.0	15	/442.7/

22 days for unplucked skin. Mitotic indexes in unplucked skin are below the control value until 9 days, while the plucked skin responds nearly immediately. The survival curves are probably similar for both plucked and unplucked skins as the values of $(D - D_1)_{24h}$ are the same [18].

The analysis for SAS/TO plucked skin reaction (the data by Emery et al. [19]) is in Table 6. The estimations of the parameters are (d_0 and γ taken from Table 1):

$$DFT = 183.0 \qquad T_0 = 0.0 \qquad \beta_0 = 6.7.$$

The schedule 2fr./21 days was excluded owing to experimental uncertainties confirmed by authors [19]. A very good value of correlation coefficient suggests again that the repopulation can be seen as exponential growth at a constant average speed (Fig.2). The doubling time can be determined according to the equation $T_d = \ln 2/(\beta_0 \cdot a)$ taking $a = 0.034$:

T_d = 2.0-2.5 for fractionated irradiation (exp. of Field et al.)
T_d = 1.7 days for irregular schedules (exp.of Denekamp et al.)
T_d = 3.0 for plucked skin (exp. of Emery et al.)

A somewhat greater value for fractionated irradiation (compared with irregular schedules) is quite understandable owing to radiation induced delay after each fraction (actual number of days of repopulation should be a little smaller).

A higher value for plucked skin could be due to a higher normal turnover rate as the turnover rate T_t = 100 hours turns to T_t = 47 hours during 20-24 hours after plucking [17]. Our values were determined from radiation response and do not include other than radiation cell loss. In fact the population is reduced by two factors: radiation damage and cell loss which is characteri-

Table 6

Split dose experiments for SAS/TO mice, plucked skin[19]. Experimental doses D_E in Gy and DF factors are shown. Theoretical doses D_T are calculated with optimal parameters $T_0 = 0.0$, $\beta_0 = 6.716$, DFT = 182.9

SCHEDULE	$D_E \pm$S.D.	DF	D_T
Single dose	15.98±0.14	180.49	16.11
2fr./1 d	21.68±0.25	191.80	21.52
2fr./3 d	22.28±0.30	200.36	22.47
2fr./7 d	24.58±0.42	234.68	24.27
2fr./14d	27.09±0.54	274.90	27.21

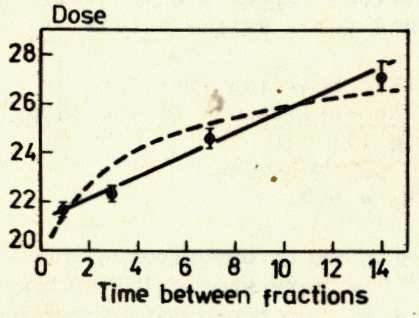

Fig.2. The time dependence of the total dose producing the same effect to plucked skin of SAS/TO mice. Experimental points and theoretical curve have been taken from Table 6. The dashed line corresponds to the formula of Ellis' type $D = NSD \cdot N^{\nu} \cdot T^{r}$ with optimal parameters ($\nu = 0.318$, $r = 0.105$, NSD = 1598). 95% confidence intervals have been shown. The ordinate: dose in Gy, the abscissa: time in days.

zed by the normal turnover rate. The cell loss constant is $\beta_{tn} = \ln 2 / T_t = 0.17$ for normal skin and $\beta_{tp} = 0.35$ day^{-1} for plucked skin. The repopulation after irradiation is characterized by constants $\beta_{rn} = \beta_{on} \cdot \alpha = 0.41$ for normal skin and $\beta_{rp} = \beta_{op} \cdot \alpha = 0.23$ for plucked skin. The sum $\beta_{tn} + \beta_{rn} = \beta_{tp} + \beta_{rp} = 0.58$ in both normal and plucked skin and represents probably maximum possible speed of repopulation for given tissue: $\beta = 0.58$ day^{-1} with the doubling time $T_d = 28.8$ hours.

Repopulation was not found for 16 days in the case of WHT/HT mice[8] after the beginning of irradiation. Nevertheless, after 14 x 3 Gy during 18 days a rapid repopulation was observed[15]. The values of DF factors and repopulation coefficients are given in Table 7. The speed of repopulation is markedly higher than in the case of SAS/TO mice as $\beta_0 = 23.7 \pm 3.0$.

Table 7

Schedules, doses and DF factors for WHT/Ht mice[15]. The DF factors are shown to higher doses than in the case of SAS/TO mice as the survival curve used is valid up to 23 Gy. The repopulation coefficients β_0 have been calculated assuming $T_0 = 18$ days. D_T... test dose (Gy)

SCHEDULE	Reaction 1.0		Reaction 1.5		Reaction 2.0	
Daily frac./days	D_T	DF	D_T	DF	D_T	DF
Single dose	19.0	241.1	22.0	308.9	26.4	421.9
13x3 Gy + D_T/17	7.2	250.4	12.1	314.0	15.4	369.4
14x3 Gy + D_T/18	5.7	251.0	10.3	303.4	13.7	355.0
14x3 Gy + D_T/26	16.9	413.1	21.5	512.1	23.2	553.1
14x3 Gy + D_T/33	17.3	421.0	23.1	550.7	26.0	-
β_0		20.3		26.1		24.8

The process of repopulation is likely to be influenced by many factors and may be probably different for various strains, too. White and Hornsey[20] arrived at the similar conclusion comparing their results with that of Van der Kögel[21]. Assuming the survival curve parameter $\alpha = 0.034$ for SAS/TO mice and a somewhat higher value of $\alpha = 0.041$ for WHT/Ht mice due to greater sensitivity[19], we can calculate the values of doubling times: $T_d = 16.7$ hours for WHT/Ht mice and $T_d = 40.8$ hours for SAS/TO mice. The value of about 16.7 hours for WHT/Ht mice is in agreement with 22 hours determined by Withers[22] for plucked mice. A longer doubling time could be due to a shorter normal turnover rate for plucked mice.

ACUTE REACTION OF PIG SKIN

The experimental data published by Bewley et al.[23] and Fowler et al.[24] are consistent with survival curve parameters derived for mouse skin (Table 8). The difference between 18-28 days leads to the estimation of the repopulation constant $\beta_0 = 6.8$. Earlier considerations concerning the power function in Ellis' formula led to great discrepancies between the two sets of experiments[23,24] - see discussion in the paper by Fowler[25].

The results of experiments of Berry et al.[26] do not fit in the picture given above. The difference between doses for

Table 8

Schedules, doses, and DF factors for pig skin[23,24]. Schedules are given in N/T notation, doses in Gy. The average values of DF have been calculated for the latent period DF_L and for T = 28 days, DF_R.

SCHEDULE	DOSE	DF	SCHEDULE	DOSE	DF
S.D.	18.4	228.4	5/28	38.1	276.9
2/2	23.5	218.3	9/28	47.3	289.0
2/3	25.0	241.2	21/28	60.9	309.5
3/3	30.2	255.8	DF_R		302.7 ±4%
5/5	34.2	235.4			
9/17	39.0	221.4			
15/18	47.3	244.8			
DF_L		235.2 ±4%			

30 fr./39 days and 6 fr./18 days is 10-15 Gy only, which is too low owing to great differences in fraction numbers and time. The conclusion can be drawn that the schedule 30/39 is very effective. It could be due to greater effectiveness in radiation killing or lower rate of repopulation. Similar situation was reported by Withers et al.[27] where 32 fr./45 days were more effective than 13 fr./45 days for nearly the same total dose.

It seems that the effect is not restricted to pig skin only. The mouse skin experiments by Field et al.[12] showed that 32 fr. can be as effective as 16 fractions in 43 days for doses about 65 Gy, although there is a marked difference for stronger reactions. Doses for a level of 1.0 are in agreement with theoretical formulae including repopulation. Similar behaviour exhibits rat skin. Two possible explanations can be suggested:

1) the population of stem cells is more sensitive in the repopulation phase of the schedule,

2) the latent period T_0 is longer for the schedules with low doses per fraction.

Both mechanisms may be effective and their investigation would be of great value for human radiotherapy.

DISCUSSION

The process of repopulation was assumed to start at the time T_0 after the first dose fraction. The time T_0 = 20 days is in correlation with the time of stem cell maturation, which suggests that differentiated cells trigger stem cell population. T_0 may slightly depend on the degree of tissue damage. Analysing the large data sets[3] separately for each reaction, the dependence of T_0 on the reaction level could be noticed. T_0 = 15.0 days for level 1 of reaction in the case of rat skin and T_0 = = 21.2 for level 5; T_0 = 33.2 hours for 100 cells per circumference in mouse colon and T_0 = 41.1 hours for 10 cells per circumference. This findings are in agreement with independent measurements by Hegazy and Fowler[18] for mouse skin and Lesher and Lesher[29] for intestinal cells.

The assumption of exponential growth was confirmed by several data sets. There is, however, difference between the speed of repopulation during fractionated regims and the speed of free repopulation. Some dose-dependent delay should be considered with in a more detaild approach.

There are still other more unknown factors that may influence the picture. For example, if there exists some regime-dependent cell loss factor or if the gross reaction does not follow the cell survival. The correspondence between cell survival and macroscopic tissue reaction was experimentally confirmed[28,19], but in the case of protracted irradiation the maximum tissue reaction reflects rather minimum cell level in the tissue, which may be at the end of the latent period.

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Острая реакция кожи после фракционированного облучения

На основе новой концепции моделирования действия излучения на ткань анализируются данные по острой реакции кожи мыши и свиньи на фракционированное облучение гамма- или x-лучами. Обсуждается возможность использования квадратично-экспоненциальной формулы и формулы Хаджета для описания летального действия излучения и сопоставляются результаты. Оказывается, что обобщенная формула Хаджета описывает экспериментальные данные намного лучше. Определяется скорость репопуляции при фракционированном облучении и при некоторых нерегулярных режимах облучения. Показано,что скорость репопуляции меньше при фракционированном облучении. Максимальная скорость репопуляции приводится в соответствие с длиной клеточного цикла. Она отличается для разных штаммов мыши /T_d = 28,8 часов для SAS/TO и T_d = 17 часов для WHT/Ht мышей/, но не меняется для участков кожи с выщипанным покровом. Репопуляция хорошо описывается экспоненциальной зависимостью после некоторого периода латенции, Обсуждаются дальнейшие факторы, влияющие на эффективность действия излучения: длина латентного периода, изменение кривой выживания во время облучения.

Работы выполненв в Лаборатории ядерных проблем ОИЯИ.

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Acute Skin Reaction after Fractionated Irradiation

Experimental data on acute mouse and pig skin reaction after fractionated γ or X irradiation have been analysed in terms of a new cell tissue kinetic model. The exponential-quadratic and generalized Huggett formulae have been used for cell lethality description. Fairly better results could be demonstrated with generalized Huggett's formula. The speed of repopulation has been determined for fractionated regimes as well as for some irregular schedules. The repopulation is slower in the case of fractionated treatment. On considering the normal cell loss factor in the tissue, minimum cell cycle time has been calculated. Its value differs for various strains (T_d = = 28.8 hours for SAS/TO mice and $T_d \leq 17$ hours for WHT/Ht mice) and does not differ for plucked skin. The repopulation has been shown to follow exponential dependence after some latent period. Other factors influencing the effectiveness of radiation treatment (the length of the latent period or the changes of the survival curve during fractionated irradiation) have been considered, too.

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

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