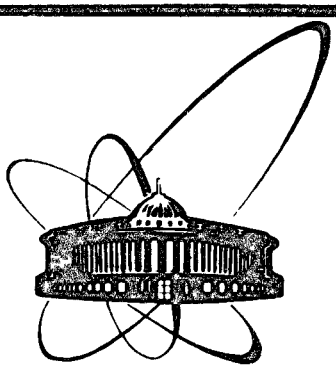

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# CUMULATIVE EFFECT OF NON-STANDARD RADIATION

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## INTRODUCTION

The potential advantages of using various particles in cancer radiotherapy have been considered for a long time. Some types of radiation /charged particles/ provide excellent dose-distribution in irradiated volume, others /neutrons and heavy particles/ possess high-LET component with greater RBE and smaller OER (e.g./1/). The medical beams of heavy particles, $\pi$-mesons and fast neutrons as well as $\gamma$-ray unit will be available at the Laboratory of Nuclear Problems, JINR/7/.

The dose-distributions of such beams can be measured or calculated with sufficient accuracy at present time; on the other hand radiobiological properties of them are less known. A lot of comparative experiments have been devoted to cell survival of in vitro cultured cells (e.g./4/). On the basis of these experimental data several theoretical approaches have been tested/11,17,18/ and survival curve parameters have been determined. The models enable us to calculate survival curves for given cell line and given radiation beam.

Cancer therapy is limited by the response of normal tissues. Experiments concerned normal tissue tolerance to various types of radiation have been carried out and RBE values have been determined (e.g./33/). The RBE was measured mostly for single exposure. Several experiments have been performed with fractionated irradiation of normal tissues mainly with fast neutrons (e.g./34,37,13/). These experiments showed that RBE depends on fractionation regime and differs for various tissues.

The cumulative effect of $\gamma$-radiation has been mostly discussed in terms of NSD /nominal standard dose/conception/8/. This conception seems to be disproved at present time/10,20-22,38/. New formulae have been proposed/19-23/. The new formulae will be used for the analyses of the data on fractionated irradiation of normal tissue with non-standard beams.

## CELL SURVIVAL AFTER IRRADIATION WITH NON-STANDARD BEAMS

Several attempts have been made to explain the LET dependence of cell survival. KATZ et al./17/ considered separately high-LET and low-LET components of each radiation. The survival probabi-

lity is then given as the product of cell lethality after high-LET irradiation and low-LET irradiation with corresponding doses. The high-LET component is assumed to provide single-hit inactivation whilest the low-LET component acts through multitarget or multihit model.

Kellerer and Rossi[18] provided the theory of dual radiation action where sublesions produced proportionally to the specific energy absorbed in the cell nucleus can interact in pairs and produce lesions connected with cell lethality.

Günther et al.[11] tried to bind up DNA lesions with cell survival. The lesions are produced again proportionally to the specific energy absorbed in the cell nucleus. The efficiency of their production depends on radiation quality. The given number of DNA lesions determines the probability of survival. This dependence is taken from the $\gamma$-ray survival curve.

The predictions from the mentioned models are mostly fairly consistent with experimental cell survival for different types of radiation beams. This fact does not, however, mean that the basic processes of radiation action on biological objects have been well understood. All mentioned models need fitting a series of parameters to cell survival measurements. The predictions can be then considered as interpolated or extrapolated values. The quality of such a model can be checked by means of an independent experiment only, e.g., by measurements of lesion production.

Direct measurements of DNA lesion production /SSB - single strand breaks or DSB - double strand breaks/ are difficult to evaluate owing to experimental uncertainties. For example, enzymatic lesions measured as double strand breaks may be quickly repaired as single strand breaks in the case of E. coli[2]. The production of breaks strongly depends on the conditions of irradiation and measurement. There are probably several types of SSB and DSB.

Another independent experiment is fractionated or sequential irradiation with various beams (e.g.[29,30]). Some of these experiments suggested that $\gamma$-rays and high-LET particles act independently, others[30] showed that there existed some interaction. The interaction was harder than could be expected from Katz's model[30]. The suggestion of Rossi that repair of sublethal damage should be the same for given dose also was not confirmed.

Further experiments have shown that the shoulder of the survival curve of cells after previous repair is smaller[29]. This suggests that there exists some irreparable sublethal injury in the surviving cells previously irradiated at the time of another exposure. This effect is well known in the case of yeast cells where the cells were shown to contain irreparable damage accumulated with fractionation. The fraction of irreparable damage is



probably LET dependent. For example, chromosomal lesions of cornea epithelium cells of mice were shown to be intensively repaired between divided exposures to $\gamma$-radiation[35]. No repair was found after irradiation with accelerated heavy ions. Some evidence exists on the molecular level, too, where the reparation of $\gamma$-ray double strand breaks was shown to be more extensive than the reparation of neutron - induced DSB[12].

The models mentioned above do not allow one to explain these facts and the marked discrepancies can be expected if the predictions were used for fractionated irradiation of cell tissue. Such discrepancies have been already noticed. Katz et al.[17] noticed that measured values of RBE for neutron irradiation of human, rat, pig and mouse skin depart from the theory. The experimental slopes in ln(RBE) vs ln(d) plot were steeper than theoretical ones /d is the dose per fraction/. Günther et al. have had to use final slope of cell survival only /without shoulder/ in order to obtain measured values of RBE for cell tissue /personal communication/.

We can conclude that there is no reliable model for the prediction of cell survival or RBE. Such a model is to be invented.

## NORMAL TISSUE RESPONSE TO NON-STRAND BEAMS

The macroscopic reaction of cell tissue after single doses does not probably differ qualitatively (e.g.,[6]). The time-course of skin reaction is similar, which suggests that epithelian repopulation after single exposure does not differ from Co 60 or X-rays, too. The experiments with fractionated irradiation of mouse skin with neutrons showed the same rates of proliferation after 4 and 9 daily fractions. Lower rate of repopulation after 14 fractions of neutrons had been found but subsequent experiment led to the opposite conclusion[9].

TDF factor for fast neutrons has been introduced by Field et al.[9]. Some recent clinical results of neutron therapy have been evaluated in terms of this TDF and combined TDF for sequential irradiation with X-rays and neutrons have been considered[5].

It should be stressed, however, that these formulae arised from NSD conception and they have the same disadvantages as mentioned by Withers and Peters[38], Fischer[10], and Kozubek[19-22]. Moreover, TDF has misleading asymptotical properties, which manifests itself in the case of calculations for irregular schedules.

## IRREPARABLE SUBLETHAL DAMAGE

It was already notices that the dependence of total dose necessary to produce given tissue reaction on the number of fractions in log-log graphs is not linear but approaches some plateau region. The effect could be interpreted as the consequance of some initial slope of the corresponding survival curve or in terms of the accumulation of irreparable sublethal damage [21].

Similar effect but more pronounced has been observed with fast neutron radiation /Fig. 1/ . A lack of sparing of damage in tissues after neutrons has been interpreted as less recovery from sublethal damage after irradiation with neutrons compared to $\gamma$-rays.

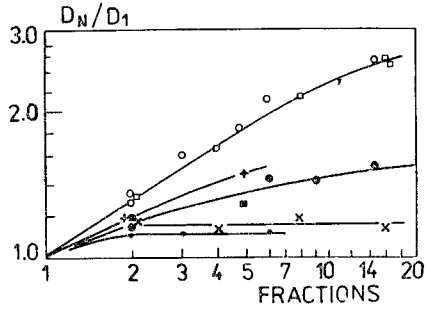



Fig. 1. The Strandquist graphs for neutrons $E_d$ = 16 MeV: (●) pig skin, (■) mouse skin, (+) mouse oesophagus, (×) mouse lung, (·) mouse jejunum. For comparison the same graph is shown for $\gamma$-rays (o) pig skin, (-□) mouse skin. Repopulation neglected ($T<T_0$). Data taken from literature.

There is considerable sparing of damage if the neutron dose is divided into two fractions and little or no sparing if the dose is further divided /e.g., [37] /. This fact was explained by increasing contribution of high-LET component of dose to biological effect for smaller doses and it was concluded that in the cases of combining $\gamma$- and neutron irradiation there will be little sparing of damage by fractionation of the neutron dose and the usual sparing by fractionation of $\gamma$-rays dose.

However, the situation is probably more complicated. According to the data on fractionated irradiation of animal tissue the survival curve should be exponential in the region 0-5 Gy /e.g., [15] /. In vitro survival curves are, however, shouldered in this region /e.g., [40] /. The parameter $\gamma$ of Huggett's formula is $\gamma$=1.15÷1.40 /see further paragraphs/. Such a behaviour can be explained by accumulation of the non-recoverable sublethal injury, mentioned above. The survival curve is not repeated after each exposure - its shoulder diminishes. Reasonable approximation can be obtained under the assumption that some part of the initial dose remains "unrepaired" in surviving cells.

So, in the cases of combining $\gamma$- and neutron irradiation there will be little sparing of damage by fractionation of the dose not only in the case of neutrons but also in the case of $\gamma$-rays if irreparable sublethal damage is accumulated.



## ANALYTICAL FORMULAE IN FRACTIONATED IRRADIATION BY NON-STANDARD BEAMS

A new attempt to describe analytically the observed regularities of the response of normal tissue to fractionated irradiation with gamma-rays has been made. Several hypotheses have been put forward [19-22]:

1/ the macroscopic tissue reaction is determined by cell survival of some stem cell population;

-2/ there exists some average /schedule-independent/ shape of a survival curve for given tissue /average value of $\gamma$ - see further paragraphs/;

3/ repopulation starts after some latent period $T_0$ independently of fractionation;

4/ the repopulation follows an exponential pattern of growth /nearly up to the initial level/.

Owing to a lack of a suitable quantitive model for cell survival, the survival curve formula suggested by Huggett and pointed out by Lokajicek et al. [25-27] has been used.

Good agreement of the results of the model based on these hypotheses with experimental data of various tissues could be demonstrated. The formulae have been simple and illustrative. Let us continue the reasoning in terms of this model.

The survival curves produced by non-standard beams are also well described by the Huggett` formula /Table 1/ so the survival after single exposure can be written as

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

where d is the dose, $\alpha$ , $\gamma$ are the parameters.

Assuming accumulation of non-recoverable sublethal damage at the rate of $\Delta$ part from the absorbed dose D , we have the formula for fractionated irradiation:

$$S = \exp\{-\alpha d^{\gamma} \sum_{i=1}^{N} ([1 + \Delta\cdot(i-1)]^{\gamma} - [\Delta\cdot(i-1)]^{\gamma})\}. \qquad (2)$$

The quantity which has to remain constant after including repopulation is:

$$DFT = \sum_{i=1}^{N} ([1 + \Delta\cdot(i-1)]^{\gamma} - [\Delta\cdot(i-1)]^{\gamma})d^{\gamma} - \beta_0 (T-T_0), \qquad (3)$$

where T is overall time, DFT characterizes the given effect DFT= $-\ln(S)/\alpha$ , $\beta_0=\beta/\alpha$ , where $\beta=\ln(2)/T_c$ and $T_c$ is the doubling time [20-22].

Table 1

The parameters of Huggett's formula and correlation coefficients of linear regression for non-standard beams

| CELLS /AUTHORS/ | RADIATION | $\alpha$ | $\gamma$ | r |
|---|---|---|---|---|
| T1 /Chapman et al. -4/ | 220 kV X-rays | 0.185 | 1.40 | 0.999 |
| | Carbon, peak | 0.642 | 1.26 | 0.999 |
| V-79 /Chapman et al. - 4/ | 220 kV X-rays | 0.101 | 1.59 | 0.996 |
| | Carbon, peak | 0.650 | 1.12 | 0.999 |
| V-79 /Hall -from 36/ | Co 60 | 0.102 | 1.61 | 0.990 |
| | Protons, peak | 0.151 | 1.52 | 0.995 |
| T1 /from 1/ | X-rays | 0.140 | 1.62 | 0.998 |
| | Fast neutrons | 0.730 | 1.21 | 0.995 |
| | $\pi$ mesons | 0.678 | 1.12 | 0.996 |
| V 2 FAF /Yarmonenko et al. - 39/ | $\gamma$-rays | 0.135 | 1.75 | 0.992 |
| | $\pi$ mesons | 0.545 | 1.10 | 0.950 |
| V-79 /Kampf and Tolkendorf - 24/ | X-rays | 0.082 | 1.62 | 0.995 |
| | Fast neutrons | 0.867 | 1.15 | 0.999 |
| HeLa S3 /Zeitz et al. - 40/ | X-rays | 0.306 | 1.358 | 0.998 |
| | Fast neutrons depth = 2 cm | | | |
| | D + Be | 1.104 | 1.30 | 0.994 |
| | $^3$He + Be | 0.964 | 1.39 | 0.996 |
| | depth = 13 cm | | | |
| | D + Be | 1.114 | 1.15 | 0.992 |
| | $^3$He + Be | 1.093 | 1.17 | 0.995 |
| V-79 /Raju and Carpenter - 33/ | X-rays | 0.115 | 1.61 | 0.998 |
| | Fast neutrons | 0.545 | 1.37 | * |

* few experimental points



Denoting I(N) the factor of irreparable sublethal injury:

$$I(N) = 1/N \cdot \sum_{i=1}^{N} ([1+\Delta(i-1)]^{\gamma} - [\Delta(i-1)]^{\gamma}) \qquad (4)$$

we can rewrite Eq. (3):

$$DFT = N \cdot I(N) \cdot d^{\gamma} \qquad \text{for } T \leq T_0 \qquad (5a)$$

$$DFT = N \cdot I(N) \cdot d^{\gamma} - \beta_0 (T - T_0) \qquad \text{for } T > T_0 . \qquad (5b)$$

The repopulation starts at $T = T_0$ .

The state of irradiated biological system is not fully defined by the survival S . Further behaviour also depends on the level of accumulated sublethal damage. It can be expected that $\Delta$ will be smaller for very great intervals between fractions.

For $I(N) = 1$ Eq. (5) gives

$$DFT = N \cdot d^{\gamma} \qquad \text{for } T \leq T_0 \qquad (6a)$$

$$DFT = N \cdot d^{\gamma} - \beta_0 (T - T_0) \qquad \text{for } T > T_0 \qquad (6b)$$

used in the analyses of rat skin data and rat spinal cord data.

More general formulae have been used in the case of mouse colon:

$$DFT = N \cdot (d + d_0)^{\gamma} \qquad \text{for } T \leq T_0 \qquad (7a)$$

$$DFT = N \cdot (d + d_0)^{\gamma} - \beta_0 (T - T_0) \qquad \text{for } T > T_0 , \qquad (7b)$$

where $d_0$ is a low dose region parameter [19]. For doses great enough / $\gtrsim$3 Gy for skin/ the parameter $d_0$ can be omitted and Eq. (7) turns to Eq. (6).

The two different corrections of Huggett's formula /parameter $d_0$ for X-rays and parameter $\Lambda$ for high-LET particles/ reflect qualitative differencies between the two types of radiation.

## RBE AND DOSE PER FRACTION

The dependence of RBE on the dose per fraction is often represented in log-log plot both for cells in vitro [3,4] and for tissues /e.g. [37] /, being linear in a broad range of variables, for example see Fig. 2. The parameters of such lines are given in Table 2. The greatest values of RBE for 1 Gy of fast neutrons / $E_d$ = 15 MeV/ have been obtained for spinal cord and jejunum, the greatest values of the slope have been obtained for spinal cord.

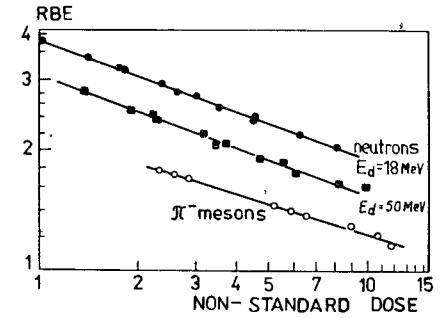
Table 2

The dependence of RBE on the dose per fraction. The parameters of Eqs. (9) are shown

| BIOLOGICAL SYSTEM /AUTHORS/ | $\varkappa_n$ | $\varkappa_x$ | $RBE_{1n}$ |
|---|---|---|---|
| NEUTRONS $E_d$=16 MeV | | | |
| Mouse, pig and human skin /Hornsey - 13/ | -0.246 | -0.326 | 3.52 |
| Spinal cord of rat /13/ | -0.355 | -0.544 | 3.70 |
| Oesophagus /Hornsey and Field - 14/ | -0.146 | -0.172 | 3.41 |
| Mouse jejunum /Withers et al. - 37/ | -0.300 | -0.430 | 3.80 |
| NEUTRONS 15 MeV | | | |
| Rat thyroid /Malone et al. - 28 | -0.261 | -0.350 | 3.13 |
| Mouse intestine /Broerse and Roelse - from 3/ | -0.282 | -0.390 | 2.61 |
| Rat capillary endothelium | -0.103 | -0.093 | 2.06 |
| Human kidney cells /3/ | -0.333 | -0.500 | 2.52 |
| NEUTRONS $E_d$=50 MeV | | | |
| Mouse jejunum /Withers et al. - 37/ | -0.300 | -0.430 | 3.01 |
| Pulmonary metastasis /Mason and Withers - 37/ | -0.153 | -0.180 | 2.42 |
| $\pi^-$ MESONS | | | |
| Mouse skin /Raju et al. - 34/ | -0.200 | -0.249 | 1.97 |
| Mouse jejunum /Withers et al. - 31/ | -0.246 | -0.326 | 2.19 |
| Renal injury /Jordan et al. 16/ | -0.320 | -0.470 | 2.42 |
| CARBON BEAM, PEAK | | | |
| V-79, air /Chapman et al. - 4/ | -0.358 | -0.558 | 3.45 |
| V-79 $N_2$ /Chapman et al. - 4/ | -0.350 | -0.538 | 6.55 |
| T1 /Chapman et al. - 4/ | -0.204 | -0.256 | 2.67 |



Fig. 2. The dependence of RBE on the dose per fraction in log-log plot. The experimental data on mouse jejunum crypt survival[31,37] are shown for two energies of neutrons (d+Be) and $\pi^-$-mesons.




Basic Eqs. (6) give following dependence for RBE:

$$RBE = \left(\frac{\alpha_n}{\alpha_x}\right)^{1/\gamma_x} \cdot d_n^{\gamma_n/\gamma_x - 1} = \left(\frac{\alpha_\mu}{\alpha_x}\right)^{1/\gamma_n} \cdot d^{1-\gamma_x/\gamma_n}, \quad \frac{\alpha_n}{\alpha_x} = \frac{DFT_x}{DFT_n}, \tag{8}$$

where the indexes refer to non-standard and $\gamma$ - or X-radiation. These formulae give linear dependences in log-log graphs:

$$\ln(RBE) = \ln(RBE_{1n}) + \kappa_n \ln(d_n), \quad RBE_{1n} = \left(\frac{\alpha_n}{\alpha_x}\right)^{1/\gamma_x}, \quad \kappa_n = \frac{\gamma_n}{\gamma_x} - 1 \tag{9a}$$

$$\ln(RBE) = \ln(RBE_{1x}) + \kappa_x \ln(d_x), \quad RBE_{1x} = \left(\frac{\alpha_n}{\alpha_x}\right)^{1/\gamma_n}, \quad \kappa_n = 1 - \frac{\gamma_x}{\gamma_n} \tag{9b}$$

The absolute value of RBE is determined by the ratio of parameters $\alpha$ of survival curves, the slope is in direct relation to the shoulders represented by the parameters $\gamma_n$ and $\gamma_x$. Owing to the fact that $\alpha_n > \alpha_x$, and $\gamma_n < \gamma_x$ the value of RBE is greater than 1 and the slope is negative in most cases. The relationships between the slopes can be derived:

$$\kappa_x = \frac{\kappa_n}{\kappa_n + 1} \qquad \kappa_n = \frac{\kappa_x}{1 - \kappa_x} \tag{10a}$$

$$RBE_{1x} = RBE_{1n}^{1/(\kappa_n - 1)} \qquad RBE_{1n} = RBE_{1x}^{1/(1-\kappa_x)}. \tag{10b}$$

Relations (9) can be used for the first orientational analysis in the case of cell tissue. For example, the slopes from Fig.2 are $\kappa_n = 0.30$ for neutrons and $\kappa_n = 0.245$ for $\pi^-$-mesons. The value of $\gamma_x$ can be determined from fractionated irradiation up to 5 fractions: $\gamma_x = 1.537$. We have, therefore, $\gamma_n = 1.076$ for

neutrons and $\gamma_\pi = 1.159$ for $\pi^-$-mesons. More detail analysis, however, shows that there is somewhat smaller slope for constant number of fractions and somewhat greater slope for constant reaction. The same values of the slope for both $E_d$= 16 MeV neutrons and $E_d$ = 50 MeV ones suggest that the shoulders are the same although the sensitivities differ. The ratio of RBEs is therefore dose-independent.

The condition $\Delta \approx 0$ is not mostly satisfied in the case of neutrons as neutrons produce more non-recoverable damage than $\gamma$-irradiation. Nevertheless, this harder damage arises probably at the biological level of radiation effect on cells, after chemical processes and after some component of fast repair. Therefore, better repair should lead to lower $\Delta$ and greater effect of fractionation. On the other hand if the intervals between fractions do not allow full recovery, the value of $\Delta$ could be greater.

Oesophagus is the case of resistant and intensively repairing tissue. $LD_{50}$ for oesophageal death in mice is of about 30 Gy and $D_2 - D_1 = 8{,}5$ Gy. Misonidazole as well as hyperbaric oxygen markedly sensitizes the tissue, which suggests that the tissue could be hypoxic.

On the basis of experiments by Hornsey and Field [14] the following set of parameters can be derived for our orientational analysis:

$$\gamma_x = 1.57, \quad DF_x = 213 \qquad \gamma_n = 1.34, \quad DF_n = 31.1,$$

where DF≈DFT for $T \leq T_0$; the values of DF correspond to 50% mortality at 28 days. RBE can be determined from Eq. (8). There is a great absolute value of $RBE_{1n} = 3.4$ for 1 Gy of neutron dose but the slopes are near to zero: $\kappa_n = -0.146$, $\kappa_x = -0.172$. As the value of $\Delta$ is low, the given RBEs would not depend on the reaction level. The repopulation in oesophagus begins ≳7 days after the beginning of irradiation [32] and significant sensitization of the tissue occurs. Our considerations are therefore valid for $T < 7$ days.

On the other hand the experiments by Withers et al. [37] were performed under such conditions where the value of $\Delta$ was very great / $\Delta \approx 0.3$/. The great value of $\Delta$ may be connected with unusual repair system of the tissue; the intervals between fractions were 3 hours and the reparation of repairable sublethal damage could be incomplete. The cell cycle effect could play some role, too /the curves are probably somewhat shifted to the left/.

For the values of $\Delta$ great enough the dose necessary to produce given macroscopic tissue reaction does not depend on the number of fractions. The RBE can be rewritten as



$$RBE = RBE_{1n} \cdot d_n^{1/\gamma_x - 1} \qquad \text{where} \quad RBE_{1n} = \left(\frac{DF_x}{D_n}\right)^{1/\gamma_x} \tag{11a}$$

$$\ln(RBE) = \ln(RBE_{1n}) + (1/\gamma_x - 1)\ln(d_n), \tag{11b}$$

where $RBE_1$ is a constant for given reaction, $D_n$ is the total dose of non-standard irradiation. This approximation as well as Eqs. (9) are reaction independent.

The slope $\kappa_n = 1/\gamma_x - 1$ depends on the shoulder of the $\gamma$-ray survival curve. The greater the shoulder, the greater the absolute value of the slope. For example, the parameters of rat spinal cord have been determined: $\gamma_x = 1.55$, DFT= 163.5 for 50% myelopathy after 1 year [22]; for $N > 2$ we can use Eqs. (11). The parameters are $RBE_{1n} = 3.70$; $\kappa_n = 1/\gamma_x - 1 = 0.355$ and $\kappa_x = 0.55$ in agreement with the value given by Hornsey $\kappa_n = 0.544$ [13].

The fact that $(1/\gamma_x - 1)$ gives steeper slope than $(\gamma_n/\gamma_x - 1)$ for $\gamma_n > 1$ explains the discrepancy between Katz's theory and experimental data on fractionated irradiation.

In a general case the function I(N) must be considered and $d_0 \neq 0$:

$$RBE = \left(\frac{DF_x}{DF_n}\right)^{1/\gamma_x} \cdot [I(N)]^{1/\gamma_x} \cdot d_n^{\gamma_n/\gamma_x - 1} - d_0/d_n \quad \text{for} \quad d_n \geq \frac{d_0}{RBE\,(\gamma_x - 1)} \tag{12}$$

and we obtain a series of lines in log-log plot for various N. The series of the lines for mouse and pig skin is shown in Fig.3.

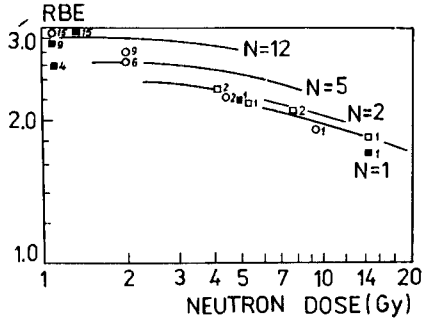



Fig. 3. The dependence of RBE on the dose per fraction in log-log plot. The experimental data on mouse and pig skin are shown with the number of fractions: (o) pig skin, (□) clones counting technique, (●) mouse skin.

The lethality parameters for neutrons have been estimated from Fig. 1: $\gamma_n = 1.40$; $\Delta = 0.15$; $\gamma$-ray parameters have been given earlier [21]: $\gamma_x = 1.816$, $d_0 = 1.5$.

The dependence on the number of fractions is caused by the accumulation of irreparable sublethal injury. The addition of

another equal fraction of neutron dose increases the tissue reaction more rapidly than the addition of another fraction of $\gamma$-ray dose. The plateau region of the lines corresponds to the fact that both neutron and $\gamma$-ray dose cannot be further increased by fractionation beyond some critical dose per fraction /e.g., [9,37] /.

If given reaction is considered in a general case, the number of fractions must be determined from Eq. (5a) /$T \leq T_0$ is assumed/. The RBE values are shown in Fig. 4 for reactions 1.0 - 2.0 for mouse and pig skin. The dependence for given reaction is nearly linear as could be expected. RBEs for greater reaction are somewhat greater as greater number of fractions is necessary for given $d_n$. There exists recovery from the additional fraction of $\gamma$-rays but little or no recovery from neutron additional dose. Similar effect can be also noticed in the case of other tissues [14,15,37].

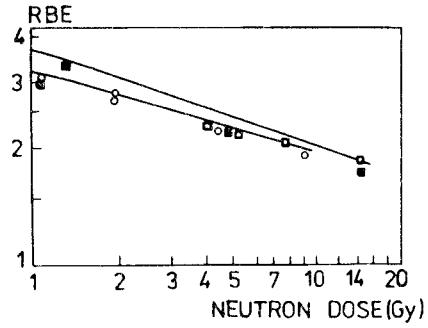



Fig. 4. The dependence of RBE on the dose per fraction in log-log plot. The same experimental points as in Fig. 3 are shown. The lines represent theoretical RBEs for reaction 1.0 /lower curve/ and 2.0 /upper curve/ of mouse skin.

## REPOPULATION AND RBE

Denekamp et al. showed that the time dependence of an average mouse skin reaction is the same both for X-rays and neutrons. Later on several other authors reached the same conclusion both for single exposure to heavy ions and for fractionated irradiation with mesons [34]. It seems that the repopulation parameters could be assumed the same for some tissues independently of the quality of radiation used.

Under this assumption several remarks concerning RBE can be done. The repopulation only increases DF factor as $DF = DFT + \beta_0(T - T_0)$ and so RBE should not differ for given dose per fraction which corresponds, however, to lower reaction. The same reaction is reached with decreased RBE as the dose per fraction is greater.

The results of fractionated irradiation of skin with X-rays, neutrons and pions have been interpreted in terms of NSD and



plotted in log-log plot as the dependence of $D/T^{0.11}$ of the number of fractions /e.g., [9] /. This interpretation was shown to be incorrect as it overestimates the role of time factor /underestimates the role of fractionation/ for small number of fractions and underestimated the role of time /overestimates the role of fractionation/ for great number of fractions [19,21,38].

The estimations of skin lethality and repopulation parameters have been done for X-rays, neutrons /$E_d$= 16 MeV and $E_d$=50MeV/, and pions /the value of $\Delta$ could not be established, it will be assumed as equal to zero/:

$\gamma_x = 1.816$ $d_0 = 1.5$ $\beta_{0x} = 9.0$ $DFT_x = 235$ for X-rays, Eq.7

$\gamma_n = 1.40$ $\Delta_n = 0.15$ $\beta_{0n} = 0.9$ $DFT_n = 23.5$ for neutrons, $E_d = 16$ MeV

$\beta_{0n} = 1.1$ $DFT_n = 30.3$ for neutrons, $E_d = 50$ MeV

$\gamma_\pi = 1.255$ $\Delta_\pi = 0$ $\beta_{0\pi} = 1.2$ $DFT_\pi = 31.3$ for pions, Eq.6.

The lethality parameters have been determined from experiments with fractionated irradiation. The repopulation parameter $T_0$ has been taken equal to 18 days. The rate of growth in the case of X-rays has been estimated to $\beta_{0x}$=9 near to the values determined for pig skin and SAS/TO skin. The other parameters $\beta_{0n}$ for neutrons, $\beta_{0\pi}$ for pions can be determined if the ratios $DFT_x/DFT$ or the ratios $\alpha/\alpha_x$ are known. The first ratios can be determined from the experiments with cell tissue, the second - from the experiments with cells in vitro. The ratios could be extimated to $DFT_x/DFT_n$ = 10.0 for $E_d$= 16 MeV neutrons, $DFT_x/DFT_n$ = 7.75 for $E_d$= 50 MeV neutrons, $DFT_x/DFT_\pi$ = 7.5 for mesons.

Similar values could be determined from in vitro experiments: $\alpha_n/\alpha_x$ = 9.5±2 for neutrons of various energies, $\alpha_\pi/\alpha_x$ = 6.3 ± ±1.5 for pions. Strandquist's graphs are shown in Fig. 5 and compared with experimental data points for X-rays, neutrons /$E_d$= 16 MeV/, and pions. The formulae give predictions in a broad range of independent variables. For example, Fig. 6 shows the dependence of the total dose necessary for given effect /reaction 1.0/ on the overall treatment time for 8-9 fractions. There are experimental data for X-radiation; theoretical curves are shown for neutrons and pions. A rough estimation has been done also for protons $DFT_p$= 188, $\beta_{0p}$ = 7.2, the lethality parameters taken from X-rays.

The ratios $DFT_x/DFT$ determined from the cell tissue experiments well correspond to the values of $\alpha/\alpha_x$ determined from in vitro experiments. It suggests that the in vitro experiments really can be utilized in fractionated radiation therapy.

The formulae (5) - (7) are not valid for small dose fractions if $T > T_0$ [21].

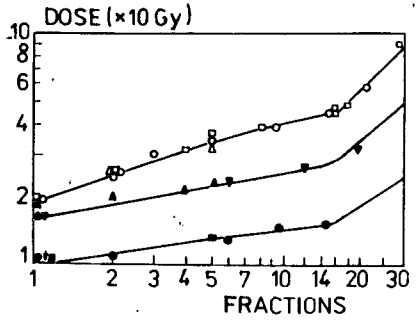



Fig. 5. The Strandquist graph for various beams: (o) pig skin, (□) mouse skin, (Δ) mouse skin; (▲) mouse skin, mesons, (▼) mouse skin, mesons; (●) pig skin, neutrons $E_d$ = 16 MeV, (■) mouse skin, neutrons $E_d$ = = 16 MeV. Data taken from literature.

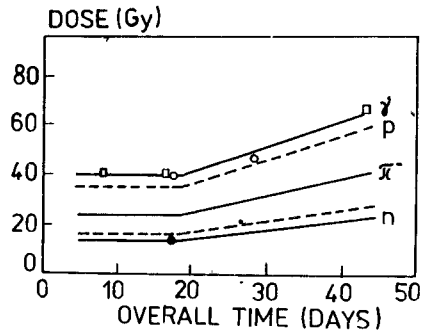



Fig.6. The dependence of the dose producing given end-point /reaction 1.0/ on the overall time for N = 8÷9 fractions. The experimental data points are the same as in Fig.5.The lines for mesons and protons are determined for Bragg peak region; full line for neutrons corresponds to $E_d$=16MeV, dashed line to $E_d$ = 50 MeV.

## DISCUSSION

The biological effects of non-standard irradiation are intensively investigated at present time owing to the fact than neutron, proton and $\pi$-meson beams become available for therapeutical purpose. On the other hand, the mechanisms of biological effects of radiation have not been fully understood yet and further investigation is urgently needed. The results of such experiments cannot be transferred into radiotherapy immediately; general quantitative laws should be discovered and utilized in the practice. It is difficult to interprete experiments without referring to model equations and parameters; in the case of radiobiological experiments for therapeutical purposes the formulae are an indispensable aid.

The suggested formulae are based on the hypothesis that the repopulation can be treated as simple autogenesis after some latent period[19–22]; further assumptions have been added for neutrons and other particles. Cell lethality has been described by Huggett's formula. It is reasonable to assume single-hit inactivation for high-LET particles. Therefore, the exponential-quadratic formula may become more suitable in some cases. Assuming the existence of non-recoverable injury / Δ part of the dose



delivered/ we can derive: $DF = N \cdot d + \beta_0 \cdot d^2 \cdot N[1 + \Delta(N-1)]$, where $\beta_0 = \beta/\alpha$ , $\alpha$ and $\beta$ are the parameters of the formula.

It would be desirable to describe cell survival by the radiobiological model equation. Such a model should include physical factors /microdosimetry, tract structure/, biological processes /various levels of intracellular repair/ and chromosome organization.

The analyses have been performed for acute tissue reaction. It seems that human skin parameters are near to the mouse or pig skin ones and so the graphs in Fig. 5 and Fig. 6 would probably correspond to acute human skin reaction of small fields. Late reactions are, however, important in the radiotherapy of malignant tumours. Further experimental and theoretical work is needed.

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Козубек С. E19-82-820
Кумулятивный эффект нестандартного излучения

На основе модели кинетики ткани анализируются экспериментальные данные по кумулятивному действию разных типов излучений. Рассматривается зависимость ОБЭ от дозы на фракцию. Показано, что восстановительные процессы на уровне ткани приводят к уменьшению ОБЭ. Критикуется фактор ТДФ для нейтронов.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

Препринт Объединенного института ядерных исследований. Дубна 1982

Kozubek S. E19-82-820
Cumulative Effect of Non-Standard Radiation

Experimental data on cumulative effect of non-standard beams are evaluated and analysed in terms of cell kinetic model. The dependence of RBE on the dose per fraction is derived. The repopulation is shown to diminish RBE. The "neutron TDF" proposed for clinical purposes is criticized.

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

Preprint of the Joint Institute for Nuclear Research. Dubna 1982