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THE BIOLOGICAL EFFECTS AND RBE OF THERMAL NEUTRONS

Many reports on the biological effects and the clinical application of various kinds of high LET radiation including neutrons, protons, heavy particles and pions are accumulated in the present time. As to neutrons, fast neutrons are mainly focused in biological and clinical researches. However, we have a few reports on the biological effects of thermal neutrons which are the final form of fast neutrons losing their energies in materials. The thermal neutrons in the present article mean the neutrons having the energies of 0.250E-7 MeV, though thermal neutrons are described as the neutrons having energies below the effective cadminium cut-off which is in the neighbourhood of 0.5 eV [14]. There are some reasons why the biological effects of thermal neutrons are not studied intensively. That is, it is not easy to study the effects of thermal neutrons. Furthermore, the clinical application of thermal neutrons is less attractive in comparison with fast neutrons. In this meaning, the study on epithermal neutrons is also in a similar situation.

The problems to be dissolved in radiation biology of thermal neutrons are classified into two categories.

A. Physicotechnological factors.

1. The complexity of nuclear reactions induced with thermal neutrons in tissues.

2. The contaminations of γ-rays and other kinds of neutrons in the thermal neutron beam, or, the difficulty to get practically pure thermal neutron fluence.

3. $^{10}B(n,\alpha)^{7}Li$ reaction.

4. $^{31}P(n,\gamma)^{32}P$ reaction.

5. The others.

B. Biological factors.

1. The comparative radiosensitivity of normal and malignant cells to thermal neutrons.

2. The distributions of elemente, eepecially, ^{1}H, ^{10}B, ^{14}N, ^{23}Na or ^{31}P in cells.

3. The volumes and the shapes of materials irradiated to thermal neutrons.

4. The biological effects of mixed radiation.

5. The characteristics of biological effects of high LET radiation.

These factors are discussed mainly in reference to the radiobiological experiments in this article.

1. THE TECHNOLOGICAL PROBLEMS

One of most important keypoints to realize the experimente in radiation biology of thermal neutrons, is to provide a radiation field to get the massive and practically pure thermal neutron beam contaminated hardly with the primary γ-rays and other kinds of neutrons. We can not cut down comletely the primary γ-rays and neutrons except thermal neutrons. It is essentially impossible to get the absolutely pure thermal neutron beam in the nuclear reactor beam. The primary γ-rays mean those induced not only in the core of nuclear reactor but also in the wall of reactor, in the present article. The problem is how we get the radiation field of thermal neutrons with low γ-thermal neutron ratio and low Cd ratio.

Fortunately, we are able to use the radiation field meeting our expectation in the Research Reactor Institute of Kyoto University (KUR). The field is constructed according to the bismuth scatter method [17]. When there is no material to induce the secondary γ-rays in radiation field, the γ-thermal neutron ratio is about 0.005 at 15 cm from the bismuth window surface set in the lead wall of reactor, where the thermal neutron fluence of $0.96 \times 10^{9}\ n/cm^{2}$ is assumed to one rem and the exposure in R of primary γ-rays is divided by the rem value of thermal neutrons. The ratio is about one order less than the values of other institutions in the world published before our publication [17]. Table 1 shows the γ-thermal neutron on the technological constitutions and the characteristics of our radiation field of thermal neutrons for biomedical purposee were reported in 1975 [17].

Table 1

γ-rays contamination in nuclear reactor beams

Reactor	Institution	Power (KW)	γ/n^*
KUR	Kyoto Univ.	5,000	0.005
HTR	Tokyo Inst. of Nucl. Indust.	100	0.08
MRR	BNL	1.000	0.029
MITR	MIT	5,000	0.020
BARN	ITAL	100	1.47

*$0.96 \times 10^9 n/cm^2$ is assumed to 1 rem.

2. THE INDUCTION OF THE SECONDARY γ-RAYS

The biological substances, that is, cells, culture medium, mammalian body or many experimental equipments induce the various energies of γ-rays when these are irradiated to thermal neutrons. In them, γ-rays of $^1H(n, \gamma)^2H$ should be taken into account in biological experiments, because of the large amount of hydrogen element and the comparatively high energy of 2.22 MeV of γ-rays. For these reasons, the volume of culture medium should be kept minimum to reduce the secondary γ-rays induced in the medium. The secondary γ-rays induced in the experimental equipments are far large in comparison with the dose of thermal neutrons or the dose of thermal neutrons or the primary γ-rays and increase the absorbed dose of cells, if unsuitable experimental conditions are used. The typical cases are shown in Figure 1 [33]. The contribution of γ-rays is shown in thermal neutron fluence to γ-rays($n\ cm^{-2} R^{-1}$) in the figure.

The curve I, II, III or IV shows the experimental condition incubator, a circulating water to keep temperature in the incubator, a plastic cell container and a conventional experimental wooden wagon were used. The materials of these equipments include a large amount of hydrogen and other elements which induce the secondary γ-rays through nuclear reactions with thermal neutrons. On the contrary, under the condition IV, a thin Teflon box, a dry circulating air to keep temperature in the box, a Teflon cell container and a special paragamma wagon constructed with Teflon, bismuth and a small amount of aluminium, were used. These materials induce

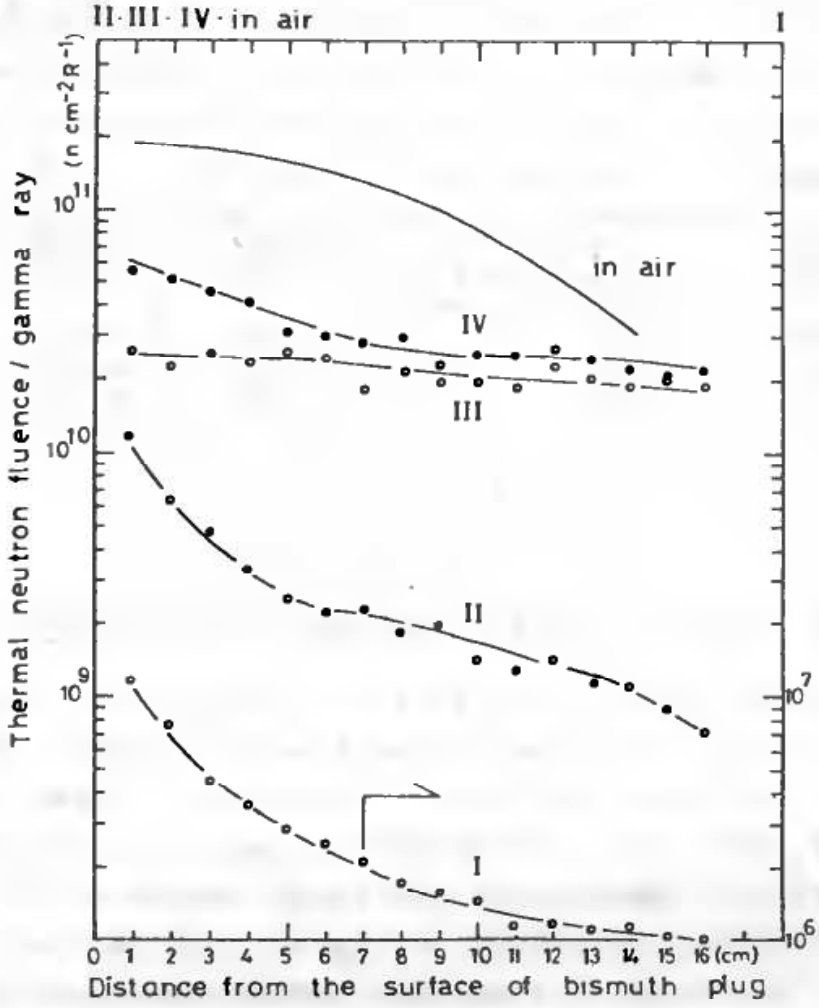

Fig. 1. The thermal neutron fluence/γ-rays retios in various experimental conditions (I, II, III, IV) and in air

Table 2

The various experimental conditions tested to irradiation of nuclear reactor beams of KUR

	Experiments			
	I	II	III	IV
Materials of apparatus	Glass	Glass	Teflon	Teflon
Shape of apparatus	Large cylinder	Large cylinder	Box	Box
Flow of warm water	(+)	(-)	(-)	(-)
Cell container	Commercial plastic microtest plate	Commercial plastic microtest plate	Teflon microtest plate	Teflon small cylinder
Paragamma wegon	(-)	(-)	(+)	(+)

a few secondray γ-rays. Table 2 shows these experimental conditions [33].

Our experimental conditions on cells have been carried out under the condition IV, though the ratio in the figure is smaller under the condition IV than in air which is a kind of ideal eituation.

3. THE DISTRIBUTION OF ELEMENTS IN CELLS

To estimate absorbed dose of thermal neutrons, it is requested to know not only the macroscopic but also the microscopic distributions of elements. The distributions of chemical substances need not be taken into account, because the problem is the distribution of elemente which induce the deleterious nuclear reactions due to thermal neutrons, here. Tabla 3 shows the main nuclear reactions occuring in biological materials [17].

Considering the amount of element in tissues, the released energy and the cross-section to thermal neutrons, ^{1}H, ^{10}B and ^{14}N are the most important elemente, which induce the reactions of

$^{1}H(n,\gamma)\,^{2}H$

$^{14}N(n,p)\,^{14}C$

$^{10}B(n,\alpha)\,^{7}Li$ or $^{10}B(n,\alpha)\,^{7}Li^{*}$.

The nuclear reaction of $^{31}P(n,\gamma)\,^{32}P$ plays the decided role to cell killing, if ^{31}P in DNA molecules transmutates to ^{32}P [19]. The actual killing effect of thermal neutrons to amoebae was higher than the killing effect estimated with the absorbed doses in the nuclear reaction. The nuclear reaction of $^{23}Na(n,\gamma)\,^{24}Na$ is also noticeable, because of the unnegligible amount of ^{23}Na in culture medium and the high released energy with 2.75 MeV (maximum) of ^{24}Na, but the physical half-life of ^{24}Na is short, that is, 14.96 hours. The details of macroscopic distribution of elements in various tissues of the standard man are published [13]. The amount of ^{10}B is negligibly little in mammalian tissues. Table 4 shows the distribution of various biological materials reported by many authors [32].

For these reasons, it is better to measure the amounts of hydrogen and nitrogen in cells before the experiment. It should be

Table 3

Main nuclear reactions of thermal neutrons in biological materials

Element	Natural abundence (%)	Thermal neutron cross-section (b)	Reaction	Released energy (MeV)	Comment
^{1}H	99.985	0.332	$^{1}H(n,\gamma)^{2}H$	2.22	
^{2}H	0.0145	0.0005	$^{2}H(n,\gamma)^{3}H$	6.25	
^{12}C	98.892	0.0034	$^{12}C(n,\gamma)^{13}C$	4.95	
^{13}C	1.11	0.0009	$^{13}C(n,\gamma)^{14}C$	8.17	
^{14}N	99.635	1.81	$^{14}N(n,\gamma)^{14}C$	0.63	
^{15}N	0.365	0.000024	$^{15}N(n,\gamma)^{16}N$	2.48	
^{16}O	99.759	0.00018	$^{16}O(n,\gamma)^{17}O$	4.14	
^{17}O	0.037	0.24	$^{17}O(n,\gamma)^{14}C$	1.82	
^{18}O	0.204	0.00021	$^{18}O(n,\gamma)^{19}O$	3.95	
^{10}B	19.61	3837	$^{10}B(n,\gamma^{*})^{7}Li$	2.79 (γ=0.48)	93.9%
			$^{10}B(n,\gamma^{*})^{7}Li$	2.79	6.1%
^{11}B	80.39	0.005	$^{11}B(n,\gamma^{*})^{12}B$	3.37	

Table 4

Distributions of main elements in biological materials g%

Conger and Giles (1950) Tradescantia: 11(H), 1 (N)
King et al. (1955) Drosophila: 10(H), 4(N)
NBS Handbook No. 75 (1961) wet tissues: 73(O), 12(C), 10(H), 4(N)
Bach and Caswell (1968) standard man: 65(O), 18(C), 10(H), 3(N)
ICRU #13 (1969) as listed above
Moutschen and Moutschen-Dahmen (1969) Nigell seeds: 20(O), 57(C), 9(H)
Davis et al. (1970) HeLa: 65(O), 18(C), 10(H), 1.4(N)
Zamenhof et al. (1975) tissues: 71(O), 15(C), 10(H), 3.5(N)
Kawai et al. (1976) amoeba, M-type: 58(C), 10(H), 23(N) P-type: 58(C), 10(H), 23(N)
Saigusa and Ujeno (1978) CHO: 65(O), 18(C), 10(H), 3(N)

noticed that the amount of hydrogen changes depending upon tha phase of cell cycles [4]. For example, hydrogen is more in M-phase than in S-phase.

4. THE DOSE ESTIMATION

The main factors giving absorbed dose into cells are thermal neutrons and γ-rays in our experimental conditions. Even if we can use the experimental conditions suitable to thermal neutron radiation, we can not remove culture medium which induce the secondary γ-rays. The volume of experimental equipments and the geometrical relationships of equipments in radiation field also modify the thermal neutron fluence and the absorbed doses of primary and secondary γ-rays. For these reasons, it is requested to measure the thermal neutron fluence and the absorbed doses of γ-rays at each position in equipments at each irradiation. The thermal neutron fluence is measured with a gold foil end γ-rays are measured with TLD powder

in a special small Teflon tube to avoid the induction of secondary δ-rays in TLD containers themselves.

4.1. THE DOSE OF THERMAL NEUTRONS

There are some estimations of absorbed dose with the fluence. The conversion factor of 9.36×10^8 n cm^{-2} to 1 rem was published [12]. However, this is the value which should be used in the field of health physics but not in the field of radiation biology. There is an internationally authorized value, that is, 0.272E-01 to $10^7 \times (\mu_k/\rho)E$ in erg $cm^2 g^{-1}$ tissue approximation [14]. The Kerma factor of thermal nutrons is not given to tissue approximation in ICRU #26 [15]. And a relationship of Kerma/fluence was given in a graph [30]. But these values are different from each other, because of the difference in basic data to calculation. Depending on the values used in calculation, the finsl data of calculation must be different from each other. For this reason, it is approvable to use the values calculated by authors themselves in each material in each experiment. The conversion from thermal neutron fluence to absorbed dose is described in detail [5, 22]. In these references, the Kerma values are not the same due to the difference in the orginal date [3, 30].

As the first spproximation, the following equation is used in our experiment.

$$D\ \text{rad} = \sum_i \sum_l (\text{rad} \cdot \text{cm}^{-2} \cdot n^{-1}) p_l f(\text{cm}^2) + 1.77 \times 10^{-10} p_H(g)\, \Phi(\text{cm}^{-2})\, \Delta t(\text{cm}),$$

where $\frac{E}{i}$ is the Kerma value in rad of element i, that is ^{14}N, p_i is the abundance of element i, p_H is the weight of hydrogen in one gramme of material, Φ is the thermal neutron fluence and Δt is the thickness of material.

If neutrons with various energies are included in the nuclear reactor beams, we have to calculate the absorbed dose to neutrons with each energy. For example, Z a m e n h o f [37] calculated these values using LASL 42 of S a n d m e i r et al. [29] with the code of ANDY of H a r r i s [11] and the data of ANISN of E n g l e [10].

The important point is that man can not use directly eny other datum to calculate the absorbed dose in his experiment.

4.2. THE PROBLEM OF VOLUME OF MATERIALS

As shown in the above mentioned equation, the absorbed dose of γ-rsys of $^{1}H(n,\gamma)\ ^{2}H$ is modified by the volume, that is, the Δt vslue. For example, it is about 5×10^{-4} cm for a cell but it is s vslue listed in the table on average geometrical fsctors of L o e v i n g e r et al. [24] for the tumours or bodies. The difference in Δt values of cells and bodies reaches more than several orders. The value is roughly 0.89 cm for our Teflon tube of cell container in our experiments.

4.3. THE DOSE OF $^{10}B(n,\alpha)^{7}Li$ REACTION

In connection with the neutron capture therapy, this is the most important reaction. The energy of α or ^{7}Li is 1.492 MeV or 0.852 MeV and the average track length of both particles is about 8.96 μm or 4.81 μm in water, respectively. For the length, the reactions occuring not only in cell nucleus but slso in cell plasma or even on the surface of cell membrane can destruct the DNA molecules. On the other hand, if the reaction occurs more than 9 μm far from cells in culture medium, the absorbed dose in cells must be zero. The dose of the reaction in cells has to be calculated depending on the experimental conditions. The details of dose calculation of the reaction are reported by K i t a o [21]. The absorbed dose of α and ^{7}Li in the model tumours and in the wall of fine blood vessels is able to be estimated with his "combined LET" method and the geometrical factors. This calculation gives the mathematical bsses to the neutron capture therepy to brain tumours. On the hand, an approach to estimete the input with the number of track crossing the cell nucleus developed [22].

It is hardly to express quantitatively the contribution of the reaction to total absorbed dose depending upon the amount of ^{10}B. Some authors axpress it in RBE value [8, 25, 28], in maximum usuable depth (MUD) [37], in boron accumulation effect (BAE) [17], in boron localization effect (BLE) [22]. Which expression does reflect the biological effects, especially, in radiation biology and neutron capture therapy, is the problem hardly to answer at the present time. Therefore, the better expression could be the absorbed

dose in rad or Gy. Expressing the contribution with the absorbed dose, man can compare the biological effects in verious papers. The example is shown in Table 5. Here, the data calculated with the track structure theory [6, 28] are compared with those calculated with the track number theory [22]. The track structure theory will be discussed later. In spite of differences in assumptions to calculation, the doses inducing low surviving fraction are similar to each other. This is favourable in practice of neutron capture therapy, too.

T a b l e 5

Comparison of data calculated with tha track structure theory [6, 28] and the track number theory [22]

Ref.	Object	Neutron Fluence	^{10}B concentration $\mu g/g$	
			0	20
[28]	CHO cell	10^{12}	40 red $6.5 \cdot 10^{-1}$*	200 rad 1.1×10^{-1}*
[22]	Rossi's solution	10^{12}	20 rad $7.0 \cdot 10^{-1}$*	184 rad 1.0×10^{-1}*

*Surviving fraction.

5. THE CHARACTERISTICS OF BIOLOGICAL EFFECTS OF MIXED RADIATION AND THE MODIFICATION OF THE EFFECTS

The nuclear reactor beams are a typical mixed radiation. The problem whether the biological effects of mixed radiation are simply added effects of each component of mixed radiation or not, is interesting. A report [1] singled out that the biological effects of the nuclear reactor beams followed with γ-rays are different from those of irradiations in the reversed order. This result suggests that the repair processes of damages due to thermal neutrons are different from those of γ-rays damages, qualitatively and/or quantitatively.

The characteristics of nuclear reactor beams are observed too in the chromosome aberration. Table 6 lists the data on chromosome aberration in cells of Muntiacus muntjak by KUR beam [27]. As Table 6 shows, the multitype and isochromatid aberrations are observed dominatly after the irradiation of nuclear reactor beams. This result suggests that the chromosomes suffer more seriously due to irradiation of thermal neutron beams than of γ-rays. And this can give an explanation to the results of A k a b o s h i et al. [1].

Table 6

Chromosome aberration of Muntiacus muntjak cells after irradiation to the nuclear reactor beams of KUR

Absorbed dose (rad)*	Scored metaphases	Normal chromosome**	Abnormal chromosome**		
97.4	100	68%	32%	minites	1%
				multi.	10%
				iso.	17%
				dicentrics	4%
186.6	100	47%	53%	gaps	2%
				minutes	3%
				multi.	21%
				iso.	20%
				atypical	2%
				dicentrics	5%
331.7	100	32%		gaps	2%
				multi.	47%
				iso.	13%
				trirad.	3%
				dicentrics	3%

* Whole doses of KUR beams.** Treatment of colcemid: 26 hrs, collection time: 6 hrs.

The absorbed dose of thermal neutrons increases with the increase in the amount of hydrogen element in materials. If some parts of hydrogen in materials exchenge to deuterium, the absorbed dose of thermal neutrons must reduce to decrease the biological effects. This speculation was certified on the inactivation of DNase I [2]. However, the killing effect of thermal neutrons to mammalian cells increased in culture medium including D_2O which is less the amount to reduce the plating efficiency of cells [34]. This result suggests that the deuterium element interfer to biological processes, probably to the repair processes of radiation damages of mammalian cells. The results are listed in Table 7.

The deuterium enhancement ratio (dER) was higher in irradiation of X-rays with low LET than in irradiation of nuclear reactor beam with comparatively high LET.

Table 7

The deuterium enhancement ratio (dER) to the killing effect to HeLa cells due to the nucleer reactor beams of KUR

Radiation	20% of D_2O	(dER)	
		D_o	10% of survival
X-rays	(-)	1.00	1.00
X-rays	(+)	1.07	1.27
Nuclear reactor beams	(-)	1.00	1.00
Nuclear reactor beams	(+)	1.04	1.05

6. THE THEORETICAL ESTIMATION OF DOSE AND RBE OF THERMAL NEUTRONS

The estimations of dose-survival curves using the track structure theory [6] were reported by us [28]. The four parameters of the theory to estimate curves were E_o = 190 rad, m = 2.5, σ_0 = = 4.6×10^{-7} cm^2, κ = 1400 to hamster cells in our experimental conditions, where E_0 means a D_0 value, m is an extrapolation number, σ_0 is a plateau value of the extrapolated cross-section, κ is $z^2/\beta^2 \times 1/4$, z is an effective charge number and β is a relative speed. Here, the dose meaned the whole dose of primary and secondary γ-rays and thermal neutrons. Figure 2 shows the calculated dose-survival curves of hamster cells including various concentrations of ^{10}B element. The ratio of KUR was roughly correspondent to 0.005 in air [16]. The dotted lines were named the "isosurvival curves". The RBE value is about 3.0 on 10^{-8} surviving fraction at the γ-rays contemination of 0.005.

Let us compare these values to other our experimental data on subcutaneous B16 melanoma in mouse body [35] and on HeLa cells [33]. The data were shown in Table 8.

The RBEs of nuclear reactor beams on the tumour level similar to those on the cellular level, in spite of the difference in materials. The RBEs of thermal neutrons on the tumour level slightly smaller than those on the cellular. This is based on that the contribution of γ-rays induced in tumour-bearing mouse body is not taken into account in the calculation on thermal neutrons. These data also were smaller than the theoretically estimated data in Figure 3. This is caused by the condition that the contamination of γ-rays in practical experimental conditions is larger than that estimated theoretically in air. The RBE of 1.3~1.4 at the surviving fraction of 0.01 is correspondent upon the ratio of 0.1. The ratio is roughly correspondent upon the ratio calculated by us with the data in

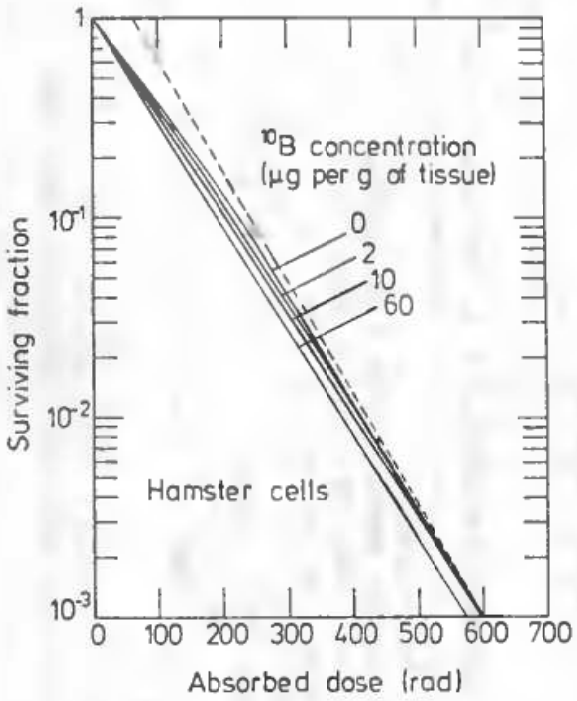

Fig. 2. Calculated survival curves of hamster cells irradiated by thermal neutrons. A dotted line is the extrapolated linear portion of the survival curve for zero ^{10}B concentration

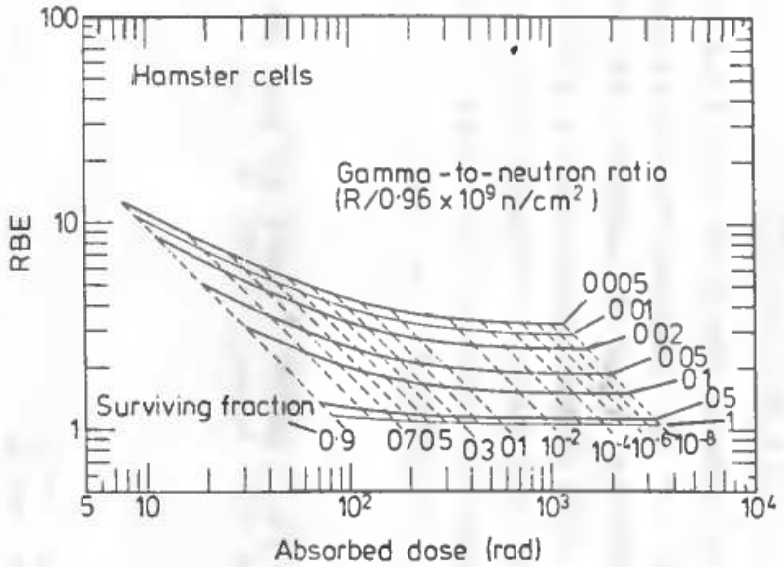

Fig. 3. Calculated RBE values of thermal neutron beams with different γ-to-neutron ratios for hamster cells. The ^{10}B concentration is zero μg per g of tissue

ref.[33]. The value could be accepteble to the experimental condition. Table 9 shows the published RBE values [31].

7. CONCLUSION

As described above, there are some difficulties in the study on the biological effects of thermal neutrons, comparing with the study on fast neutrons. However, these are not essentially undissolved problems. The keypoint to study the biological effects of thermal neutrons is the close corporation with biologists, chemists, physists and technologists. The study is the typical inter-faculty science in this meaning.

Table 8

The RBE values of nuclear reactor beams of KUR and the thermal neutrons on Melanoma B16 tumours [35] and HaLa cells [33]

Surviving fraction	10%	3.7%	1%
RBE (on the tumour level)			
nuclear reactor beams	1.56	1.44	1.32
thermal neutrons	2.22	1.94	1.80
RBE (on the cellular level)			
nuclear reactor beams	1.40	1.44	1.44
thermal neutrons	2.53	2.33	2.17

Table 9

The RBE values of various radiations in nuclear reactor beams

Matsumura et al. (1962)		
seeds of Triticum monococcum flavescens		
chromosome aberration, α and ^{7}Li		23 ± 10
chlorophyl mutation, α and ^{7}Li		29 ± 10
Davis et al. (1969)		
cell killing, MITR beam		1.51
neutrons		2.2
gamma		0.8
Davis et al. (1970)		
cell killing, α		3.7
Zamenhof et al. (1975)		
tissue, more than 200 rad, thermal neutron		2.0
gamma		1.0
α and ^{7}Li		3.7
Kanda et al. (1975)		
tiussue, p and α		5
Saigusa and Ujeno (1978)		
cell killing, more than 200 rad		
protons and α		2.3 ~ 2.5

It is especially interesting that we can arrange freely the macroscopic and microscopic doses and the kind of radiations with the change in amounts of elements in materials.

The problems on neutron capture therapy and its basic problems are not refered in the present article. One of problems to be dissolved before realizing the therapy, is to improve the chemical substances of carriers bringing a large amount of ^{10}B into tumours. This is a chemical, pharmaceutical and pharmacological studies on ^{10}B and the knowledges on boron chemistry will be useful means. The clinical data on neutron capture therapy are accumulating in Japan. These problems and data will be discussed in other opportunities.

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EFEKTY BIOLOGICZNE I WZGLĘDNA EFEKTYWNOŚĆ BIOLOGICZNA NEUTRONÓW TERMICZNYCH

S t r e s z c z e n i e

Zastosowanie neutronow termicznych w terapii nowotworowej wiąże się z koniecznością zbadania wielu problemów fizykotechnologicznych i radiobiologicznych dotyczących tych neutronów. Problemy fizykoche-

miczne obejmują m. in. minimalizację produkcji wtórnego promieniowanie gemma, określenie rozkładu pierwiastków w komórkach i ocenę dawki promieniowania neutronowego. Problemy radiobiologiczne dotyczą m.in. addytywności efektów biologicznych różnych rodzajów promieniowania oraz rediouczulającego działania deuteru i ^{10}B.

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