INVESTIGATION MADE AT CERN INTO THE BIOLOGICAL EFFECTIVENESS OF HIGH-ENERGY RADIATIONS

J. Baarli, A.H. Sullivan and M. Bianchi
European Organization for Nuclear Research (CERN)
Geneva, Switzerland

and

M. Quintiliani
Istituto Superiore di Sanità
Rome, Italy

1. INTRODUCTION

The radiation environment near high-energy accelerators and in space poses problems of estimating the hazard to human beings from exposure to very high energy radiation. High-energy radiation deposits energy by nuclear interactions. This type of interaction is not normally occurring with radiations of conventional energies.

For radiation protection purposes a quality factor is defined to take account of the different hazards involved with different types of energies of radiation. This factor is normally calculated for high-energy radiation on the basis of the ICRP-recommended QF-LET relationship[1]. Very little experimental verification exists of the validity of this procedure and it is therefore thought essential that radiobiological studies are carried out as the first step towards making an independent assessment of the validity of these calculations.

The need for more experimental evidence of the biological effectiveness of very high energy radiation arises also in the possible therapeutic applications of these radiations.

A basic problem in carrying out radiobiology experiments is the low intensity of secondary particle beams (neutrons, pions, etc.) that are available. The biological systems have therefore to be carefully chosen such that they have adequate sensitivity, and the low dose-rate response of the system must first be studied in detail using X-rays.

2. BEAM MEASUREMENTS AND PROPERTIES

The high-energy particle beams available for radiobiological experiments at CERN are from the 600 MeV Synchro-cyclotron which can be made to produce beams of protons, neutrons or pions. The properties of these beams of interest for radiobiology are summarized in Table 1. The proton beam is the extracted beam from the machine. This is transported into the underground beam area and defocused to give as large an area of uniform cross-section as possible. The extracted beam is normally more than 10^{11} protons/sec. This intensity can be reduced to about 10^{8} protons/sec using collimators and defocusing the beam at its exit from the cyclotron.

A high-energy neutron beam is produced by irradiating a beryllium target in the machine. The neutrons produced by proton collisions in the target are taken out down a beam pipe in the forward direction. The design of the machine shielding is such that the target has to be placed at a radius in the machine where the protons are at 400 MeV and then there is a suitable beam pipe through the shielding wall to obtain the neutron beam. The neutrons have a broad energy distribution with maximum intensity at about 350 MeV[2]. The magnetic field of the accelerator turns any charged particles emitted from the target and the beam contamination is small.

Pions are produced in an internal target in the machine. The target position and machine magnetic field determines the momentum of the pions that will be deflected into a beam channel. The pion beam is turned after passing through the channel to rid it of neutral particle contamination, and then focused on to the irradiation position. The beam is positive or negative depending on the direction of the cyclotron magnetic field. Measurements in these beams have been published elsewhere[3].

The dose-rate in the beams varies strongly with depth in an absorber. Dose as a function of depth (normalized to unity at a depth of 1 g/cm^2) for the beams used for radiobiology is shown in Fig. 1. The dose in the neutron beam builds up rapidly due to the creation of charged secondaries. The effect is less pronounced in the proton beam, where the major contribution to the dose is from

direct ionization by the protons. In the pion beam the pions lose energy while slowing down in the absorber. When near the end of their range, the dose increases due to the increased rate of energy loss and for negative pions, capture reactions liberate an additional 20 MeV[3]. The peak from positive pions is the Bragg peak plus the energy loss of the muon produced in pion decay.

As the dose-rate varies with depth it is necessary to know precisely the thickness of material in front of the dosimeter with which dose measurements are made. The dose-rate is determined with a parallel-plate tissue-equivalent ionization chamber[2]. The spacing of the plates is 3 mm so that the position of the sensitive volume can be accurately located. On account of the small diameter of the pion beams a chamber with a collector of 20 mm diameter is used. The geometry of both these chambers is known so that the dose-rate can be calculated from the current output. They are also calibrated against known gamma sources.

3. THE BIOLOGICAL SYSTEMS

The choice of suitable biological test systems for investigating the overall biological effectiveness of the high-energy radiation is important and has to be related to the properties of the beams used. For the 600 MeV proton beam where there is a sufficiently high dose-rate but where some limitations exist on beam size, the LD_{50} 30 days of mice was chosen together with testes and thymus weight loss[4]. These tests are classical and are well tested. In addition one series of experiments based on lethal mutations in Drosophila has been carried out[5].

Different criteria for the choice of suitable biological systems for radiobiological measurements in the neutron and pion beams have to be applied[6]. The most critical requirement arises from the low dose-rates available, but beam size and dose variations with depth have also to be considered. In the light of this the possible biological systems are severely restricted for these investigations of secondary beams.

A biological system suitable for experiments in beams of very low dose-rates has to fulfil several requirements: i) high radiosensitivity in order that the significant dose-effect curves may be provided within a practically feasible exposure time; ii) high degree of dose-rate independence since variation in dose-rate may affect the radiation response by facilitating or preventing repair of damage or by variations in cellular radiosensitivity as the cells progress in their cycle during exposure. Maturation and differentiation processes during exposure may also result in a change of cell population in multi-cellular systems.

Using plants as multi-cellular organisms it is possible, by using a low temperature, to slow down cell population changes. However, this cannot be applied to mammals. In addition to the above mentioned criteria come the following: iii) appropriate size of the system to ensure a homogeneous exposure of the whole target volume, and, finally, iv) good reproducibility with the absence of abscopal effects. In other words, only the dose delivered by the radiation in the target tissue or organ should be effective in producing the response under investigation.

Considering these requirements, three different mammalian tests were selected for experimental investigations using the beams of pions and neutrons with low dose-rates. These were:

(a) lethality of type B spermatogonia[7)]

(b) weight loss of testes[8)]

(c) lens opacification[9)],

all of which were made using mice. These were not only chosen in view of the limitation imposed by the properties of the radiation beams and their dose-rates, but also because the effects in mammals are more likely to be similar to effects in human beings.

4. SUMMARY OF RESULTS OF RADIOBIOLOGICAL EXPERIMENTS MADE AT CERN

The relative biological effectiveness of high-energy radiations determined from the experiments carried out so far at CERN are summarized in Table 2. The RBE values range from 1 to 6 depending

on radiation, system studied and to some extent on the range of dose and dose-rate employed. The RBE of the 600 MeV proton beam is very near to unity on account of the fact that the major proportion of energy deposition is by direct ionization from the protons and these seem to mask any effect of nuclear interactions. The RBEs in the neutron beams and the capture region of the negative pions are similar. In these cases a large proportion of the energy deposition is from nuclear spallation reactions. The RBE values for spermatogonia survival are given for 50% survival when compared to X- or Co-60 radiation. The survival curves obtained with this system when using radiation capable of producing nuclear interactions tend to show an inverse shoulder. This is illustrated in Fig. 2, which shows the survival of spermatogonia after irradiation in the 400 MeV neutron beam. This effect is also observed with negative pions[10]. These differences in shape between survival curves with high-energy radiation and X or gamma radiation makes the RBE very dose-dependent. RBE as a function of dose, deduced from the spermatogonia survival curves, is shown in Fig. 3. At very low doses the RBE becomes very high, although because of the difficulty of accurately drawing the survival curve as the dose approaches zero, it is impossible to determine the precise value above an RBE of about 10.

5. DISCUSSION

The RBE values given in Table 2 fall in the same range as those found using more conventional radiation energies. A comparison with results of other investigations is shown in Table 3. For type B spermatogonia survival there is a tendency for the RBE to increase with increasing neutron energy. For testes weight loss and lens opacification the RBEs show a spread without any apparent systematic dependence on neutron energy.

The straightforward application of these results to problems of radiation protection in high-energy radiation environments is difficult and only generalizations can be made. It appears that the RBE of high-energy neutrons is at least as high as that for 14 MeV neutrons whereas the quality factor, used to take account of the RBE

in radiation dose estimation for protection purposes, indicates a systematic decrease in effectiveness above about 1 MeV[1]. Although extrapolation of these radiobiological findings to human beings involves some gross assumptions, the fact that the effectiveness of high-energy radiation also appears to increase as the dose decreases is something that should not be ignored.

ACKNOWLEDGEMENTS

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FIGURE CAPTIONS

Fig. 1. Relative dose-rate variation with depth in water for a 600 MeV proton beam, a 400 MeV (Max) neutron beam and negative and positive pion beams.

Fig. 2. Per cent survival of spermatogonia type B of mice exposed to the 400 MeV neutron beam (pure beam and at maximum build-up) and to X-rays.

Fig. 3. RBE as a function of dose from survival of spermatogonia type B.

Table 1

Beams from 600 MeV Synchro-cyclotron
used for radiobiology

	Energy (MeV)	Beam strength	Useful diameter (cm)	Dose-rate at 1 g/cm^2 (rad/h)	Dose-rate at max. build-up (rad/h)	Depth of max. dose-rate (g/cm^2)	Contamination
Protons	600	10^8-10^{11}/sec	14	50-50,000	60-60,000	10	Small
Neutrons	400 max.	3.5×10^5/cm^2/sec	18	6	10	20	<8% gamma contribution to dose at 1 g/cm^2
Pions $\pm$	80-110	4×10^5/sec	2	Dose-rate 4 rad/h over volume 2 cm diameter in stopping region			10% of peak dose-rate from muons + electrons

Table 2

Summary of results of radiobiological experiments carried out at CERN

Radiation		Biological tests		Reference radiation	RBE values		Ref.
Beam	Energy	System	Tests		In beam	At max. build-up	
Protons	600 MeV	Mice	LD_{50} 30 days	250 kVp X-rays	0.98	-	4
Protons	600 MeV	Mice	Testes atrophy	250 kVp X-rays	1.03	-	4
Protons	600 MeV	Mice	Thymes atrophy	250 kVp X-rays	1.00	-	4
Protons	600 MeV	Drosophila	Mutation	250 kVp X-rays	1.00	-	5
Neutrons	400 MeV (E_{max})	Mice	Spermatogonia type B ED50	^{60}Co and 250 kVp X-rays	3.7	2.7	7
Neutrons	400 MeV (E_{max})	Mice	Testes atrophy	250 kVp X-rays	2.3	1.6	8
Neutrons	400 MeV (E_{max})	Mice	Lens opacities	250 kVp X-rays	5.9	2.1	9
Neg.pions	Stopped region	Mice	Spermatogonia type B ED50	^{60}Co and 250 kVp X-rays	3.7	-	6
Pos.pions	Stopped region	Mice	Spermatogonia type B ED50	^{60}Co and 250 kVp X-rays	2.3	-	6

Table 3

Summary of RBE values for neutrons

	RBE	Ref.
Intermediate and type B spermatogonia survival		
2 - 5 MeV neutrons	1.10	11
14.1 MeV neutrons	2.38	11
400 MeV	3.70	7
Testes weight loss		
Fission	4.64	12
3 MeV neutrons	2.95	12
6 MeV neutrons	4.53	13
14.1 MeV neutrons	2.21	12
400 MeV	2.27	8
Lens opacification		
0.43 MeV	7.3 - 8.9	14
1.8 MeV	5.6 - 6.6	14
400 MeV	5.9	9

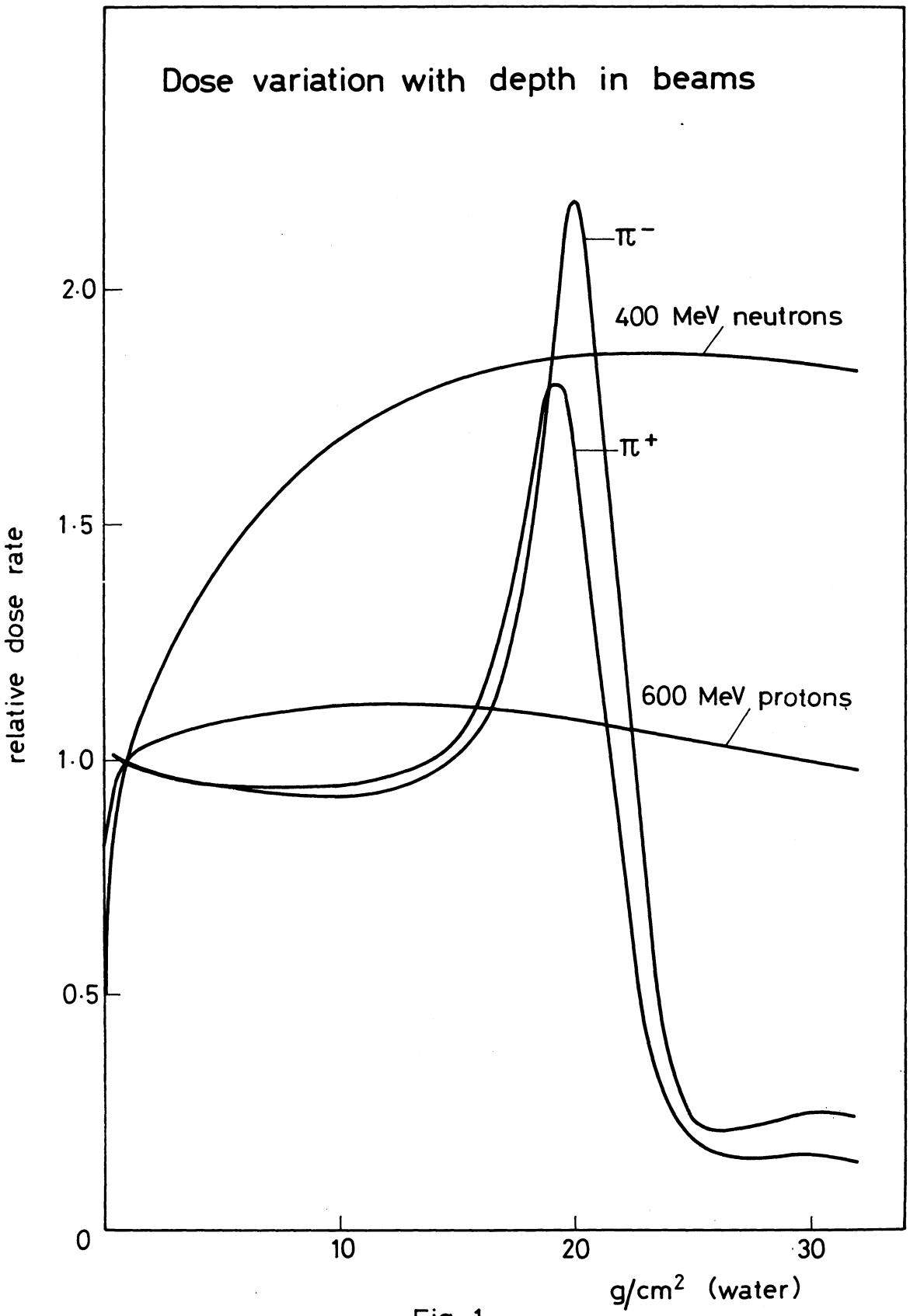
Dose variation with depth in beams
relative dose rate
2·0
1·5
1·0
0·5
0
10
20
30
g/cm² (water)
π⁻
400 MeV neutrons
π⁺
600 MeV protons

Fig. 1

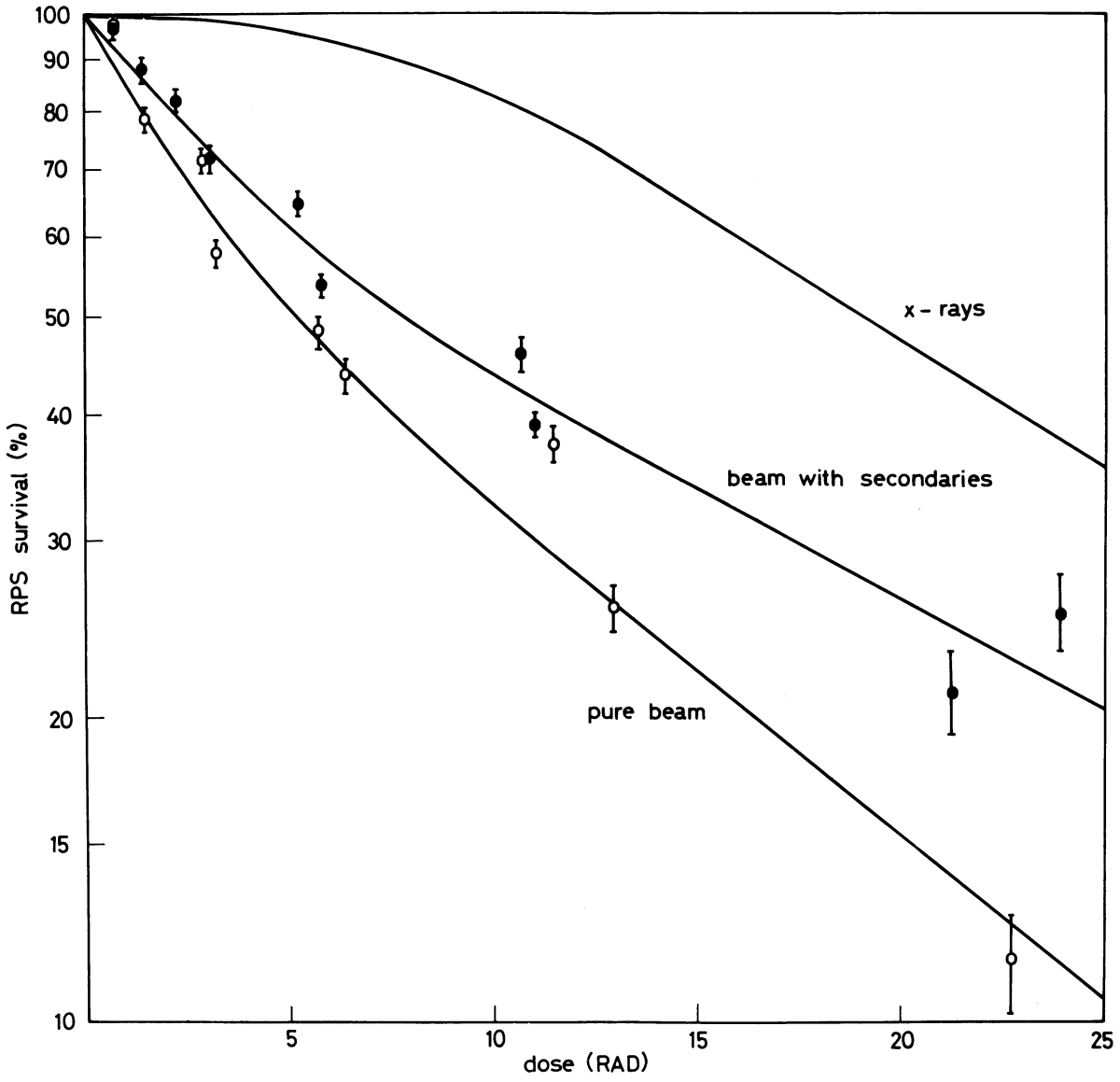
100
90
80
70
60
50
40
30
20
15
10
RPS survival (%)
5
10
15
20
25
dose (RAD)
x - rays
beam with secondaries
pure beam

Fig. 2

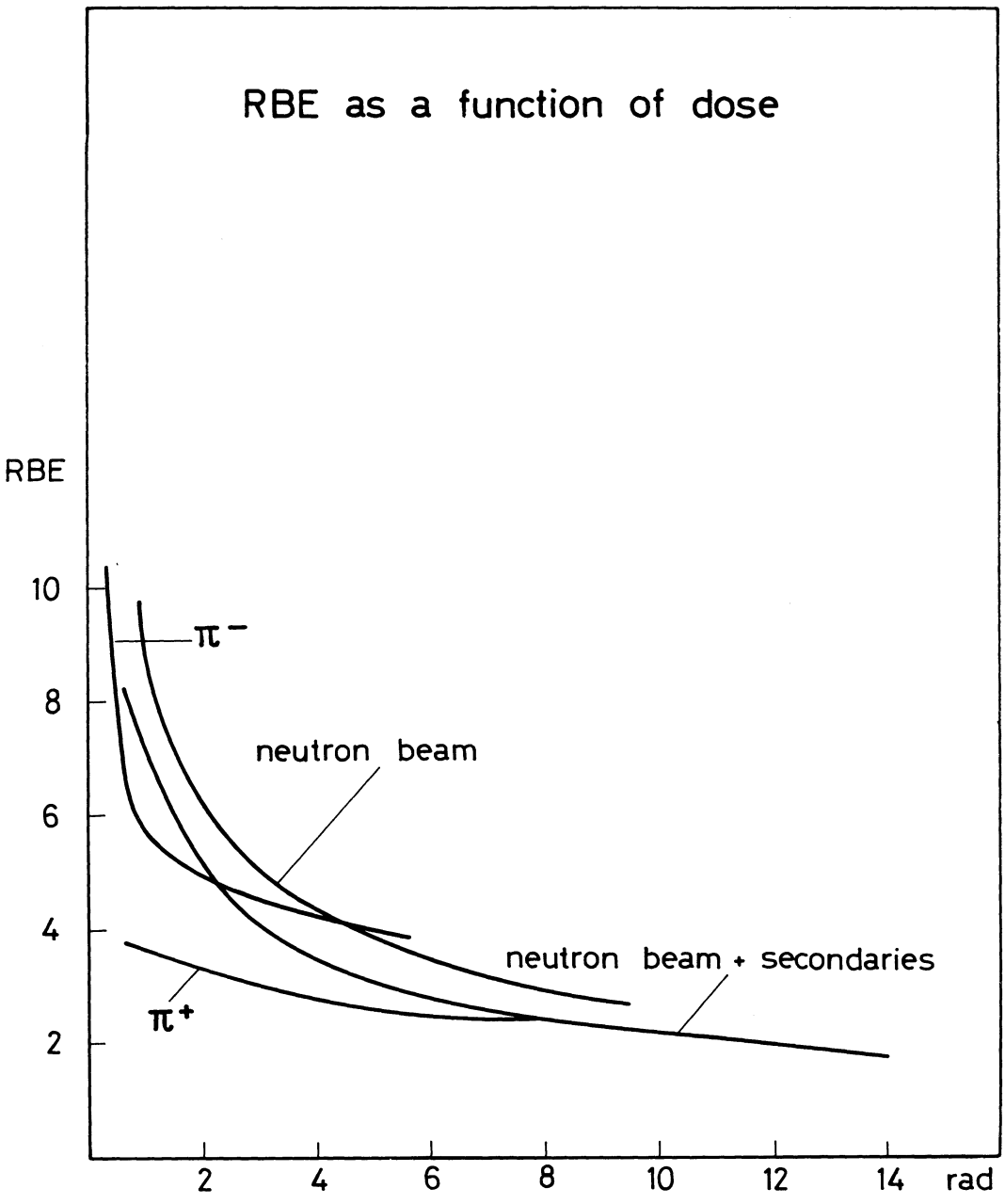
RBE as a function of dose
RBE
10
8
6
4
2
π −
neutron beam
neutron beam + secondaries
π +
2
4
6
8
10
12
14
rad

Fig. 3

Paper: Investigation made at CERN into the biological effectiveness of high-energy radiation

DARDEN: Several years ago we reported [Int. J. Rad. Biol 12, 435 (1967)] for lens opacification with 14 MeV neutrons a RBE between that for 400 MeV neutrons and low-energy neutrons: a value of about 4.5 with respect to γ-rays; with X-rays this would be perhaps three or less.

WIDEROE: Have you measured the RBE for negative pions also before the Bragg peak? Raju (I met him three weeks ago) is now doing such measurements, using human kidney cells, and he has found that RBE is highest on the peak. I also spoke with Boyd at Stanford University and he has calculated the amount of nuclear interactions of the negative pions on the track in water also before the peak is reached. There are quite a lot of them.

BAARLI: No, we have so far not made any attempt to measure the RBE before the Bragg peak. I would expect that the RBE values before the peak would be lower than on the maximum, and further that it would increase on the back part of the peak. In the beam itself I would expect a rather low RBE value. The irradiation conditions for biological studies of the pion beams is very complicated and I would not be surprised if there will be several RBE values for pions proposed even when using the same biological end point. I would like to refer to Jim Turner's paper concerning this problem where some information regarding parameters influencing the irradiation conditions will be given.

NEARY: I should like to ask Dr. Baarli two questions. First, have biological experiments been made for the proton beam after passage through tissue build-up absorbers? Second, would he comment on the fact that the Bragg peaks for the π-meson beams (plus and minus) were so much more pronounced than for the proton beam -- one might have expected that the protons, being heavier than the π-mesons and so less scattered and straggled, would have given the sharper Bragg peak.

BAARLI: We have carried out an experiment in the 600 MeV proton beam by exposing bean roots at about 1 g/cm^2 and 10 g/cm^2 of water. These bean roots have been measured as to their growth in 10 days and further we are also studying the formation of micronuclei. The results we have so far have been compared with results you have presented many years ago and we are confident that they are good. However, it remains to do the X-ray exposures before the data can be made available.

Your second question regarding the shape of the positive and negative pion curve compared to that of protons is not very easy to answer, because the shape of the peaks is dependent upon a number of parameters like: the initial momentum spread, the beam size and energy, as well as detectors used. I would like to refer you to the paper presented by Jim Turner this afternoon where these parameters will be discussed further.

MASSUE: Je suis surpris que dans votre courbe donnant la dose en fonction de la pénétration de particules vous n'ayez pas une plus grande différence entre les faisceaux de π^- à l'arrêt et les faisceaux de π^+ en fin de parcours : car les π^- à l'arrêt sont absorbés par les noyaux en donnant des particules primaires provenant de l'absorption du π^- sur un cluster et des particules d'évaporation venant de la désexcitation du noyau résiduel; tandis que les π^+ à l'arrêt se désintègrent en donnant $\pi^+ \rightarrow \mu^+ \rightarrow p$? La contribution nucléaire des π^- à l'arrêt doit être bien supérieure à celle des π^+.

BAARLI: It is correct that the dose is not very different in the two cases. In this connection you should remember that the interactions in the case of positive and negative pions are distributed over a relatively great volume. Another element arises from the resolution of the detector used, which in our case was 2 cm in diameter.

ELLIS: I am interested in the inverted shoulder of the cell survival curve. If the convex shoulder means that there is sublethal damage, which is associated with an extrapolation number greater than unity, does the concave "inverted shoulder" curve imply that, since with small doses there is an extrapolation number of less than unity, there might be a "protection" factor activated by the radiation? About 1946 I speculated in an editorial

in the BJR that since life began in a field of relatively intense radiation there might be some form of built-in protection persisting in life surviving to the present day and these observations have made me wonder again.

BAARLI: This is a very interesting problem and I do not have enough knowledge to be able to give any answer to this. The possibility of a built-in protective mechanism in biology can probably not be excluded.

BURCH: I would suggest that the simplest interpretation of the type B survival curve is in terms of a heterogeneous cell population. If we run two type-A (exponential) survival curves, of different D_0 values, then the result is a type-B survival curve. We then have to account for the type-C survival curve obtained with low LET X-irradiation experiments. If the shoulder on the curve for each type of cell is large enough and the D_0 values are not too dissimilar, then two (or more) type-C survival curves can result in a type-C curve. These days it is customary to attribute type-C curves to repair machinery that operates effectively at low but not at high dose.

BAARLI: We have also suggested the idea about mixed population as an explanation for the inversed shoulder of the survival curves shown. On the other hand, I would agree with you in saying that this is a possible explanation but might not necessarily be the right one. We have in mind to look closer into this problem and see if it is possible to find out something about the cause of the inverse shoulder for these experiments.

BOOZ: What kinds of tissue-equivalent plastics and gases are you using, and how far are these materials really tissue-equivalent for the high-energy reactions that you are studying?

BAARLI: We are using the Shanka plastic and the Rossi Failla tissue-like gas. Your question regarding the tissue-equivalence of these materials for high-energy radiation seems to me to be a standard one and in spite of the fact that I would not expect any great difference compared to tissue, I would have liked to have seen experiments made such that we could have settled this question once and for all.

SHAW D.F.: How were the values for RBE for the different radiations evaluated in your experiments, and to what extent is it valid to make comparisons with measurements at different energies carried out in other laboratories.

BAARLI: The RBE values given are for 50% survival and are calculated as the quotient between the γ-dose and neutron doses measured in rad/s. The doses were measured with a tissue-equivalent ionization chamber filled with tissue-equivalent gas, 3 mm plate spacings and 60 mm diameter. The calibration of this was made by calculations and compared to measurements using a calibrated γ-source. The calculated and measured values agreed when assuming 31.6 eV per ion pair formed.