# HIGH-LET RADIATIONS IN CLINICAL RADIOTHERAPY

Proceedings of the 3rd Meeting on Fundamental and Practical Aspects of the Application of Fast Neutrons and other High-LET Particles in Clinical Radiotherapy, The Hague, Netherlands, 13–15 September 1978

SPONSORED BY THE RADIOBIOLOGICAL INSTITUTE OF THE ORGANIZATION FOR HEALTH RESEARCH TNO. RIJSWIJK. THE NETHERLANDS

Editors

### G. W. BARENDSEN, Rijswijk

### J. J. BROERSE, Rijswijk

K. BREUR, Amsterdam

PUBLISHED AS A SUPPLEMENT TO THE EUROPEAN JOURNAL OF CANCER



PERGAMON PRESS

OXFORD · NEW YORK · TORONTO · SYDNEY · PARIS · FRANKFURT

U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
CANADA	Pergamon of Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario M2J1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia
FRANCE	Pergamon Press SARL. 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, 6242 Kronberg-Taunus, Pferdstrasse 1, Federal Republic of Germany

Copyright © 1979 Pergamon Press Ltd.

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means: electronic, electrostatic, magnetic tape, mechanical, photocopying, recording or otherwise, without permission in writing from the publicher. publishers.

First edition 1979

British Library Cataloguing in Publication Data

Britisn Library Cataloguing in Publication Data Meeting on Fundamental and Practical Aspects of the Application of Fast Neutrons and Other High LET Particles in Clinical Radiotherapy, 3rd, The Hague, 1978 High LET radiations in clinical radiotherapy. 1. Cancer – Radiotherapy – Congresses 2. Radiotherapy, High energy – Congresses 1. Title II. Barendsen, G. W. III. Broerse, J. J. IV. Breur, K. 616.9'94'0642 RC271.R3 79-40323 ISBN 0-08-024383-5

Published as a supplement to the European Journal of Cancer

Printed and bound in Great Britain by William Clowes (Beccles) Limited, Beccles and London

# Contents

G. W. Barendsen, J. J. Broerse and K. Breur	ix
Sessions I and II. REPORTS ON CLINICAL EXPERIENCE Second preliminary report of the M. D. Anderson study of neutron therapy for locally advanced gynecological tumors L. J. Peters, D. H. Hussey, G. H. Fletcher and J. T. Wharton	3
Observations on the reactions of normal and malignant tissues to a standard dose of neutrons M. Catterall	11
Results of fast neutron radiotherapy at Amsterdam J. J. Battermann and K. Breur	17
Results of fast neutron beam radiotherapy pilot studies at the University of Washington T. Griffin, J. Blasko and G. Laramore	23
Results of clinical applications with fast neutrons in Edinburgh W. Duncan and S. J. Arnott	31
Fast neutron project at Fermilab G. A. Lawrence	37
Clinical observations of early and late normal tissue injury and tumor control in patients receiving fast neutron irradiation R. Ornitz, A. Heskovic, E. Bradley, J. A. Deye and C. C. Rogers	43
Results of clinical applications of fast neutrons at Hamburg–Eppendorf H. D. Franke	51
Results of clinical applications of negative pions at Los Alamos M. M. Kligerman, S. Wilson, J. Sala, C. von Essen, H. Tsujii, J. Dembo and M. Khan	61
Results of tumor treatments with alpha particles and heavy ions at Lawrence Berkeley Laboratory J. R. Castro, C. A. Tobias, J. M. Quivey, G. T. Y. Chen, J. T. Lyman, T. L. Phillips, E. L. Alpen and R. P. Singh	67
Results of clinical applications of fast neutrons in Japan H. Tsunemoto, Y. Umegaki, Y. Kutsutani, T. Arai, S. Morita, A. Kurisu, K. Kawashima and T. Maruyama	75
Five years of clinical experience with a combination of neutrons and photons H. J. Eichhorn, A. Lessel and K. Dallüge	79

v

vi	Contents	
Hyperbaric oxygen and hypoxic cell se prospects S Dische	ensitizers in clinical radiotherapy: present state and	83
5. Disene		
Treatment at low dose rate, by low-LE B. Pierquin, E. Calitchi and R. Owen	T radiation: present status and prospects	91
Combined chemo/radiotherapy of cance radiotherapy T. L. Phillips	er: present state and prospects for use with high-LET	95
Sessions III and IV. PHYSICAL ASP	ECTS AND RADIOBIOLOGY	
Review of performance of high-LET ra D. K. Bewley	adiation sources used in clinical applications	105
Dose distributions of clinical fast neutr B. J. Mijnheer and J. J. Broerse	on beams	109
Dosimetry intercomparisons and protoc J. J. Broerse, B. J. Mijnheer, J. Eenma	ols for therapeutic applications of fast neutron beams a and P. Wootton	117
Characteristics of fast neutron sources J. B. Smathers		125
CONTRIBUTIONS ON CHARACTE	FRISTICS OF FAST NEUTRON SOURCES	120
Neutron dosimetry, radiation quality a J. Booz	nd biological dosimetry	147
CONTRIBUTIONS ON NEUTRON BIOLOGICAL DOSIMETRY	DOSIMETRY, RADIATION QUALITY AND	151
Review of RBE data for cells in cultur E. J. Hall and A. Kellerer	e	171
RBE values of fast neutrons for respon G. W. Barendsen	nses of experimental tumours	175
Neutron RBE for normal tissues S. B. Field and S. Hornsey		181
Fast neutron radiobiology H. B. Kal and A. J. van der Kogel		187
CONTRIBUTIONS ON FAST NEUT	FRON RADIOBIOLOGY	193
Dosimetry and radiobiology of negativ M. R. Raju	e pions and heavy ions	209
CONTRIBUTIONS ON DOSIMETRY AND HEAVY IONS	Y AND RADIOBIOLOGY OF NEGATIVE PIONS	213
The Committee on Radiation Oncology United States J. R. Stewart and W. E. Powers	<sup>7</sup> Studies plan for a program in particle therapy in the	237

Contents	vii
Sessions V and VI. EVALUATION OF PRESENT RESULTS AND FUTURE OF HIGH LET RADIOTHERAPY	
Evaluation of clinical experience concerning evaluation of tumour response to high-LET radiation J. Dutreix and M. Tubiana	243
Evaluation of normal tissue responses to high-LET radiations K. E. Halnan	251
The application of RBE values to clinical trials of high-LET radiations H. R. Withers and L. J. Peters	257
Doses and fractionation schemes to be employed in clinical trials of high-LET radiations J. F. Fowler	263
Review of protocols for high-LET radiotherapy in the United States S. Kramer	267
Clinical trials with fast neutrons in Europe K. Breur and J. J. Battermann	273
Summary of discussion on multi-centre collaboration in clinical trials with high-LET radiations G. W. Barendsen	277
Concluding remarks on the future of high-LET radiotherapy G. W. Barendsen, K. Breur and J. J. Broerse	281
List of participants of the 3rd meeting on Fundamental and Practical Aspects of the Application of Fast Neutrons and other High-LET Particles in Clinical Radiotherapy	283

## Review of RBE data for cells in culture<sup>1</sup>

ERIC J. HALL\* AND ALBRECHT KELLERER†

\*Radiological Research Laboratory, College of Physicians & Surgeons of Columbia University, New York, N.Y., U.S.A.

†Institut Für Strahlenkunde der Universität, Wurzburg, Germany

**Abstract**—The relative biological effectiveness has been compared for ten neutron facilities used for clinical radiotherapy in the United States, Japan, Continental Europe and Great Britain. Mammalian cells in culture were used and in order to exploit the precision of which the in vitro technique is capable, facilities were intercompared in pairs, within a given experiment on the same day. Tables are presented of the relative potency of the various neutron beams. Determinations of the oxygen enhancement ration (OER) have been made for a wide range of neutrons produced by cyclotrons or linear accelerators using the deuteron or proton on beryllium reactions. The OER increases with increasing energy of the charged particle used from 1.5 for 15 MeV d<sup>+</sup>  $\rightarrow$  Be to 1.9 for 101 MeV p<sup>+</sup>  $\rightarrow$  Be. For a clinically used 14-MeV d<sup>+</sup>  $\rightarrow$  T generator the OER was found to be 1.6.

### Introduction

The clinical trial of neutrons involves a substantial cost and investment of effort. Consequently, the need for full cooperation between the few centers using these particles has been recognized from the outset. Each of the neutron therapy beams in clinical use is characterized by a different energy spectrum, and as a consequence there are significant variations in their biological effectiveness. To facilitate the pooling of experience and the comparison of clinical results a number of investigators have compared the various neutron beams using a variety of biological systems, and early results have already been published (Hall, 1977; Hall et al., 1978). The present report summarizes the results of a new series of biological intercomparisons performed by three groups of investigators using mammalian cells cultured in vitro.

The design of these experiments was based upon two important considerations.

(a) It is a characteristic of cell-culture experiments that variations *within* an experiment are much smaller than those between experiments. Consequently, to exploit the precision of which the *in vitro* technique is capable, neutron facilities were intercompared in pairs, within a given experiment, using cells from a common culture irradiated on the same day.

(b) A standardized treatment fixture was used

at all facilities, constructed of lucite, with space for six tissue culture flasks, and provision for an ionization chamber to be inserted into the jig to determine the dose received at the position occupied by the cells. Full build-up was ensured because the cells were overlaid with 2 cm of tissue culture medium. Α substantial international effort to achieve compatible dosimetry was mounted by the physicists at the various installations engaged in neutron therapy, as a consequence of which there is agreement to within  $\pm 1.5\%$  for dose measurements in air. The use of the standard treatment fixture was an attempt to extend the compatible dosimetry to a practical set-up for the irradiation of cell cultures.

### **RBE** intercomparison

The neutron facilities visited, together with their principal characteristics, are listed in Table 1. For the most part, this paper will be concerned with our own experiments in the United States, Japan, Britain and Continental Europe, in which Chinese hamster V79 cells were used for RBE intercomparisons. In a typical experiment, appropriate numbers of cells were plated into Falcon tissue culture flasks and allowed to attach by overnight incubation at  $37.5^{\circ}$ C. The flasks were then filled brimful with medium, sealed, and the temperature lowered to  $17^{\circ}$ C. For each

<sup>1</sup>Based on work performed under Contract EP-78-S-02-4733 from the United States Department of Energy, and Grant Number CA-18506 awarded by the National Cancer Institute, Department of Health, Education and Welfare.

Fermilab Tamvec	Batavia Illinois College	Production process	Energy of accelerated particle (MeV)	Mean neutron energy (MeV)
	Station, Texas	p <sup>+</sup> →Be	66	25
NRL/Manta	Washington, D.C.	d <sup>+</sup> →Be	50	19.3
Univ. Wash.	Ohio Seattle	d <sup>+</sup> →Be	35	14.3
	Wash.	d <sup>+</sup> →Be	25	10
MRC, Hammersmith MRC, Edinburgh	London Edinburgh	d+→Be	22	8
	-	d+ → Be	16	7
Antoni van Leuwenhoek	Amsterdam	d+→Be	15	6
Hospital		d⁺→ T	_	14
NIRS	Chiba Tokyo	d <sup>+</sup> → Be	30	12
	Fermilab Tamvec NRL/Manta NASA/Glanta Univ. Wash. MRC, Hammersmith MRC, Edinburgh Antoni van Leuwenhoek Hospital	FermilabBatavia IllinoisTamvecCollege Station, TexasNRL/MantaWashington, D.C.NASA/GlantaCleveland, OhioUniv. Wash.Seattle, Wash.MRC, Hammersmith MRC, EdinburghLondon EdinburghAntoni van Leuwenhoek HospitalAmsterdam Tokyo	FermilabBatavia IllinoisProduction processTamvecCollege Station, Texas $p^+ \rightarrow Be$ NRL/MantaWashington, D.C. $d^+ \rightarrow Be$ NASA/GlantaCleveland, Ohio $d^+ \rightarrow Be$ Univ. Wash.Seattle, Wash. $d^+ \rightarrow Be$ MRC, Hammersmith Leuwenhoek HospitalLondon Edinburgh $d^+ \rightarrow Be$ NIRS IMSChiba Tokyo $d^+ \rightarrow Be$	FermilabBatavia IllinoisProduction processaccelerated acceleratedTamvecCollege Station, Texas $(MeV)$ Station, Texas $p^+ \rightarrow Be$ 66NRL/MantaWashington, D.C. $d^+ \rightarrow Be$ 50NASA/GlantaCleveland, Ohio $d^+ \rightarrow Be$ 35Univ. Wash.Seattle, Wash. $d^+ \rightarrow Be$ 25MRC, Hammersmith 

Table 1. Clinical neutron facilities intercompared

experiment, half of the flasks were transported to the Naval Research Laboratory (NRL) cyclotron in Washington, D.C., and half to one of the other facilities listed in Table 1. The cells were transported in insulated water-jacketed carriers, with the temperature maintained at 17°C. It was found by trial and error that this temperature prevents cell division and progression through the cycle, while maintaining high plating efficiency (which was а characteristically in excess of 80%) for a period of 24 hours. Irradiations were performed simultaneously at the two neutron facilities to be compared, and the cells returned to an incubator for 8 days to assess the proportion able to form colonies.



Fig. 1. The relative potency, or RBE relative to the Naval Research Laboratory, as a function of mean neutron energy, for various facilities in clinical use.

The data from each experiment were analysed by a new non-parametric method, which evokes no form for the dose-response relationship. The survival data for the two neutron beams to be compared were fitted by curves of the same shape, the only constraint being that the curve must be convex upwards, and the dose factor necessary to allow a common fit computed. This factor is then the best estimate of the relative potency or RBE difference between the two beams, based on the data from all dose levels studied. The results are shown in Fig. 1; the potency of each beam relative to NRL is plotted as a function of the mean neutron energy. The data points for accelerators using the  $d^+ \rightarrow$ Be reaction fall close to a common line indicating a gradually increasing RBE with decreasing mean neutron energy.

The data are summarized in a way that is more widely useful in Table 2, which consists of factors relating the RBE's between pairs of machines. This table also includes a summary of data collected by two other investigators. Dr. Paul Todd, Pennsylvania State University, has used T<sub>1</sub> cells of human kidney origin to intercompare a number of neutron beams in clinical use. Dr. Raymond Meyn, M.D. Anderson Hospital, Houston, Texas, used CHO cells for intercomparisons. The details of the experimental methods used by these investigators have been published previously (Gragg et al., 1976; Todd et al., 1978). Both utilized a standardized treatment fixture and most of their recent experiments were designed so that pairs of machines were compared on the same day within the same experiment, though this was not true of earlier studies. The potency factors quoted were calculated at a cell survival

	Table 2.	Relative p	otency of v	various be	ams inter	compared			
The numbers quo	ted repres	ent the d	ose (in G	ray) neces	ssary with	h the facil	lity in the	left-hand	t
column to be equiv	alent to 1	Gray with	the facilit	ty in the to	op row. (I	n each squ	are, the to	op figure i	s
due to H	E. J. Hall, t	he middle	to Paul To	odd and th	e lower to	Raymon	d Meyn.)		
IMS	Edin.	Ham.	Amst.	U.W.	Clev.	NIRS	NRL	Tam.	F

	IMS	Edin.	Ham.	Amst.	U.W.	Clev.	NIRS	NRL	Tam.	Fermi.
IMS	*	_	_		0.96		0.82	0.84		
			1.00	0.95	0.95	0.95	0.91	0.90	0.86	0.82
Edin.		*								
		1.00	—							
		1.00	-	0.95	0.95	0.95	0.91	0.90	0.86	0.82
Ham.			•							
			1.07		0.85	0.88	0.76	0.77	0.72	0.84
		1.06	1.06		1.00	1.01	0.95	0.95	0.90	0.87
Amst.				-					_	
		1.00	1.00	1 00		1.01		0.05		
		1.06	1.06	1.00		1.01	0.96	0.95	0.90	0.87
U.W.	1.04				-		0.85	0.99		
			1.18		0.00	1.04	0.89	0.91	0.85	0.99
		1.05	1.05	0.99	0.99		0.95	0.94	0.90	0.86
Clev.						-		0.95		
			1.13		0.96	1.05	0.85	0.87	0.81	0.95
		1.10	1.10	1.04	1.04	1.05	<b>.</b>	1.00	0.95	0.91
NIRS	1.22				1.18		-	1.00	0.05	
			1.32		1.12	1.17	1.005	1.02	0.95	1.11
		1.11	1.11	1.05	1.05	1.06	1.005		0.95	0.91
NRL	1.19				1.01	1.05	1.00	-		
			1.30		1.10	1.15	0.98	1.05	0.93	1.09
T		1.17	1.1/	1.11	1.11	1.12	1.06	1.05	*	0.96
Tam.							1.00	1.07	-	
			1.39		1.18	1.23	1.05	1.07	1.04	1.1/
<b>F</b> .		1.22	1.22	1.15	1.15	1.10	1.10	1.10	1.04	*
Fermi.		_	1.10		1.01	1.05	0.00	0.01	0.95	-
			1.19		1.01	1.05	0.90	0.91	0.85	

level of 0.3. In all cases, comparisons have been made on the basis of *TOTAL DOSE*, i.e. neutron and gamma-ray dose. For the European machines, consisting of a  $d^+ \rightarrow T$  generator and two lower-energy cyclotrons, the gamma-ray contribution is both larger and more variable than for the higher-energy installations in the United States.

It can be seen from Table 2 that there is, in general, close agreement between the three sets of measurements regarding potency ratios, or RBE differences, between the various neutron beams used clinically. This is particularly true for inter-comparisons between machines within the United States and also for NIRS in Japan. This reflects the greatest effort that has been made to date. By contrast, few direct Transatlantic intercomparisons have so far been completed.

The title of this paper indicates that its scope is restricted to *in vitro* data. However, recent reports (Hall *et al.*, 1978) have summarized RBE intercomparisons performed with *in vivo* systems, such as skin and jejunal crypt cells in mice, as well as for various cultured mammalian cells. The closeness of the agreement observed bears out the suggestion made in the Part II meeting (Hall, 1977) that for intercomparing two neutron beams that differ in energy by only a modest amount, it matters little which biological system is chosen. Systems and endpoints which result in widely different values for the RBE of neutrons relative to X-rays give similar values for the RBE *difference* between two closely related neutron energies. Consequently, the choice of a biological system for intercomparisons should be governed largely by its portability, repeatability and convenience.

### **OER** survey

No review of neutron data for cells in culture would be complete without reference to values obtained for the oxygen enhancement ratio (OER). During the past 2 years a standard biological technique has been used to determine the OER for neutron beams generated by the  $d^+ \rightarrow Be$  or  $p^+ \rightarrow Be$  processes, where the energy of the accelerated charged particle has ranged from 15 to 101 MeV. For these experiments hamster V79 cells were used and hypoxia produced by crowding a large number of cells into a small volume so that oxygen was consumed by respiration (Hall *et al.*, 1974). The results are shown in Fig. 2. There appears to be a



Fig. 2. Values of the oxygen enhancement ratio (OER) for various neutron beams produced by the  $p^+ \rightarrow Be$ , or  $d^+ \rightarrow T$  reactions. Experiments at the University of Maryland at 80 MeV were repeated with a thick beryllium target and with a thin Be and A1 target; the latter resulted in a neutron spectrum with a higher mean energy.

continuous increase in OER with mean neutron energy, and our experience does not confirm the lower OER at high neutron energies previously reported (Harrison *et al.* 1975, 1976). Using the same biological system, it has been shown also that a *collimated* beam of neutrons from the  $d^+ \rightarrow T$  generator at Amsterdam is characterized by an OER equal to that of the clinically used cyclotrons in the United States. The value obtained, however, is significantly *lower* than the OER previously reported for 14 MeV  $d^+ \rightarrow T$ neutrons in a scatter free environment.

Acknowledgements-The implementation of this project was totally dependent upon the cooperation and dedication of the staff at the various neutron facilities where experiments were performed. Special thanks are due to Drs. D. Bewley, J. Parnell and S. B. Field at the Hammersmith Hospital, London; Dr. Peter Bonnett at the Western General Hospital, Edinburgh; Drs. B. J. Mijnheer and K. Breur at the Antoni van Leeuwenhoek Hospital, Amsterdam; Drs. J. Broerse and G. W. Barendsen at the Radiobiological Institute TNO, The Netherlands; Drs. K. Misonon, H. Ohara, T. Inada, K. Kawashima and Dr. Umegaki at NIRS, Chiba; Dr. S. Suzuki at IMS, Tokyo; Drs. Richard Theus, Leon August, and P. Shapiro at the Naval Research Laboratory, Washington, D.C.; Dr. Juri Eenmaa at the University of Washington, Seattle; Dr. James Smathers at the Texas A&M Variable Energy Cyclotron, College Station, Texas; Dr. Miguel Awschalom at the Fermilab, Batavia, Illinois; Drs. Horton and R. Antunez of the Cleveland Clinic.

#### References

- GRAGG, R. L., R. M. HUMPHREY and R. MEYN (1976) The response of Chinese hamster ovary cells to fast neutron radiotherapy beams. 1. Relative biological effectiveness and oxygen enhancement ratio. *Radiat. Res.* 65, 71-82.
- HALL, E. J. (1977) Radiobiological intercomparison in vivo and in vitro. Proc. of Particles and Radiation Therapy Second International Conference. Int. J. Radiat. Oncol. Biol. Phys. 3, 195-201.
- HALL, E. J., S. LEHNERT and L. ROIZIN-TOWLE (1974) Split-dose experiments with hypoxic cells. *Radiology* 112, 425-430.
- HALL, E. J., H. R. WITHERS, J. P. GERACI, R. E. MEYN, J. RASEY, P. TODD and G. E. SHELINE (1978) Radiobiological intercomparisons of fast neutron beams used for therapy in Japan and the United States. Int. J. Radiat. Oncol. Biol. Phys. (in press).
- HARRISON, G. H., E. B. KUBICZEK and J. E. ROBINSON (1975) OER of neutrons from 80 MeV deuterons on beryllium. *Brit. J. Radiol.* 48, 409-410.
- HARRISON, G. H., E. B. KUBICZEK and J. E. ROBINSON (1976) OER reductions with high-energy neutrons. *Brit. J. Radiol.* 49, 733.
- TODD, P., J. P. GERACI, P. S. FURCINITTI, R. M. ROSSI, F. MIKAGE, R. THEUS and C. B. SCHROY (1978) Comparison of the effects of various cyclotronproduced fast neutrons on the reproductive capacity of cultured human kidney (T-1) cells. Int. J. Radiat. Oncol. Biol. Phys. (in press).