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Sessions V and VI. EVALUATION OF PRESENT RESULTS AND FUTURE OF HIGH LET RADIOTHERAPY

Review of RBE data for cells in culture [1]

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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 $d^+ \rightarrow$ Be to 1.9 for 101 MeV $p^+ \rightarrow$ Be. For a clinically used 14-MeV $d^+ \rightarrow$ 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. A 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°C. The flasks were then filled brimful with medium, sealed, and the temperature lowered to 17°C. For each

[1]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.

Table 1. Clinical neutron facilities intercompared

	Facility	Location	Production process	Energy of accelerated particle (MeV)	Mean neutron energy (MeV)
U.S.A.	Fermilab	Batavia Illinois	$p^+ \rightarrow Be$	66	25
	Tamvec	College Station, Texas	$d^+ \rightarrow Be$	50	19.3
	NRL/Manta	Washington, D.C.	$d^+ \rightarrow Be$	35	14.3
	NASA/Glanta	Cleveland, Ohio	$d^+ \rightarrow Be$	25	10
	Univ. Wash.	Seattle, Wash.	$d^+ \rightarrow Be$	22	8
U.K.	MRC, Hammersmith	London	$d^+ \rightarrow Be$	16	7
	MRC, Edinburgh	Edinburgh	$d^+ \rightarrow Be$	15	6
Netherlands	Antoni van Leuwenhoek Hospital	Amsterdam	$d^+ \rightarrow T$	—	14
Japan	NIRS	Chiba	$d^+ \rightarrow Be$	30	12
	IMS	Tokyo	$d^+ \rightarrow Be$	15	6

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 a high plating efficiency (which was 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.

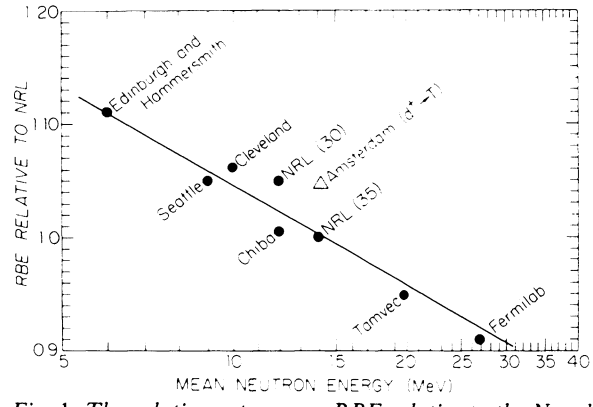

Fig. 1. The relative potency, or RBE relative to the Naval Research Laboratory, as a function of mean neutron energy, for various facilities in clinical use.

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_1 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 potency of various beams intercompared
The numbers quoted represent the dose (in Gray) necessary with the facility in the left-hand column to be equivalent to 1 Gray with the facility in the top row. (In each square, the top figure is due to E. J. Hall, the middle to Paul Todd and the lower to Raymond Meyn.)

	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		0.95	0.95	0.95	0.91	0.90	0.86	0.82
Ham.	—	—	*	—	—	—	—	—	—	—
	—	—		—	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.	—	—	—	*	—	—	—	—	—	—
	—	—	—		—	—	—	—	—	—
	—	1.06	1.06	1.00		1.01	0.96	0.95	0.90	0.87
U.W.	1.04	—	—	—	*	—	0.85	0.99	—	—
	—	—	1.18	—		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		0.85	0.87	0.81	0.95
	—	1.10	1.10	1.04	1.04	1.05		1.00	0.95	0.91
NIRS	1.22	—	—	—	1.18	—	*	1.00	—	—
	—	—	1.32	—	1.12	1.17		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		0.93	1.09
	—	1.17	1.17	1.11	1.11	1.12	1.06	1.05		0.96
Tam.	—	—	—	—	—	—	—	—	*	—
	—	—	1.39	—	1.18	1.23	1.05	1.07		1.17
	—	1.22	1.22	1.15	1.15	1.16	1.10	1.10	1.04	
Fermi.	—	—	—	—	—	—	—	—	—	*
	—	—	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 inter-comparisons 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

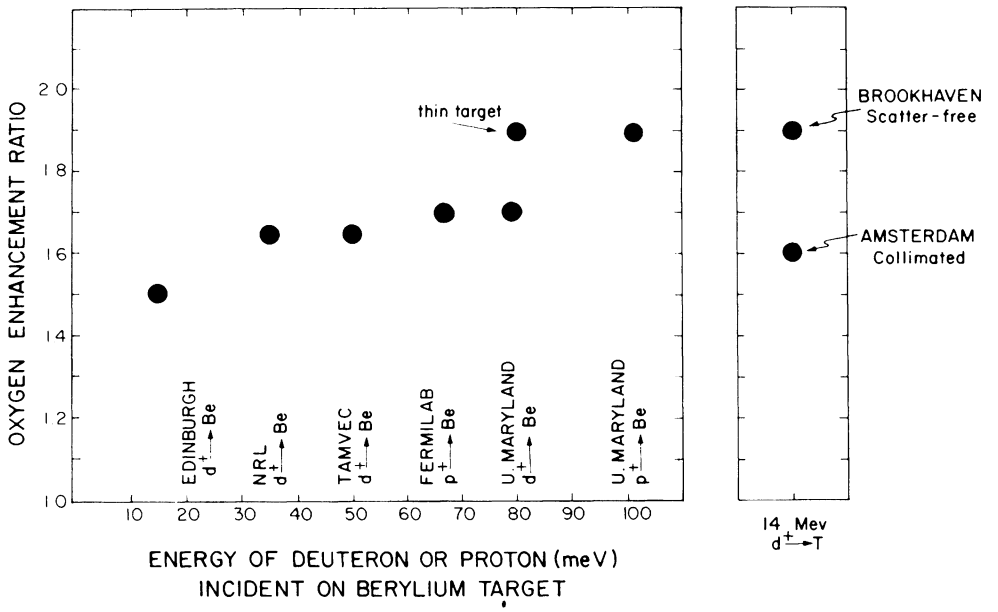

Fig. 2. Values of the oxygen enhancement ratio (OER) for various neutron beams produced by the $p^+ \rightarrow Be$, or $d^+ \rightarrow T$ reactions. Experiments at the University of Maryland at 80 MeV were repeated with a thick beryllium target and with a thin Be and Al target; the latter resulted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

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