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MANAGING EDITOR: ODDVAR F. NYGAARD

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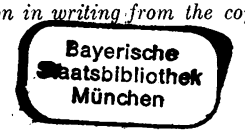

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ANNUAL MEETINGS

1974: July 13–20, Fifth International Congress of Radiation Research, Seattle, Washington

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VOLUME 55, 1973

Councilors Radiation Research Society 1973–1974

PHYSICS

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RADIATION RESEARCH 55, v–vii (1973)

CONTENTS OF VOLUME 55

NUMBER 1, JULY 1973

B. E. LEONARD AND JOHN W. BORING. *The Average Energy per Ion Pair, $\bar{W}$, for Hydrogen and Oxygen Ions in a Tissue Equivalent Gas* 1

TZU-LIN TUNG AND ROBERT R. KUNTZ. *The Reactions of Hydrogen Atoms in Aqueous Solutions: Thiols* 10

J. GITS AND G. B. GERBER. *Electrolyte Loss, the Main Cause of Death from the Gastrointestinal Syndrome?* 18

JAMES M. PARRY AND ELIZABETH M. PARRY. *Allelic Interaction at the* rad *1 Locus in Diploid Cultures of UV-Irradiated Yeast* 29

WARREN K. SINCLAIR. *N-Ethylmaleimide and the Cyclic Response to X-Rays of Synchronous Chinese Hamster Cells* 41

SHIRLEY HORNSEY. *The Effectiveness of Fast Neutrons Compared with Low LET Radiation on Cell Survival Measured in the Mouse Jejunum* 58

NORMAN N. LICHTIN, JECHIEL OGDAN, AND GABRIEL STEIN. *Fast Intramolecular Radical Processes in Reactions of Aqueous Solutions of Ribonuclease-S-Peptide and Ribonuclease-S-Protein With H Atoms* 69

M. DOMON AND A. M. RAUTH. *Cell Cycle Specific Recovery from Fractionated Exposures of Ultraviolet Light* 81

PAUL TODD. *Fractionated Ultraviolet Light Irradiation of Cultured Chinese Hamster Cells* 93

THOMAS J. DOUGHERTY. *Transannular Peroxides as Radiation Sensitizers* 101

J. L. REDPATH. *Radioprotection of Enzyme and Bacterial Systems by Dithiothreitol* 109

WATARU NAKAMURA. *Effect of Thrombocyte-Rich Plasma on X-Ray Induced Bone Marrow Death in Mice* 118

NORMAN COHEN AND MCDONALD E. WRENN. *Metabolic Characteristics of ^{241}Am in the Adult Baboon* 129

D. W. BAXTER, M. W. ROSENTHAL, AND A. LINDEBAUM. *Decorporation of Monomeric Plutonium from the Dog by Glucan and/or DTPA* 144

STANLEY R. NELSON. *Effects of Microwave Irradiation of Enzymes and Metabolites in Mouse Brain* 153

I. MALÁTOVÁ, V. DVOŘÁK, AND L. PIFFLOVÁ. *Assessment of the ^{220}Rn Fraction Retained in Mice after a Single Injection of ^{224}Ra* 160

JOHN H. DAUGHERTY AND CHARLES D. BARNES. *Sites of Radiation Sensitivity in the Visual System as Assessed by Double Light Flash* 169

F. WENDLING, P. JULLIEN, AND P. TAMBOURIN. *Hematopoietic CFA in Mice Infected by the Polycythemia-inducing Friend Virus. II. Survival of Lethally Irradiated Mice Grafted with Spleen or Bone Marrow Cells from Infected Donors* 177

W. F. WARD, R. K. MEYER, AND R. C. WOLF. *DNA Synthesis in Rat Blastocycts X-Irradiated During Delayed Implanation* 189

CORRESPONDENCE

P. M. MCILVAINE, G. LENGYEL, AND V. H. HUTCHISON. *Infrared-Induced Thermoelectric Potentials in Extracellular Recording Electrodes* 197

ANNOUNCEMENT 202

NUMBER 2, AUGUST 1973

M. ISAACSON, D. JOHNSON, AND A. V. CREWE. *Electron Beam Excitation and Damage of Biological Molecules; Its Implications for Specimen Damage in Electron Microscopy* 205

EINAR SAGSTUEN. *ESR and INDO–MO Studies of Radicals and Radical Reactions in Irradiated Single Crystals of 5-Nitro-6-Methyluracil* 225

R. W. MATTHEWS. *Effect of Solute Concentration and Temperature on the Ceric–Cerous Dosimeter* 242

TZU-LIN TUNG AND ROBERT R. KUNTZ. *Hydrated Electron Reactions with Thiols in Acidic Aqueous Solutions* 256

ERNEST C. POLLARD AND ELEANOR P. RANDALL. *Studies on the Inducible Inhibitor of Radiation-Induced DNA Degradation of* Escherichia coli 265

GEORGE M. HAHN, MALCOLM A. BAGSHAW, RICHARD G. EVANS, AND LOUISE F. GORDON. *Repair of Potentially Lethal Lesions in X-Irradiated, Density-Inhibited Chinese Hamster Cells: Metabolic Effects and Hypoxia* 280

A. BECCIOLINI, P. CASTAGNOLI, L. ARGANINI, AND G. DE GIULI. *Post-Irradiation Enzyme Activities of Rat Small Intestine: Effects of Dose Fractionation* 291

A. FERENCZ, E. J. HIDVÉGI, L. D. SZABÓ, AND V. VÁRTERÉSZ. *The Effect of Whole-Body X-Irradiation of Guinea Pigs on the Liver Ribonuclease and Ribonuclease-Inhibitor System* 304

YUTAKA OKUMURA, TOSHITERU MORITA, AND TAIJU MATSUZAWA. *The Effects of Temperature on the Dying Process of Lethally Irradiated Cultured Mouse Mammary Carcinoma Cells* 318

AHMED EL-METAINY, SHIGEMITSU TANO, KEIJI YANO, AND HIKOYUKI YAMAGUCHI. *Chemical Nature of Radiation-Induced Single-Strand Breaks in the DNA of Dormant Barley Seeds* in Vivo 324

CHRISTOPHER D. TOWN, KENDRIC C. SMITH, AND HENRY S. KAPLAN. *The Repair of DNA Single-Strand Breaks in* E. coli *K-12 X-Irradiated in the Presence or Absence of Oxygen; the Influence of Repair on Cell Survival* 334

EMMANUEL VAN DER SCHUEREN, KENDRIC C. SMITH, AND HENRY S. KAPLAN. *Modification of DNA Repair and Survival of X-Irradiated* pol, rec, *and* exr *Mutants of* Escherichia coli *K-12 by 2,4-Dinitrophenol* 346

GUNNAR SAXEBØL, THOR B. MELØ, AND THORMOD HENRIKSEN. *Electron Spin Resonance Studies of Electron Irradiated Peptides. A Single Crystal of N-Acetylglycine at 77* K 356

RAYMOND PAGEAU. *Effects of Irradiation Schedules on a Murine Ependymoma* 369

TAKASHI AOYAMA AND SHUNZO OKAJIMA. *Early Morphological Changes in the Cortical and Medullary Thymocytes of the Rat after Whole-Body Irradiation. II. Quantitative Investigation* 379

CORRESPONDENCE

LUIS FELIPE FAJARDO AND J. MARTIN BROWN. *Cardiac Mural Thrombi Caused by Radiation* 387

Obituary for Bernard Smaller 390

NUMBER 3, SEPTEMBER 1973

HAYA ZEMEL AND P. NETA. *The Mechanism of Oxidative Denitration of 5-Nitrouracil and 5-Nitro-2-Furoic Acid by Hydroxyl Radicals* 393

R. D. PHEMISTER, R. W. THOMASSEN, R. W. NORRDIN AND R. S. JAENKE. *Renal Failure in Perinatally Irradiated Beagles* 399

IZHAK J. PAUL AND ARTHUR M. ZIMMERMAN. *Macromolecular Synthesis and Cell Division in X-Irradiated* Tetrahymena 411

ERIC J. HALL AND ALBRECHT M. KELLERER. *The Biophysical Properties of 3.9–GeV Nitrogen Ions. III. OER and RBE Determinations Using* Vicia *Seedlings* 422

ERIC J. HALL AND SHIRLEY LEHNERT. *The Biophysical Properties of 3.9–GeV Nitrogen Ions. IV. OER and RBE Determinations Using Cultured Mammalian Cells* 431

A. G. UNDERBRINK, L. A. SCHAIRER, AND A. H. SPARROW. *The Biophysical Properties of 3.9–GeV Nitrogen Ions. V. Determinations of the Relative Biological Effectiveness for Somatic Mutations in* Tradescantia 437

ALBRECHT M. KELLERER AND HARALD H. ROSSI. *The Biophysical Properties of 3.9–GeV Ions. VI. Interpretation of Results* 447

D. C. SWARTZENDRUBER AND KARL F. HÜBNER. *Effect of External Whole-Body X-Irradiation on Gallium-67 Retention in Mouse Tissues* 457

B. IVANOV, A. LEONARD, AND GH. DEKNUDT. *Blood Storage and the Rate of Chromosome Aberrations After in* Vitro *Exposure to Ionizing Radiations* 469

IAN TANNOCK AND ANTHONY HOWES. *The Response of Viable Tumor Cords to a Single Dose of Radiation* 477

CLARENCE E. STYRON AND GLADYS J. DODSON. *Responses of a Grassland Arthropod Community to Simulated Radioactive Fallout* 487

CORRESPONDENCE

ELIA NUNES DE LANGGUTH AND CARL A. BEAM. *The Effects of Ploidy Upon Cell Cycle Dependent Changes in X-Ray Sensitivity of* Saccharomyces cerevisiae 501

Abstracts of Twenty-first Annual Meeting of the Radiation Research Society, St. Louis, Missouri, April 29–May 3, 1973 507

ANNOUNCEMENTS 607

AUTHOR INDEX 610

Subject Index for Volume 55 will appear in the December issue as part of a cumulative index for the year 1973.

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VOLUME 55, NUMBER 2, AUGUST 1973

Radiation Research
Volume 55, Number 2, August 1973

CONTENTS

M. Isaacson, D. Johnson, and A. V. Crewe. *Electron Beam Excitation and Damage of Biological Molecules; Its Implications for Specimen Damage in Electron Microscopy.* 205

Einar Sagstuen. *ESR and INDO–MO Studies of Radicals and Radical Reactions in Irradiated Single Crystals of 5-Nitro-6-Methyluracil.* 225

R. W. Matthews. *Effect of Solute Concentration and Temperature on the Ceric–Cerous Dosimeter.* 242

Tzu-Lin Tung and Robert R. Kuntz. *Hydrated Electron Reactions with Thiols in Acidic Aqueous Solutions.* 256

Ernest C. Pollard and Eleanor P. Randall. *Studies on the Inducible Inhibitor of Radiation-Induced DNA Degradation of* Escherichia coli. 265

George M. Hahn, Malcolm A. Bagshaw, Richard G. Evans, and Louise F. Gordon. *Repair of Potentially Lethal Lesions in X-Irradiated, Density-Inhibited Chinese Hamster Cells: Metabolic Effects and Hypoxia.* 280

A. Becciolini, P. Castagnoli, L. Arganini, and G. De Giuli. *Post-Irradiation Enzyme Activities of Rat Small Intestine: Effects of Dose Fractionation.* 291

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Yutaka Okumura, Toshiteru Morita, and Taiju Matsuzawa. *The Effects of Temperature on the Dying Process of Lethally Irradiated Cultured Mouse Mammary Carcinoma Cells.* 318

Ahmed El-Metainy, Shigemitsu Tano, Keiji Yano, and Hikoyuki Yamaguchi. *Chemical Nature of Radiation-Induced Single-Strand Breaks in the DNA of Dormant Barley Seeds* in Vivo. 324

Christopher D. Town, Kendric C. Smith, and Henry S. Kaplan. *The Repair of DNA Single-Strand Breaks in* E. coli *K-12 X-Irradiated in the Presence or Absence of Oxygen; the Influence of Repair on Cell Survival.* 334

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Obituary for Bernard Smaller. 390

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RADIATION RESEARCH 55, 447–456 (1973)

The Biophysical Properties of 3.9-GeV Nitrogen Ions

VI. Interpretation of Results[1]

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KELLERER, A. M., AND ROSSI, H. H., The Biophysical Properties of 3.9-GeV Nitrogen Ions. VI. Interpretation of Results. *Radiat. Res.* 55, 447–456 (1973).

Biological data obtained on *Vicia faba, Tradescantia,* and mammalian cells with a 3.9-GeV nitrogen ion beam are related to microdosimetric measurements. The relative biological effectiveness near the Bragg peak of the depth-dose curve can be explained on the basis of the microdosimetric data and the theory of dual radiation action. A comparison is performed with the results obtained on the same biological systems with monoenergetic neutrons, and essential agreement is found with earlier conclusions derived from the comparison of track-segment experiments and neutron irradiations. The oxygen-enhancement ratio for the nitrogen ions is higher than expected from the microdosimetric data; this is taken as an indication that the oxygen effect may at least partly depend on the energy concentration over distances of the order of nanometers. The implications of the results to the use of heavy ions in radiotherapy are considered.

INTRODUCTION

Dosimetric and microdosimetric analysis as well as radiobiological studies performed at the Princeton Particle Accelerator with nitrogen ions of 3.9-GeV initial energy have been described in previous publications (*1–5*). This paper is an attempt to link the physics studies with the radiobiological results, and to compare the observed relative biological effectiveness and oxygen enhancement ratio with the results which are expected on the basis of the microdosimetric data and also with results which have earlier been obtained for the same biological systems with monoenergetic neutrons of various energies.

PREDICTIONS BASED ON MICRODOSIMETRIC DATA

In an earlier analysis concerned with the theory of dual radiation action (*6*) it has been found that for a wide range of cellular radiation effects one can assume that the yield of primary lesions is proportional to the square of the specific energy z in a site with a diameter of approximately 2 μm:

$$\epsilon(z) = kz^2. \tag{1}$$

[1] This investigation was supported by Contract AT-(11-1)-3243 from the U.S. Atomic Energy Commission and Research Grant CA 12536 from the National Cancer Institute.

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The specific energy, z, is defined as the ratio of energy imparted to a microscopic region to its mass (*7*). The mean value of this random variable is the absorbed dose, but z can deviate significantly from D.

Equation (1) provides a basis for the analysis of dose–RBE relations in a great variety of radiation effects on higher organisms. The yield of primary cellular lesions, $\epsilon(z)$, can, however, in general not be equated to the observed effect, and the dose-effect relation is, therefore, not always directly obtained by averaging $\epsilon(z)$ over the probability distribution, $f(z; D)$, of the values of z which occur at a given dose. Dose-effect relations can be considerably more complicated not only because they depend on such factors as the oxygen concentration and the position of the cells in their cycle but also because they are influenced by other stochastic factors in addition to the statistics of energy deposition; only the latter are accounted for by the integration of Eq. (1) over the distribution of z. If, however, exponential or nearly exponential dose-effect curves are observed, as is frequently the case in cellular survival studies with densely ionizing radiation, one may assume that the statistics of the energy deposition is the dominant factor; one can then postulate an exponential relation between survival and primary cellular lesions:

$$S(z) = e^{-c\epsilon(z)} = e^{-k'z^2} \quad \text{with } k' = ck. \tag{2}$$

Analogous relations can be assumed if exponential dose-effect relations are found for experimental endpoints other than cellular survival. As has been shown in earlier publications (*3*, *10*), this is the case in the growth reduction of *Vicia faba* by nitrogen ions.

At small values of z Eq. (2) reduces to proportionality between the observed effect, e.g., the reduction of survival, and the yield of primary cellular lesions. At higher values of z the observed effect changes more slowly than the quantity $\epsilon(z)$, and one may, therefore, speak of a saturation effect. Various interpretations can be given to this saturation effect (*6*); in the following only the basic formulae will be derived.

In order to facilitate the comparison of the microdosimetric studies with the LET analysis which has been applied to cellular inactivation experiments based on the so-called track-segment method[2] (*8*) one can use the variable y instead of z. The lineal energy, y, is closely related to z and it refers to the same sites of approximately 2 μm; but it is defined as the energy deposited in one absorption event divided by the mean traversal length of the reference region (*7*, *9*). Formulated in terms of this variable y, which is the microdosimetric analogue of LET, Eq. (2) for the survival probability takes the form:

$$S(y) = e^{-(y/y_0)^2}. \tag{3}$$

From an analysis of the cellular inactivation studies of Barendsen (*8*) and Todd[3] the value $y_0 = 125$ keV/μm has been deduced, and by application of this result to various observations obtained with monoenergetic neutrons it

[2] P. N. Todd, Thesis, Univ. of California, Lawrence Radiation Laboratory, UCRL-11614 (1964).

[3] P. N. Todd, Thesis, Univ. of California, Lawrence Radiation Laboratory, UCRL-11614 (1964).

has been concluded (*6*) that the same value of y_0 may also apply to other cellular effects such as growth reduction in *Vicia faba* and to the induction of mutations in *Tradescantia*.

At any position in the beam one is dealing with a range of values of y; these distributions have been given in an earlier publication (*2*). One must integrate Eq. (3) over the full spectrum, $f(y)$, of the values of y produced in one event in order to obtain the survival probability S_1 when one event has taken place:

$$S_1 = \int_0^\infty e^{-(y/y_0)^2} f(y)dy. \tag{4}$$

If one considers not the survival probability but the effect level, one has the following proportionality:

$$E_1 \sim \int_0^\infty (1 - e^{-(y/y_0)^2}) f(y)dy. \tag{5}$$

Finally, if one wants to obtain the effect per unit absorbed dose, one has to multiply E_1 by the event frequency, Φ, per unit dose (*9*). The event frequency per unit dose is proportional to the inverse of the mean value of y:

$$\Phi \sim 1 \Big/ \int_0^\infty y f(y)dy. \tag{6}$$

Accordingly the effect probability per unit absorbed dose is proportional to the following quantity:

$$y_A{}^* = y_0{}^2 \int_0^\infty (1 - e^{-(y/y_0)^2}) f(y)dy \Big/ \int_0^\infty y f(y)dy. \tag{7}$$

This quantity can be considered as an effective lineal energy; the subscript A is used to indicate that the quantity refers to aerated conditions. For effects which are proportional to dose one expects the relation:

$$E = \kappa y_A{}^* D \tag{8}$$

while in exponential dose-effect relations the exponent is proportional to $y_A{}^*$

$$S = e^{-\kappa y_A{}^* D}. \tag{9}$$

The normalization constant $y_0{}^2$ has been inserted so that $y_A{}^*$ is equal to the so-called dose average $\bar{y}_D$ (*9*) for sparsely ionizing radiations, i.e., if all values of y are small as compared to y_0 and if, therefore, saturation plays no role. The value of $y_A{}^*$ can be calculated for any measured microdosimetric spectrum, and such calculations have been performed for the data (*2*) obtained on the nitrogen beam in various depths in the phantom.

The formulae given above apply to experiments performed under aerated conditions. A similar analysis has been performed with regard to hypoxic conditions. In this case one obtains a formula which is basically equivalent to

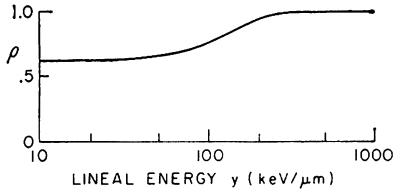

FIG. 1. Relation between the reduction factor ρ and the lineal energy y. This relation which has been deduced (*6*) from track-segment experiments is used in the computation of y_{II}^*.

Eq. (7), but which contains a reduction factor, ρ, for the production of primary lesions:

$$y_{II}^* = y_0^2 \int_0^\infty (1 - e^{-(\rho y/y_0)^2}) f(y)dy \Big/ \int_0^\infty y f(y)dy. \tag{10}$$

The simplest assumption would be that ρ is constant, i.e., independent of the microdistribution of energy. The data obtained in the track segment experiments by Barendsen (*8*) and the observations obtained with monoenergetic neutrons indicate, however, that the reduction factor ρ varies with y, and the functional dependence in Fig. 1 has been found (*6*) to be in satisfactory agreement with the experimental data.

The fact that ρ tends towards 1 with increasing y is of considerable interest because it could mean that saturation alone does not account fully for the observed small OER for densely ionizing radiation, and that one may have to invoke additional mechanisms (e.g., the production of oxygen in the tracks of densely ionizing particles). There is, however, an alternative interpretation of the increase of ρ. In the experiment of Barendsen as well as in the neutron experiments one deals with very narrow particle tracks when one approaches values of y in the vicinity of 100 keV/μm; this may lead to an increase in saturation which would correspond to a smaller value of y_0. The two different possibilities can not readily be distinguished. The fact, however, that from Todd's data[3] no variation of ρ can be deduced, favors the second interpretation. The analysis of Todd's data is complicated because in his experiments the particle tracks are wide enough that the indirect events in which a particle does not enter the nucleus but injects δ-rays into it can not be neglected; y can, therefore, not simply be equated with LET. An accurate analysis would have to be based on microdosimetric data; however, a study by Curtis (*13*) indicates that the difference between the data of Barendsen and Todd may indeed be partly due to the different lateral extension of the tracks in the two cases. In the next section the situation will be examined in the light of the data obtained for nitrogen ions. To this purpose Eq. (10) has been evaluated with the microdosimetric data (*2*) for the nitrogen ions and with the reduction factor given in Fig. 1. The resulting quantity y_{II}^* is presented in Fig. 2 together with $\bar{y}_D$ and y_A^*. The quantity $\bar{y}_D$, which is obtained if saturation is not taken into account, is given as a solid line for comparison with the quantities y_A^* (broken line) and y_{II}^* (dotted line).

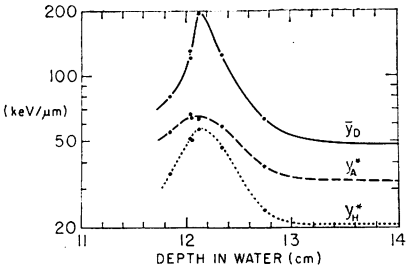

FIG. 2. Dependence of the microdosimetric quantities $\bar{y}_D$, y_A^*, and y_H^* on depth in the phantom. The heavy dots indicate those positions where microdosimetric spectra have been determined. Toward their right end the curves have been extrapolated to values obtained at the depth of 15.1 cm.

COMPARISON OF EXPERIMENTAL AND THEORETICAL DATA

Figure 3 represents the observed effectiveness, α, for the growth reduction of *Vicia faba* of the nitrogen beam as a function of depth in the phantom. The values α have been obtained by a least-squares fit (*3*) of the experimental data to dose-response curves of the form:

$$G = G_0 e^{-\alpha D}, \tag{11}$$

where G is the observed growth and G_0 is the least-squares estimate for the controls. The results are indicated by rhomboids. The horizontal extension of these rhomboids covers the range of depths in the phantom occupied by the

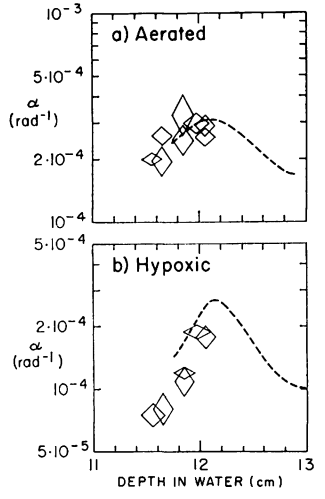

FIG. 3. Dependence of the effectiveness of nitrogen ions, α, for the growth reduction of *Vicia* seedlings on depth in the phantom. The rhomboids indicate the thickness of the irradiated samples (horizontal extension) and the standard deviation of α (vertical extension). The broken curves represent the theoretical relation $\alpha = \kappa y_A^*$ for the aerated condition and $\alpha = \kappa y_H^*$ for the hypoxic condition. The value $5 \cdot 10^{-4}$ (keV/μm)$^{-1}$ rad^{-1} for κ has been assumed.

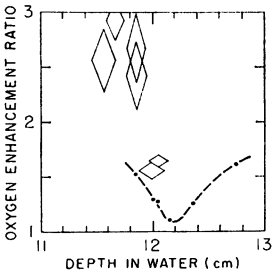

FIG. 4. Dependence of the oxygen enhancement ratio for nitrogen ions and the growth reduction of *Vicia* seedlings on depth in the phantom. The rhomboids indicate the thickness of the irradiated samples (horizontal extension) and the standard deviation of the OER (vertical extension). The broken line represents the theoretical value y_A^*/y_H^* of OER according to microdosimetric data. The dots indicate those positions where microdosimetric spectra have been determined.

plants; the vertical placement and extension correspond to the value of α and its standard deviation, respectively. RBE is proportional to α; the numerical relation between the two quantities for different effect levels has been given in the earlier publication (*3*).

According to the considerations in the preceding section the observed values of α should be proportional to the microdosimetric quantity y_A^*. The broken line in Fig. 3a corresponds to the relation $\alpha = \kappa y_A^*$ with the proportionalty constant $\kappa = 5 \cdot 10^{-4}$ (keV/μm)$^{-1}$ rad^{-1}. The range in depth as well as the statistical accuracy of the data are not sufficient to verify or reject the propotionality between α and y_A^*; the results are, therefore, neither a confirmation of the basic tenets of the considerations in the preceding section nor a confirmation of the numerical value of y_0 used in Eq. (7). One may, however, accept the relation $\alpha = \kappa y_A^*$ on the basis of the earlier evidence (*6*) from track-segment experiments and studies with monoenergetic neutrons (*10*), and it is then of considerable interest to compare the values of κ obtained with *Vicia faba* in the present studies and in the earlier experiments with monoenergetic neutrons. The data obtained with monoenergetic neutrons are in near agreement with the relation $\alpha = \kappa y_A^*$. However, the decrease of α with increasing neutron energy is somewhat steeper than the decrease of y_A^*. In the energy range between 200 and 600 keV one obtains a value of κ of about $9.3 \cdot 10^{-4}$ (keV/μm)$^{-1}$ rad^{-1} while the value at 14 MeV is $6.2 \cdot 10^{-4}$ (keV/μm)$^{-1}$ rad^{-1}. The reason for this finding is at present not completely clear; but one can think of two likely factors. One reason why the low-energy neutrons should be relatively more effective than expected could be that the charged particle secondaries have in this case ranges which are considerably smaller than the nuclear diameter of the cell. This would lead to a diminished saturation effect and thereby to increased effectiveness. At 14 MeV, on the other hand, almost all of the recoil protons and most of the heavier charged particles have ranges comparable to the diameter of the cell nucleus and the saturation effect should, therefore, be comparable to the one observed with charged particles in the experiments by Barendsen and Todd. Another possible reason is that at a given value of y or,

in the more conventional terminology, at a given LET the radial profile of energy deposition around the particle track is narrower in the case of protons near their Bragg peak than in the case of heavier charged particles of the same stopping power. Since protons near their Bragg peak are probably mainly responsible for the effects at low and intermediate neutron energies, one could expect a somewhat increased effectiveness due to this difference. It may, at present, not be possible to decide which of the two factors is more important. But independently of the answer to this question one would have to expect that due to the long range of the particles and the extended delta-ray halo the case of the nitrogen ions corresponds more closely to the case of 14-MeV neutrons than to that of the lower energy neutrons. This is indeed borne out in the experiments and one concludes that the theoretical considerations on RBE presented in the preceding section are equally consistent with the track-segment experiments, with the experiments with fast neutrons, and with the present studies with nitrogen ions.

Discrepancies both with the data of Barendsen and with the neutron data arise as far as the oxygen enhancement ratio is concerned. On the basis of Eq. (10) and the value of κ obtained under aerated conditions one predicts the effectiveness in anoxic conditions which is indicated by the broken line in Fig. 3b; this line corresponds to the quantity y_{II}^* plotted in Fig. 2, which, in turn, is based upon the dependence of ρ on y (see Fig. 1) inferred from Barendsen's data and the experiments with monoenergetic neutrons. Although the experimental data and the theoretical predictions based on the microdosimetric measurements do not cover exactly the same depth range in the phantom, one must conclude that the observed effectiveness under anoxic conditions is below the calculated values. Figure 4 shows this somewhat more explicitly in a comparison of the oxygen enhancement ratio which is theoretically predicted and the values which are experimentally observed. One concludes that the observed values of OER are higher than would correspond to Barendsen's observations of cellular inactivation by the so-called track-segment method. One could assume that this merely reflects a difference in the two biological systems. However, the growth reduction studies with monoenergetic neutrons and *Vicia* seedlings (*10*) have led to oxygen-enhancement ratios which are in agreement with the values predicted under the assumption of a variable ρ. The larger values of OER obtained in the present experiments would indicate that ρ does not change with y, and this may be due to the more extended radial profile of energy deposition at a given LET in the case of nitrogen ions. The results, therefore, support the conclusion (*13*) which has been drawn from the data obtained by Todd. One infers that the value of y in a region of one to several micrometers is not the only relevant quantity but that the effectiveness of densely ionizing radiation is also influenced by the width of the track.

The other biological experiments performed with the nitrogen beam are less extensive than the studies performed on *Vicia faba* but they conplement and support the basic conclusion reached for this system. In the induction of pink mutations in *Tradescantia* by nitrogen ions (*5*) the geometrical extension of the irradiated samples is larger than in the case of *Vicia* seedlings; consequently

it is more difficult to establish an accurate dependence between RBE and the depth of the sample in the phantom. One can, however, perform an overall fit of the observed yield, $Y(D)$, of pink mutations per stamen hair at small doses to the relation:

$$Y(D) = \kappa y_A^* D, \tag{12}$$

where y_A^* is the value of the microdosimetric quantity defined in Eq. (7) at the mean depth of the sample. The resulting value is $\kappa = 1.8 \cdot 10^{-4}$ $(\text{keV}/\mu\text{m})^{-1}$ rad^{-1}. Again, as in the case of the growth-reduction studies on *Vicia faba*, a comparison with neutron data[4] shows that the value is only slightly smaller than the value ($\kappa = 2 \cdot 10^{-4}$ $(\text{keV}/\mu\text{m})^{-1}$ rad^{-1}) obtained for 14-MeV neutrons but considerably smaller than the value for 430-keV neutrons ($\kappa = 5.2 \cdot 10^{-4}$ $(\text{keV}/\mu\text{m})^{-1}$ rad^{-1}). The experiments on the induction of pink mutants in *Tradescantia* support, therefore, the conclusion that the analysis of RBE given in the preceding section applies equally to the track-segment method, to the experiments with high-energy neutrons, and to the present studies with nitrogen ions. The rather close agreement of the values κ obtained with 14-MeV neutrons and with nitrogen ions is particularly significant in view of the fact that the microdosimetric distributions for 14-MeV neutrons and for nitrogen ions near their Bragg peak differ widely, as shown in the earlier report on the microdosimetric studies (*2*). It should be noticed that $\bar{y}_D$ which is the microdosimetric analog of the dose mean LET, $\bar{L}_D$, and which varies rapidly near the Bragg peak is not correlated to the observed RBE in *Vicia* seedlings and in *Tradescantia*, while the explicit microdosimetric analysis which leads to the quantity y_A^* is in substantial agreement with the data.

No experiments under anoxic conditions have been performed with *Tradescantia*. But two dose-effect curves which have been obtained with mammalian cells as close as possible to the Bragg peak of the depth-dose curve have resulted in an oxygen enhancement ratio of 1.25. This is close to the predicted oxygen enhancement ratio, but because only one position has been tested, one cannot decide whether this agreement occurs only at the very close vicinity to the Bragg peak. It should also be pointed out that even with x-rays the OER obtained with mammalian cells under the same experimental conditions is relatively low (*10*).

DISCUSSION

As shown elsewhere (*6*), Eq. (1) can also be written in the form

$$\epsilon(D) = \kappa(\zeta D + D^2), \tag{13}$$

where ζ is the dose average of individual increments of specific energy. This quantity can be expressed in terms of y; for a unit density spherical volume

[4] A. G. Underbrink, unpublished.

of diameter d one has (*9*):

$$\zeta = \frac{20.4}{d^2} \int_0^\infty y^2 f(y)dy \Big/ \int_0^\infty y f(y)dy$$
$$= \frac{20.4}{d^2} \bar{y}_D. \tag{14}$$

At small doses one can disregard the quadratic component in Eq. (13) and the relation then corresponds to the linear relation considered in the preceding section. However $\bar{y}_D$ must be replaced by the quantity y_A^* [see Eq. (7)] because of saturation effects.

One interpretation of Eq. (13) or of its modified forms is that the expression in the brackets represents the square of the energy concentration in sites (which as mentioned above have dimensions of the order of micrometers) and κ represents the effectiveness with which this energy inactivates loci within the site as well as the probability with which pairs of these loci interact within the site. It was assumed that the loci are much smaller than the site and that in a first approximation κ might be considered to be independent of radiation quality. In this case Eq. (13) represents the dependence of biological effect on both dose and radiation quality with the latter entering only through ζ.

It has already been pointed out that this first approximation may be inadequate in some instances (*11*, *12*) and it would appear that the experiments that have been analyzed here are an example where it is insufficient because of differences of energy concentration at the locus level (perhaps in the nanometer range). One may also surmise that such differences are even more important in the absence of oxygen which by the agency of various active radicals might enhance radiation effects depending on energy concentrations within a typical diffusion distance of a few nanometers.

Although such a dependence of κ on radiation quality might be an adequate qualitative explanation of the observed effects it must remain tentative until adequate quantitative information is available. This underlines the need for microdosimetric data in the nanometer range.

Regardless of the reasons involved it is apparent that the OER for these ions exceeds that for lighter ions of comparable LET. This has negative implications for the utilization of ^{14}N ions in radiotherapy. However, it might be expected that further enhancement of the LET (e.g., in irradiation with argon ions) would overcome the difficulty. In this case delta rays will be spaced more closely which makes the ionization density within individual delta rays less critical. The narrow Bragg peak for nitrogen ions would seem to require the use of heavier particles as well.

With an increase in atomic number one could approach the situation where the biological effectiveness per particle is substantially independent of energy (i.e., the RBE in the Bragg peak is less than further upstream) with a more extensive zone of uniform tissue destruction. This, together with an anticipated

OER near 1.0 and minimal lateral scatter, should constitute conditions of considerable interest to radiotherapy.

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