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FAST NEUTRON RADIATION THERAPY*

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INTRODUCTION

Cancer therapy continues to advance on two fronts concerned respectively with ablation of local and regional disease by surgery or radiation and control of distant spread or dissemination by immunotherapy and chemotherapy. Local control of nonresectable cancer by irradiation frequently fails (in about one-third of patients referred) due to a relative radioresistance of the tumor. In this context "radioresistance" implies that the dose of radiation required to sterilize the tumor with any degree of certainty exceeds that which the associated normal tissues could tolerate without unacceptable complications. Radioresistance of tumor cells has been attributed to three mechanisms:

1) The presence of oxygen deficient regions within the tumor.

2) The capacity of many cells to sustain and repair radiation damage to critical target molecules.

3) Variation in cellular radiosensitivity at different phases of the cell division cycle.

Since a large proportion of the radiation damage sustained by living cells is mediated through oxidizing radicals, hypoxic cells require 2.5 - 3 times the dose which would inactivate a similar population of well-oxygenated cells. Second, the capacity for repair of radiation damage induced by sparsely ionizing (low-LET) radiation, believed to be due to redundancy in critical targets,

is characterized by a large initial shoulder in the cellular survival curves (Fig. 1) which renders moderate doses of radiation relatively ineffective. Finally, cells are relatively tolerant, at least to low-LET radiation, in the resting phase of the cell cycle and markedly more radiosensitive in the premitotic or mitotic stages of cell division, so that slowly cycling tumors may be relatively radioresistant.

These three factors are most evident in the case of low-LET radiation. However, cellular radiosensitivity is much less variable with heavily ionizing high-LET radiation. High-LET particles are presumed to induce irreparable and directly lethal changes in chromosome structure almost independently of cellular metabolism or biochemical state. For this reason tumors resistant to conventional radiotherapy are relatively more sensitive to high-LET radiations. Normal tissues are generally well-oxygenated and with few exceptions have consistent cell cycles (comparable number of cells in various phases of the cycle) and consistent chromosomal structure, and consequently exhibit little variation in cellular radiosensitivity. The therapeutic ratio is, therefore, likely to improve markedly with use of high-LET radiations for radioresistant tumors.

Exploration of the possible role of high-LET radiations in the treatment of relatively radioresistant tumors is clearly indicated. Equally important is the determination of the

tolerance of the associated normal tissues and organs to high-LET beams. This information permits the radiation oncologist to estimate the therapeutic ratio (ratio of tissue tolerance to tumor lethal doses) for both low and high-LET radiations, and to identify those clinical contingencies in which the use of high-LET radiations might be advantageous.

NEUTRON BEAMS: PHYSICAL CHARACTERISTICS, DOSIMETRY, GENERATION AND MODERN CLINICAL FACILITIES

Introduction and Definitions

This section is written assuming the reader is familiar with conventional x-ray therapeutic beams, their generation, properties, dosimetry, and use in patient treatment. Therefore, the emphasis will be on the differences between photon and neutron beams intended for such use. Simplifications and generalizations are made to keep the presentation brief and focused on the more important processes and properties.

DEFINITIONS In this article, "tissue" means any tissue in humans, animals, or cultures. However, when specific references are made to tissue properties, "tissue" is human muscle tissue. "Radiation" means incident photons or neutrons and, following

their interactions with tissue electrons or atomic nuclei, the scattered particles as well. "Particle" means positive and negative electrons, neutrons, protons, deuterons, alphas, and heavy ions such as carbon, nitrogen, oxygen, and heavier atoms stripped of their atomic electrons. "Heavy particle" means any "particle" excluding electrons. The energy ranges considered are, for electrons up to 45 MeV; for photons, x-rays produced by electrons of energies up to 45 MeV; and for neutrons, up to about 65 MeV.

Physical Characteristics of Beams

Photon beams penetrating tissues generate a mixture of photons and high velocity electrons. This means that as photons interact and the photon-electron cascade develops and penetrates deeper into tissue, the nature of this cascade is rather stable. On the other hand neutron beams generally create low velocity heavy particle recoils, photons, and radioactive nuclides. The neutron cascade is characterized by a large variety of inelastic reactions with different energy thresholds (minimum energy necessary for the reaction to take place), leading to the emission of photons, neutrons, and charged particles. For example, as the energy of the scattered neutrons in and out of the beam decreases with depth, the $p(n,\gamma)d$ process (photon emission following thermal neutron capture) becomes more significant. From the point of view

of particle interactions and dosimetry, the most important characteristic of tissues is the low average atomic number of their elemental composition and large water content of most cells except for cortical bone (32). In the case of photon beams, this low atomic number means that the dominant process for photon energy transfer to matter is Compton scattering. In the case of neutron beams, it means that recoiling heavy nuclei may have typical ranges of 600-800 μm (4) and, may therefore traverse tens to hundreds of cells before stopping. Moreover, a low atomic number means that relatively few long-lived radionuclides are produced and thus the dose to tissue from nuclear transmutations is small (19). In this section, differences between cortical bone and soft tissues are ignored. No distinction will be made between primary electrons (from electron beams) and scattered electrons (from photon beams). Processes which contribute insignificantly to therapeutic doses such as photon-nucleon processes (60), bremsstrahlung by electrons, and high energy (n,γ) and (n,d) reactions in tissue are ignored. The details of photon and neutron interactions have been described elsewhere (5, 35, 38). From a microscopic point of view, the most important characteristic of modern clinical photon and neutron beams are shown in Table 1.

The actual energy transfer from neutral beams to matter occurs when the recoiling charged particles from photon or neutron collisions with electrons or nuclei, passing through tissue,

excite and ionize its molecules. This energy transfer from the recoiling charged particles to the local medium is called linear energy transfer (LET) since heavy particles move mostly along straight paths (33). Taking sufficiently short path lengths, this concept is equally applicable to all charged particles. To a first approximation, this energy transfer is directly proportional to the square of the particle charge and inversely proportional to the square of the velocity. Thus, the heavy particles are generally more likely to produce larger energy transfers to tissue per unit path length than electrons because they move more slowly and may have larger charges. Heavy particles from neutron interactions have LETs that are typically 10 to 1000 times larger than electron LETs if some of the higher energy proton recoils are excluded. Recoiling electrons and, by extension, photon beams are commonly referred to as low-LET radiation, while recoiling heavy particles and, by extension, neutron beams, are referred to as high-LET radiation. However, recoiling protons may be low- or high-LET radiation depending on their energies. For example, about 97% of the track length of a 30 MeV proton has an LET of less than 10% of the maximum LET (37).

The biological effects of low- and high-LET particles are eventually the same (29), given sufficiently large doses. However, high-LET particles are more efficient than low-LET particles in producing some effects in target molecules in tissue cells. The biological effects of radiation may be divided into

direct and indirect. Direct effects are those that are effected by the ionization of particles traversing a target molecule. For example, one heavily ionizing particle passing through or very closely to a DNA molecule may cause irreversible changes by breaking several intramolecular bonds. Indirect effects are those in which ionizing particles create free radicals such as OH^- and these radicals, in turn, cause changes in target molecules. Thus, the same or other lethal changes in a DNA molecule may be effected by such free radicals. For example, breaking the DNA's double strand is possible for a single high-LET particle while, generally, it may take several low-LET particles to accomplish the same effect. An introduction to these processes may be found in (29, 50, 52).

Dosimetry

MACRODOSIMETRY Photon beam dosimetry is relatively simple because tissue, water, and plastics convenient for the fabrication of ionization chambers are all composed of low atomic number materials and because the dominant process for energy transfer is the Compton effect (5, 38). In the case of neutrons, the problem is more complex because, (a) The energy to produce electron-ion pairs in the gas filling the chamber is dependent on the nature and energy of the recoiling charged particle (36); (b) Plastics suitable to fabricate ionization chambers have compositions rich

in carbon (58), but tissues are rich in oxygen (34), and thus the ratio of kermas (kinetic energy released to charged particles per unit mass) of wall and tissue is not constant as a function of neutron energy (1, 19); (c) The hydrogen content of the plastic must be adjusted carefully to match that of tissue since the hydrogen partial kerma in tissue varies from about 94% for 0.1 to 1 MeV neutrons to about 55% for 70 MeV ones; (d) The relative stopping power of the gases to the chamber wall material depends on nature and energy of the charged particle recoils, unless an atomic match of wall and gas compositions may be achieved (as in the case of A-150 plastic (6)); (e) The difference in the kerma function for tissue and for ion chamber wall material makes it necessary to calculate the tissue-wall material kerma ratio at the point of measurement. This is particularly important when making in-phantom measurements in the beam, in the penumbra and in the umbra.

A good manual for neutron ionometric dosimetry including analysis of uncertainties has recently been published (2). Additional information is also available (15, 16). The Europeans are developing a similar set of recommendations (17). Other techniques with different limitations and not in routine use also exist such as calorimetry (45), TLDs using ^{6}LiF and ^{7}LiF, Fricke dosimeter and pin-diodes (34).

Reporting of "dose" in neutron irradiations is done differently in Europe and the USA. In the USA, the practice has been of reporting the neutron dose as total dose which includes a photon (gamma) component. In Europe, it has been the custom to report the gamma and either the neutron or the total doses separately. Although superficially the European approach may seem better than the American one, it must be remembered that the response of "total dose" (also known as "neutron sensitive") detectors as well as that of the so called "neutron insensitive" detectors are functions of the neutron and photon energies (63). Thus, the neutron energy spectrum must be known at the point of measurement. Unfortunately, the spectrum is generally not well known in a phantom or in a patient. Furthermore, the exact meaning of low-LET and high-LET responses as determined by the two-detector technique (34) is not well defined. A second difference in the practices on opposite sides of the Atlantic is the use of phantoms filled with TE solution in the USA (2) and filled with water in Europe (17).

MICRODOSIMETRY An alternative to macrodosimetry is microdosimetry. Typically, this technique measures the number of events in which a certain energy is deposited by charged particles crossing a small spherical volume of tissue of nano- or micro-meter diameter (5,13, 33). The ratio of this energy to the diameter of the sphere is the event size, Y. Y is usually specified in keV/μm. These types of measurements are commonly made

with proportional chambers 1-2 cm in diameter (5), with walls made of A-150 plastic (58) and filled at low gas pressure. Other detector arrangements have also been reported (13, 14, 18, 26). The product of the event size and the number of events of that size is the differential dose distribution D(Y). Integrating D(Y) between suitable limits gives the energy deposited in a sphere of specified diameter, in the given Y-range. The same caveats about kerma ratios, energy to create electron-ion pairs, chamber wall and gas compositions are applicable to these detectors. In practice, the measurements and calculations needed to get D(Y) are laborious because of the large dynamic range of Y, typically 10^4-10^5, requiring somewhat complex equipment. Thus, they do not lend themselves to routine use.

TREATMENT PLANNING Treatment planning for neutron beams is analogus to photon treatment planning. Essentially any technique that is satisfactory for photons will do for neutrons (10, 54, 57), since dose distributions are similar (10, 12, 16, 21, 54, 57).

Neutron Sources

For external beam therapy, neutron fluences large enough to produce clinically acceptable dose rates in tissue (0.2 Gy/min at D_{max} for a 10x10 cm^2 field, at SSD $\geq$ 100 cm) can be produced by

low T(d,n)He or high [Be(d,n)B or Be(p,n)B] energy particle beams. The (d,T) neutron sources have relatively low penetration, low dose rate (30) and wide penumbra. The historical d(Be,B)n reaction (51, 59) produces intense neutron beams but, as the energy of the deuterons is increased to obtain higher dose rates and better neutron beam penetration in tissue, most neutrons are projected into a shrinking solid angle and beam flatteners are needed to obtain suitable isodose distributions for treatment planning (49). For several reasons, the Be(p,n) reaction (7, 8, 9, 23, 55) is gaining acceptance as a neutron source for modern clinical facilities. Some of these reasons are: (a) For a given size cyclotron (fixed cost) protons may be produced with twice the energy of deuterons. (b) Using a Be-target, neutrons produced by protons have a wider angular distribution than those produced by deuterons so that flattening filters are not needed even for 66 MeV protons on Be (54); (c) For a fixed beam current and cyclotron size, protons produce a larger dose rate than deuterons for the same treatment conditions (d) Be-targets bombarded by protons of twice the deuteron energy are easier to cool than those bombarded by deuterons; (e) Skin sparing is better and depth for half maximum dose is greater for p-Be neutron beams when the protons have twice the energy of the deuterons.

The notation, e.g., p(66)Be(49) neutrons, signifies that the neutrons are produced by 66 MeV protons incident on a Be-target of such thickness that protons not undergoing nuclear scattering can

only lose 49 MeV by collision with electrons (2). Future neutron therapy facilities under construction at M. D. Anderson Hospital and Tumor Institute, Houston, Texas, at University of California at Los Angeles, Los Angeles, California, and at University of Washington, Seattle, Washington, will use use p-Be neutron beams. In Europe, three facilities (Orleans, Clatterbridge, Louvain) are planning to switch over or acquire p-Be neutron beams.

Neutron Therapy Facilities

Concerning modern fast neutron radiation therapy installations, Catterall (20) listed the following minimum facility specifications for a fair comparison between neutron and photon modalities in radiation therapy, (a) Beam: reliably available at all scheduled times; (b) Dose rate high enough to allow completion of treatment in less than five minutes; (c) Depth dose and isodose shapes at least as good as those of ^{60}Co; (d) The therapy machine must be in a hospital; (e) The positioning of the patient must not be compromised by considerations outside radiation therapy.

Technology has advanced considerably since those conditions were enumerated. Intense negative hydrogen beams are now routinely used, thus beam energy changes are easily effected and variable penetration beams should become a standard feature. Furthermore, all controls and monitoring of modern particle accelerators, beam

transport systems, dose delivery systems (gantry), and patient positioning fixtures (couch) are now done through a computer. Thus, correlated motion of the gantry and the couch are easy to achieve through software. This is very important if multiple proton energies are planned for p-Be neutron generation since neutron production is a steep function of proton energy (3). Therefore, the concept of variable source to pseudo-axis distance (SPAD) can be developed and it may be implemented at negligible cost. SPAD operation is realized through software as follows: The appropriate point of the target volume ("target center") is positioned at the normal isocenter, defined by the gantry axis of rotation and the central axis of the neutron beam. Then under computer control the couch is suitably moved vertically and horizontally to change the source to "target center" distance to the desired value. This can be made to occur for any angle of the gantry whether it is fixed or changing. Thus in the light of current technology, the following specifications should be added to those of Catterall's; (f) Continuously adjustable collimators that close automatically upon completion of dose delivery; (g) At least two proton beam energies (for example 30 and 70 MeV) to have a low penetration beam, comparable to ^{60}Co, and a high penetration beam, comparable to 8 MeV x-rays (61); (h) SPAD operation of the system to reduce the distance between collimator end and the patient and thus improve the beam penumbra in the patient and increase dose rate for tumors in the head and neck region; (i) Computer set-up of most treatment parameters. The last

specification is important because it allows technologists to act as supervisors rather than operators, thus potentially reducing set-up errors.

NEUTRON RADIOBIOLOGY

Current practice in radiotherapy is founded on some 80 years of cumulative clinical experience. Researchers introducing a competing modality today cannot afford comparable clinical experience, but must of necessity optimize the new treatment on the basis of available physical and biological information.

The physical requirements for neutron therapy are now well understood. Clearly the system must provide a beam of penetrating power at least as good as that obtainable with conventional x-ray therapy equipment, with similar beam shaping capabilities, flexibility in angulation and beam direction, and dose delivery rates. In addition the biological characteristics of the beam, including its relative biological effectiveness for human tissues and tumors under various conditions of treatment, should be well established. The latter requirement necessitates comprehensive pre-clinical radiobiological characterization of each unit before clinical therapy can commence.

Cellular Survival Curves

Biological characterization of a new modality entails measurement of survival curves using cultures of mammalian cells, as well as irradiation of experimental animals. Cellular studies will in general provide data on the slope and shape of the lethality function observed with the high-LET beam compared with that obtained under near identical conditions with low-LET radiations. These studies will be carried out under conditions of normal oxygenation of the culture medium as well as under conditions of extreme hypoxia, effected by removal of all dissolved molecular oxygen from the medium. Experiments of this type provide four sets of parameters in the cellular survival function, for the oxic and anoxic cells irradiated with both modalities (Fig 1).

Comparing the neutron with the photon curves, it will be noted that the former invariably have a steeper initial slope and a smaller shoulder. The effect of anoxia is to produce a markedly different survival curve with the low-LET radiation (reduced terminal slope), but a much less altered response in the case of the neutron irradiation. From these four functions two sets of co-efficients, the Relative Biologic Effectiveness (RBE) and the Oxygen Enhancement Ratio (OER), both different for various dose levels, are derived.

Response of Mammalian Tissues and Organs

The primary impact of ionizing radiation is on the reproductive integrity of cells. Sharply defined and quite specific endpoints can be identified in intact tissues when depletion of their constituent cell populations reaches some critically low value. Macroscopic reactions have been studied in mice, rats and larger mammals. These include radiation injury to the bone marrow, gut, brain and spinal cord, esophagus, lung, kidney and skin.

Total body irradiation provides two clearly defined end points. At low dosage (between 4 and 7 Gy, photons) depression of the blood forming elements in the marrow causes death between 2 and 3 weeks after exposure. Graded doses of radiation yield a dose-effect function from which the median lethal dose and its standard error can be derived. The ratio of median lethal doses for photons and neutrons in the same strain of animals provides an estimate for the RBE specifically for hemopoietic marrow cells, within the dose range described. Similar studies using two or more fractions provide estimates of the repair and repopulation parameters for the associated cell populations. Differences in the repair capacity with different radiation modalities can then be identified and measured.

With substantially larger doses (over 10 Gy of photons) an early mortality about 4 days after exposure is observed, and this is found to be due to intestinal damage. The intestinal post-irradiation syndrome is readily distinguished from the hemopoietic syndrome by the different time course of the two processes, and comparisons between modalities including the effect of fractionation can also be studied for this system (Fig. 2).

Thoracic irradiation provides information on the radiosensitivity of the lung and the esophagus. Effects on these two tissues can be identified separately because of a dichotomy in the time course of the reactions similar to that encountered with the marrow and intestine described above. At high doses, a small mammal such as the mouse undergoes an acute esophageal reaction which is rapidly lethal, whereas lower doses directed to the chest produce a delayed mortality associated with extensive pulmonary fibrosis. Effects on the spinal cord can be observed by confining the radiation to a narrow midline port encompassing a well defined length of the thoracic spinal cord. The end point observed is paresis of the lower extremities which appears some 6 - 12 months after irradiation.

Abdominal irradiation will reproduce the intestinal phase of the post-irradiation syndrome if wide fields are used. More specific information can be obtained by localized irradiation of organs, for example, an isolated loop of intestine or carefully directed

beams to one or both kidneys. The end point observed in intestinal irradiation would be the count of surviving or regenerating functional units (crypts). The end point for renal irradiation is the onset of fatal post-irradiation nephrosclerosis.

Skin reactions are readily observed in small areas of skin, irradiated with various doses, modalities and fractionation schemes. Both early and late reactions can be graded in severity and correlated with the treatment delivered. Because of physiological differences in rodent skin compared to that of larger mammals, conclusions on the radiobiology of mouse or rat skin cannot be transferred to the clinic without careful verification. Radiation reactions in pig skin closely resemble those in man, and for this reason many studies of late changes in irradiated skin portals in pigs have been made with photons and neutrons using various treatment schemes (Figs. 3,5).

Because of interspecies differences, animal experiments can do little more than provide a rough guide to corresponding responses in humans. Where a consistent trend is observed in several species, it is probably safe to extrapolate such observations, as a first approximation, to the human response, but the precise estimates of radiosensitivity required to evaluate radiation response and recovery in man must be based on clinical obersvation. For this reason it is recognized that, in addition

to clinical evaluation of tumor response, reactions observed in all normal tissues traversed by the therapy beam should be recorded for radiobiological analysis.

RBE and OER

The Relative Biological Effectivenes (RBE) of neutrons, relative to photons, is defined in terms of the ratio of doses required to produce a similar effect or a similar cellular surviving fraction with the two modalities. This ratio is seen to vary with dosage (Fig. 1) from a value of around 4 in the initial portion of the curve to smaller values, possibly around 2 as the dosage is increased. Comparing anoxic with well-oxygenated cells (Fig. 1) provides a series of measurements of the OER, which is also a function of dosage, ranging from a maximum of about 3 with large doses of low-LET radiations and being reduced in the low dose region of the curve. The OER is consistently lower with neutrons and could reach a theoretical minimum of 1.0 with more heavily ionizing particles.

Determination of the RBE for low doses in normally oxygenated tissues provides the basis for the equivalency factor to be used in the clinical situation. However the RBE for certain specific organs may well be greater than expected, so that detailed studies in experimental animals become necessary to confirm the

predictions of the cellular survival functions and to identify any possible organs or tissues which may be exceptionally sensitive to high-LET particles. Results of an extensive series of studies are shown in Figure 4 (25). Not only is the RBE dependent upon the dose per fraction, but its value also differs significantly in different tissues.

Factors Affecting the Clinical Response

In clinical practice, a prescribed tumor dose would be one which, when delivered to a specified target volume, has a high probability of permanently eradicating the tumor while producing acceptable reactions in normal tissues. The dose required to eradicate a given tumor depends upon the intrinsic radiosensitivity of the tumor, its size and physiological state (oxygenation), and a number of technical variables including time and fractionation factors.

Ionizing radiation kills or sterilizes cells following the characteristic near-exponential lethality functions described (Fig. 1). A tumor would clearly be cured if all its constituent cells were ablated, and the probability of tumor control would then be a steep dose-effect function with a Poisson statistical distribution. The expected dose-response relationship is seldom realized in practice, presumably because of biological

differences, and hence differing radiosensitivities, among individual cells. As a consequence of this variation, and of the selective survival of the more resistant elements, the observed tumor lethal dose may be considerably greater than that computed from average cellular radiosensitivity data.

Radiation also depletes the constituent cell populations of adjacent or overlying normal tissues. Complete depopulation of normal tissues will result in irreversible destruction of the tissue or organ concerned, characterized by severe radiation injury or necrosis. Partial depopulation may lead to a reaction, which heals by repopulation from surviving cells. Both acute reactions, appearing some weeks after completion of treatment, and late effects characteristically observed up to two years following irradiation, have been identified as dose-limiting factors in the delivery of radical courses of radiation therapy.

Time-Dose Factors for Neutrons

Empirical formulae to correct for variation in fraction number and overall time have been developed by Orton and Ellis (48) using the "time-dose factor" (TDF) formulation. Different modalities, such as neutrons and photons, have different values for the parameters in these formulae, since the repair capacity of the irradiated cells is markedly different in the two cases (Fig. 6). Using the

TDF factor, values for consecutive courses with similar or different modalities can be added. The corresponding formulae can then be used to derive equivalent biological doses for neutrons, photons and mixed-beam procedures with various fraction numbers and treatment times.

The nominal single dose (NSD) for treatment with a dose of D Gy delivered in N fractions over T days is given by the formula:

$$NSD = 100.D \times N^{-\alpha} \times T^{-\beta}$$

where the exponents $\alpha = 0.24$ for low LET radiations, $\alpha = 0.04$ for neutrons and $\beta = 0.11$ independent of modality or beam quality. The TDF formula is derived from the NSD equation:

$$TDF = K \times (NSD)^{1/(1-\alpha-\beta)}$$

where K is a normalization constant (K = 0.001 for photons). Conventionally, TDFs are calculated for a given fraction size d = D/N and a specified interval between fractions t = T/N. Then:

$$TDF = K \times N \times (100.d)^{\delta} \times t^{-\tau}$$

where $\delta = 1/(1-\alpha-\beta)$ and $\tau = \beta\delta$. Since the exponent of N is unity, this formula allows for additivity of TDF values in concomitant or sequential courses.

Numerically, for photons $\delta_\gamma = 1.538$ and $\tau_\gamma = 0.169$; for neutrons $\delta_\nu = 1.176$ and $\tau_\nu = 0.129$. The normalization constant for neutrons (K_ν) is derived from clinical observation and is

numerically equal to .024 for the high-energy p(66)Be(49) Fermilab beam (24). An analogous formulation for a low-energy d(15)Be unit by Kutsutani-Nakamura (41) gave Kν=.030. Calculated TDF levels for various total neutron doses, and fraction numbers are shown in Table 3.

CLINICAL IMPLICATIONS

Rationale For Clinical Therapy With High-LET Particles

Tumors unlikely to respond to conventional doses of radiation therapy can be identified by histological type, extent of disease and contiguity with radiosensitive or critical organs. Radioresistant tumors include the adenocarcinomas of the gastro-intestinal tract (carcinomas of salivary gland, stomach, intestine and pancreas), soft-tissue and bone sarcomas, melanoma, and high grade malignant tumors of the central nervous system (glioblastoma). In addition to these intrinsically radioresistant tumor types, the relatively responsive epidermoid cancer (squamous cell carcinoma), which can readily be eradicated when the tumor is small, becomes radioresistant at the later stages of growth.

Late stage epidermoid cancer of the upper respiratory and alimentary system (pharynx, larynx and mouth), and late-stage squamous carcinoma of the cervix, are well suited for clinical research with high-LET radiations. The relatively recalcitrant intrathoracic tumors, including cancer of the lung and esophagus, as well as non-resectable pelvic tumors (bladder and prostate) have also been considered for such clinical trials. Preliminary results suggest that neutron therapy may be superior to conventional radiotherapy in some or all of these situations.

Normal Tissue Tolerance (Acute And Late Effects)

Doses large enough to ablate the tumor invariably produce changes in the associated normal tissues. Within narrow limits, the larger the tumor dose, the greater is the probability of local control. Similarly, the larger the dose, the more severe is the reaction and the greater the risk of radiation injury. A dose small enough to entail no risk of injury has little chance of effecting a cure; conversely, it is seldom possible to achieve local control without risking some incidence of significant side effects.

The acute or immediate effects of neutron irradiation appear to be little different from those seen with conventional low-LET radiations. The most readily observed acute reactions occur in

the skin and mucous membranes. With high energy neutron beams the skin within the treatment portals receives a dose considerably lower than the maximum (because of the skin-sparing or "build-up" effect) (11) so that acute tissue tolerance has generally been determined by evaluation of the reaction in mucous membranes. Early tentative estimates of the appropriate dose for neutron therapy in various centers were derived by determining the radiation dosage producing acute mucosal reactions of a standard intensity (some reddening and discomfort but no irreparable injury).

In a clinical experiment at the Fermilab Neutron therapy Facility, treatments planned to deliver 20 Gy over 6 weeks using 1, 2, 3, or 4 fractions a week were carefully tested for normal tissue tolerance based on acute mucosal reactions. Results are shown in Table 4. It will be noted that the total dose delivered is largely independent of fraction number. This is in marked contrast to experience with low-LET radiations where rapid intracellular repair mechanisms lead to a markedly increased tolerance with fractionation. The equivalent photon tolerance doses are also shown in the Table; estimated RBE values range from 3.0 (26 photon fractions of 2.4 Gy) to 2.5 (7 photon fractions of 6.5 Gy).

The clinical RBE is also energy specific, close to 3.0 for high-energy neutron beams (Fermilab) and around 3.5 for cyclotrons operating in the 12-14 MeV range. Conventional radiation therapy commonly requires doses totalling between 60 and 75 Gy in daily fractions over 6-8 weeks; the corresponding neutron doses range from 16-24 Gy, usually delivered in 2-3 fractions a week over 6 weeks.

Dose-limiting late effects of radiation therapy include vascular changes (telangiectasia) in the skin, ischemic necrosis and ulceration of mucous membranes, scarring and fibrosis in the irradiated portions of various tissues and organs, functional and secretory loss in glands (suppression of salivary, pancreatic and gastric secretion), necrosis of bone, and radiation injury to the brain and spinal cord. These late effects usually appear some 12-18 months after completion of treatment, are generally irreversible and represent a serious and disabling consequence of treatment. The risk of severe side effects can be estimated from the calculated TDF factors (Fig. 7). In practice prescribed doses have to be adjusted so that this risk is kept within acceptable limits (say < 5%).

Experimental Design and Protocols

The primary object of the high-LET research program is to determine whether an appropriate course of particle therapy would yield a better clinical result than the best alternative available. In this context "better result" means a significantly higher cure-rate with no concurrent increase in complications, or a similar cure-rate with significantly fewer complications. Here "significant" implies not only statistical significance in the strict sense but also clinical significance, that is, a sufficiently large difference to offset the increased costs (in money, time, inconvenience, and patient discomfiture) of the new modality. A significantly better treatment is believed to be one which yields an improvement of at least ten percentage points in uncomplicated control or survival rates, with a probability of less than 0.05 that the difference could occur by chance. The comparison also implies that both modalities were used optimally, with the technical variables (dose, fractions and time) most appropriate for each modality.

The conventional total treatment time (4-7 weeks) was selected empirically on the basis of many decades of clinical experience. It is believed that this optimal time period is dependent on cellular proliferation rates in normal tissues and tumors and not on the modality used, so that the same overall time may well be

equally suitable for both modalities in the proposed studies. By contrast, the effect of fractionation (number of fractions) depends on intracellular repair mechanisms, which are substantially less effective with high-LET radiations (Fig. 6). Consequently, the required dosage with neutron therapy varies with overall time, but relatively little with fractionation. If fraction number is not critical, treatment with fewer fractions would be more appropriate with neutrons. Based on the foregoing reasoning, most current protocols entail some six weeks of therapy with the photon irradiation delivered on a "daily" (5 days a week) basis, the neutrons being given over 6 weeks in 7 fractions (once a week), 13 fractions (twice a week) or 19 fractions (three times a week).

While the fractionation scheme as such may be quite flexible without disturbing the experiment, the exact doses to be delivered with the two modalities are critically important. The required dose is one which maximizes the probability of local control without unacceptable complications. A valid comparison between two modalities requires that both be delivered optimally. To this end four dose effect functions are required to measure the responses of the tumor and associated normal tissues with each of the modalities studied. Two dose levels (at constant fractionation) are sufficient to define these functions for each modality, if both the tumor control rates and observed reactions or complications are recorded for each group. For each dose level

the tumor control rate [A(d,m)] and the incidence of serious side effects [B(d,m)] is determined. [The subscripts refer to dose level (d) and modality (m) respectively.] The probability of uncomplicated control with a given dose is then C(d,m)=A(d,m)[1-B(d,m)]. The new modality is then judged superior to the old if C(max,new)>C(max,old).

These relationships are illustrated in Figure 8. They emphasize the fact that the success rate observed with neutrons could be higher or lower than that with the controls depending on the dose chosen. The question to be resolved is: "Does the optimal neutron dose yield more successes than the optimal photon dose?" The four arm study described answers this question, although accrual of patients to four experimental groups may be time consuming. A three-arm assay, that is a near optimal photon arm and 2 neutron dose levels, may be an acceptable compromise, and will probably be used in future studies.

Human Experimentation: Informed Consent

There is clearly a significant risk to patients treated with a new modality. This risk may be offset by the expectation that selected patients having tumors known to be resistant to conventional treatment would have a better chance of control with neutron therapy. What is not known is whether this expectation

will be realized in practice, how intense the immediate side effects of the new modality will be, and what unexpected long-term effects might ensue. In order to evaluate what may be quite small differences in response rates, there is need to compare the results in patients receiving neutron therapy with an equivalent group of patients receiving the best available conventional radiation. To this end an experimental design with random allocation of suitable subjects to the experimental and control groups is required. This procedure raises significant ethical questions in the use of human experimental subjects. In practice, federal guidelines for research on human subjects are followed. Institutional Review Boards, consisting of technical and lay members, evaluate treatment procedures to ensure that the therapeutic advantages are sufficient to justify the risks, that the information supplied is clear and adequate, and that no undue persuasion is applied.

A variety of "protocols" have been developed to identify patients with appropriate tumor types and stages, listing specific eligibility requirements and exclusions, together with the necessary pre-treatment studies, including detailed measurements of the extent of the disease, tumor-volume and status of associated normal structures. A schema of management, randomization procedure, stratification into specific sub-groups, details of therapy (dosage, fraction number, overall time, and size of target volume) as well as follow-up evaluation procedures

are specified in detail. Before entering a patient on study the subject's "informed consent" is solicited. For this purpose the patient is fully informed of the nature of the disease, the experimental design, procedures used and the prognosis in regard to tumor control and possible side effects or complications. An interesting observation is that patients entered into randomized trials show better results on the average, irrespective of which experimental treatment they receive, than comparable groups of patients receiving standard therapy from the same or equally competent physicians not rigorously controlled by study-protocol requirements.

Neutron Treatment Schemes

A tumor is not a sharply demarcated anatomical structure or organ, but has a diffuse growing edge, which represents a falling gradient of cell concentration extending a considerable distance from the macroscopic boundary. In all forms of therapy for localized cancer, the need to remove or irradiate a significant "margin of safety" around the growth is recognized. In practice, a "target volume" is designed to include the known tumor as well as an appropriate margin of uncertainty. The dose levels which must be specified in radiotherapy include the minimum tumor dose , that is, the smallest dose at any point within the primary target volume, and the maximum tissue dose , or the highest dose received

by any significant volume of tissue within the irradiated volume. The minimum tumor dose determines tumor response and is a critical parameter in the clinical prescription. Similarly, the maximum tissue dose is a critical determinant of the risk of complications or irreversible irradiation damage in any of the tissues or organs traversed by the beam. Ideally a treatment plan is devised in which the minimum tumor dose is effective in that the probability of tumor control is high, while maximum tissue doses are such that no serious normal tissue damage is likely to ensue. One of the requirements for treatment planning is to ensure, as far as possible, that such a relationship between minimum tumor and maximum tissue doses can be achieved.

The risk of late effects limits the total neutron dosage which may be delivered over 6 weeks to levels not exceeding 24 Gy (Fermilab), down to 20 Gy or less with the low energy cyclotron beams. Treatment times are generally around 6 weeks and the frequency of exposure ranges between 1 and 4 fractions weekly. Fraction size varies from about a maximum of about 3 Gy per fraction (6 to 7 weekly exposures) down to 1 Gy per fraction or less (for up to 24 "daily" treatments).

There has been considerable interest in the United States, mainly for logistic and economic reasons, in using mixed beam procedures, that is, neutron treatment as an adjunct to conventional radiotherapy. The neutron component has been delivered in a

regular sequence interspersed with the photon therapy (2 neutron treatments and 3 photon treatments each week, for example) or as a neutron boost following delivery of approximately two-thirds of the total tumor dosage with photons. Mixed beam procedures have the logistic advantage of reducing the number of visits to the neutron facility (in some cases quite distant from the referring center). In some centers greater penetration and better beam definition can be obtained with photons than with the neutron beam, so that better treatment plans, higher doses to the target volume and less damage to adjacent normal structures, can be obtained with, the mixed beam than with the neutron modality alone. On the other hand use of mixed beams may dilute the biological effect associated with the high-LET modality and thus minimize some of the advantages of the high-LET treatment. Nevertheless, a number of protocols involving mixed beam therapy are nearing completion. Some of these show small, though statistically significant, advantages from adding the neutron component.

Another possible application of mixed beams, which has not yet been exploited in clinical practice, is the synergism observed when high-LET particles are delivered shortly before photon irradiation. Radiobiological studies (47) have shown that modest doses of neutrons may be sufficient to inhibit intracellular repair mechanisms for several hours after exposure rendering cells exceptionally sensitive to subsequent photon irradiation at that

time. Thus a small dose of neutrons, not necessarily of high energy or well-collimated (using a small inexpensive generator), immediately preceding each dose in a well-planned course of photon beam therapy, may be clinically advantageous. The logistics of such a procedure are likely to remain formidable until hospital-based facilities, having easy acccess to both modalities, become available.

EVALUATION: ROLE OF THE ONCOLOGY DATA BASE

Investigation of a new modality, such as that envisioned in the high-LET program, requires that the response of each individual patient, in both the experimental and control arms of the study, be evaluated as throroughly as the situation permits. At the present stage of development these patients providement a unique source of data, which is unlikely to be duplicated in the future, on the response of human tissues and tumors to neutron irradiation. Such data are invaluable, not only to determine whether the new modality is superior to conventional treatment, but also to study immediate and late effects in various tissues traversed by the beam. Unpredictable or at least unanticipated effects may also be observed in long-term survivors many years after treatment. Analysis of these reactions will require review of treatment procedures, and often extensive reconstruction of treatment plans, to determine dosage factors at the site of the

reaction. Biologically significant parameters (treatment volume, time, fraction size and sequence) may also need to be re-evaluated in relation to the specific site affected. For this reason the clinical findings and all technical factors, including much seemingly irrelevant data, must be retrievable. Not only must each patient's record be available for analysis, but merged files for the statistical derivation of tolerance levels and factors affecting response will need to be generated for specific sites, dose-levels, reaction-levels and follow-up periods. A comprehensive data base is, therefore, an essential component of the program.

The radiation treatment schedule for each patient would have to include information on (a) the character and extent of the disease, (b) definition of the target volume, (c) position and direction of the radiation beams, (d) identification of tissues or organs traversed by the beams, (e) dosage distributions throughout the irradiated volume, (f) dose-fractionation sequences, and (g) biological parameters (RBE and TDF calculations) for tumor and associated normal tissues.

Given this information, the response of the tumor, the pattern of recurrence, if any, and the evolution of radiation reactions or complications, can be correlated with technical factors (dose, modality, time, volume), and characterized in terms of cellular or other models of radiation injury.

For purposes of analysis a given treatment scheme is specified by the following variables:

1. DOSE (minimum tumor dose or maximal dose within organ of interest, total for whole course);

2. Integral number of FRACTIONS;

3. Total treatment TIME (inclusive days from first exposure to last, equals elapsed time +1);

4. SIZE (field size, target-volume or tumor mean diameter);

5. GAP (interval between split courses if any; a further 4 entries for dose, fractions, time and size is needed after each gap);

END RESULTS AND LATE EFFECTS The clinical record should contain both graded and quantal data together with the pathogenetic time-sequence of the reactions and the onset and duration of tumor remission. In this regard the tumor response and the reactions of each normal tissue or organ of interest must be separately annotated.

Regression of the tumor is observed in relation to the initial response (a function of radiosentitivity and growth) and the end-result (cure or recurrence). The immediate response is assessed from a series of dated volume measurements, before, during and after the course of treatment, from which doubling times and cell loss rates can be inferred. End-results are determined by serial follow-up, noting the dates of maintained remission or of recurrence. From this information the following observable variables are derived:

1. Initial tumor volume (at first treatment);

2. Observed pre-treatment growth parameters (doubling times);

3. Rate of macroscopic regression following treatment;

4. Period of observation without recurrence;

5. Time to appearance of first recorded recurrence;

6. Tumor volume at time of observed recurrence;

7. Observed or inferred post-recurrence growth parameters.

Normal tissue reactions or late effects may appear after a latent interval, ranging from a few days to many years, may be transient or permanent, and vary widely in severity. To record this information, reactions have to be observed and graded at suitable intervals. As a general guide to grading reactions, the following 10-level ranking procedure has been proposed:

0 = No detectible reaction

1 = Doubtful, suspected or threshold response

2 = Transient radiation effect

3 = Minimal long-lasting radiation reaction

4 = Permanent radiation injury of limited extent

5 = Marked radiation damage (high-dose effect)

6 = Severe radiation injury but no necrosis

7 = Severe and extensive damage with necrosis

8 = Massive or life-threatening radiation injury

9 = Unknown or data not available

A less demanding 5-grade code preferred by some workers defines reactions as (a) mild, (b) moderate, (c) severe, (d) life-threatening, and (e) directly lethal.

RESULTS OF NEUTRON BEAM THERAPY

Radiation oncologists have traditionally been exceptionally rigorous in reporting results of clinical trials. Response is defined in terms of long-maintained remission (total disappearance of the tumor) for observation periods of 5 years or more. Control rates are determined by survival, without evidence of disease, in a subset of treated patients whose subsequent actuarial life table matches that of the normal population.

The initial response of an irradiated tumor (symptomatic relief, more or less rapid regression of the growth or its apparent disappearance) depends on the rate of removal of dead or sterile cells when cell production is temporarily arrested by the treatment, but is not necessarily a measure of the efficacy or eventual outcome of such treatment. On the other hand the frequency of maintained remission and the duration of the local response, when observations are continued over many years, is an index of the efficacy of treatment. This is true even when the disease has disseminated widely before treatment is initiated, leading to eventual death from metastases. If neutrons are more efficacious than conventional therapy, this effect should be observed most clearly in the rates of local control, and will probably be less obvious in regard to overall survival.

The combined experience of neutron therapy installations throughout the world now totals some 6,000 patients treated for a wide variety of late stage malignant tumors (Table 2). In this series there are several reports on patients with particularly radioresistant tumors, in whom gratifying long-term responses have been observed (Table 5).

RESULTS IN HEAD AND NECK CANCER Local control of advanced epidermoid carcinoma of the upper alimentary and respiratory tracts irradiated with the neutron beam facility at the Hammersmith Hospital, London, were compared with randomized controls from the same population treated with conventional high-voltage x-ray therapy. Results reported by Catterall and Bewley (21), showing markedly improved local control with neutrons, are given in Table 6 together with analogous results from Amsterdam (12). No significant differences could be demonstrated in survival rates or mean survival times for this series, probably because of the relatively high incidence of metastases appearing in those patients in whom local control is achieved.

A study of mixed beam irradiation (3 photon fractions and 2 neutron fractions each week) was initiated some years ago in the United States and is now nearing completion. These results (12, 44), show a small improvement in the mixed beam irradiated group

compared with the photon controls, which is marginally significant at the present time. A concomitant study on the addition of a small neutron "boost" following delivery of 2/3 of the total prescribed dose with conventional radiation, has not shown any advantages over a control group treated with photons throughout.

A particularly responsive group are those patients with advanced, non-resectable adenocarcinomas of salivary gland origin. These are, as a rule, slow growing, well-differentiated tumors relatively resistant to conventional irradiation. These patients have demonstrated a slow but continuing, and in most cases complete, regression of the tumor mass following neutron irradiation. It is now believed that neutron beam therapy is the treatment of choice in this group of tumors (40).

HIGH-GRADE MALIGNANT BRAIN TUMORS (GLIOBLASTOMA) These highly malignant tumors are seldom amenable to complete surgical ablation, and when incompletely resected the patient seldom survives beyond 1 year. The median survival time can be prolonged significantly by intensive radiotherapy. Early recurrence is almost inevitable and cures are exceedingly rare. Substitution of post-operative neutron beam irradiation in incompletely resected cases of glioblastoma did not prolong survival over the group receiving conventional post-operative radiotherapy (22). However, post-mortem examination of the irradiated brain in these patients

usually revealed wide-spread and often complete destruction of the tumor, accompanied by severe radiation damage to the normal brain.

A modest reduction in dosage, sufficient to avoid fatal radiation injury to the normal brain, failed to cure the tumor. This tantalizing situation suggested that changes in technique might lead to effective tumor ablation without serious brain damage. A mixed beam study (42) also failed to demonstrate improved survival and yielded a similar frequency of tumor ablation with serious brain damage in most patients so treated. Dose searching pilot studies with varying mixtures of neutrons and photons at varying intervals are still being pursued, and protocols are being developed for the combined use of neutrons in maximal safe doses, together with drugs designed to specifically sensitize the hypoxic components of the tumor.

PELVIC TUMORS (UTERUS, BLADDER, PROSTATE) Many of the neutron beam installations operate at relatively low energies and are sufficiently penetrating only for relatively accessible tumors, such as those of the head and neck. With the recent introduction of high energy units, protocols have been developed for irradiating late stage localized pelvic tumors. A common condition suitable for study is the late stage epidermoid cancer of the uterine cervix. Results of a trial of mixed beam irradiation compared with conventional photon therapy have been

reported (46). A desirable component of radiotherapy for cancer of the cervix is intracavitary irradiation by means of a radioactive insert in the uterine cavity and vaginal vault, which delivers intense but well localized irradiation to the center of the tumor. Since this procedure improves the prognosis substantially, it is used whenever possible. When intracavitary treatment was technically feasible, the addition of a neutron component to the external beam part of the treatment did not improve results significantly. On the other hand, when the intracavitary treatment could not be given, the addition of the neutron component did appear to be advantageous. Pilot studies are under way in neutron therapy of the bladder and prostate, but at the present stage no randomized controlled clinical trials have been instituted.

CARCINOMA OF THE PANCREAS This tumor is seldom seen at an early enough stage for successful surgical removal, and consequently is notoriously difficult to treat effectively. Five year survival rates with conventional radiotherapy in pancreatic cancer seldom exceed 8% (39); the median survival time is generally under 5 months. The tumor histological type, like other adenocarcinomas of the gastro-intestinal tract, is that commonly associated with intrinsic radioresistance. For this reason, a trial of neutron therapy for pancreatic cancer seemed appropriate, and an initial trial was instituted (43) at the Fermilab Neutron Therapy Facility in Chicago where a sufficiently penetrating beam is available.

It was difficult to evaluate the local response and length of maintained tumor regression, except in those few cases in whom surgery was required for other purposes so that the tumor area could be inspected. The results of the study necessarily relate to patient survival, and are consequently complicated by the tendency of this tumor to spread and metastasize. While the initial mortality is high, there may well be a residual "cured" sub-population, possibly as many as 20% of all patients treated. This appears somewhat better than historical controls. A rigorously randomized controlled clinical trial, comparing neutron irradiation in this site with high dosage precision photon beam has recently been started.

SARCOMA OF BONE AND SOFT TISSUE These tumors are conventionally treated by radical surgical procedures, often entailing amputation, along with systemic chemotherapy. In those situations where surgery is not possible or not accepted by the patient, radiotherapy with or without chemotherapy remains the only option promising some prospect of long-term control. Control rates with conventional radiotherapy delivered in maximal tolerated doses remain low. Neutron beam therapy has been tried for these conditions in several centers (12, 56). Collected results are shown in Table 5. While the numbers are small, and comparison is made only to historical controls, the initial results appear to be substantially better than any other series reported so far.

CONCLUSIONS

Summarizing the universal experience with neutron beam therapy is difficult at this stage. There are indications that high-LET radiation may be superior for certain specific tumor types, but unequivocal statistical proof of such superiority is lacking at the present time. No study thus far has indicated the neutron beam to be worse than conventional therapy.

One advantage of the neutron beam unit is the practical feasibility of reduced fractionation in radiotherapy. A 6-week course of therapy could be reduced to 7 or 13 fractions (once or twice weekly) instead of the 30 fractions required with conventional radiation therapy. This logistic advantage, together with a modest improvement in control rates and no additional morbidity, may be sufficient to offset the relatively high cost of the equipment. For these reasons the place of neutron beam units in the armamentarium of the radiation oncologist practising in a large medical center seems assured.

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TABLE 1

Extra nuclear cascades initiated by photons or electrrons and by neutrons: main differences affecting the microscopic transfer of energy to tissue.

Incident beam	PHOTONS	NEUTRONS
scattered particles	γ, e^+, e^-	γ,p,n,d,α and C,N,O ions
mass	0, 1 m	0, 1836 m or greater
velocity distributions	mostly c/4 to c	mostly 0 to c/5 except for some protons
corresponding to	17 keV (c/4)	~20 MeV protons (c/5)

m is the electron rest mass; c is the velocity of light in vacuum.

Table 2

Neutron Therapy Facilities Throughout the World (Dec. 1980)

	MAXIMUM ENERGY MeV	PATIENTS EVALUATED
Kankerinstitut, Amsterdam	D-T	420
University Hospital, Hamburg-Eppendorf	D-T	232
Zentralinstitut f. Krebsforschung, Dresden	13.5	650
Western General Hospital, Edinburgh	14	411
Hammersmith Hospital, London	15	900
University of Washington, Seattle	21	404
Cleveland Clinic (GLANTA), Cleveland	25	278
National Institute of Radiological Sciences, Chiba	30	400
Naval Research Laboratory (MANTA) Washington, D.C.	35	250
University of Texas (TAMVEC), Houston	50	719
Fermilab, Chicago	66	924

Table 3

T.D.F. EQUIVALENTS FOR NEUTRON THERAPY

(A) p(66)Be(49); K=.024; TIME = 6 WEEKS

DOSE (GY)	FRACTIONS 7	10	13	16	19	22	25
15	74	73	72	71	71	70	70
16	80	79	78	77	76	76	75
17	86	84	83	83	82	81	81
18	92	90	89	88	88	87	86
19	98	96	95	94	93	93	92
20	104	102	101	100	9	98	98
21	110	108	107	106	105	104	103
22	116	114	113	112	111	110	109
23	123	121	119	118	117	116	115
24	129	127	125	124	123	122	121
25	135	133	131	130	129	128	127

(B) d(21.5)Be(16); K=.030; TIME = 6 WEEKS

DOSE (GY)	FRACTIONS 7	10	13	16	19	22	25
15	93	91	90	89	88	88	87
16	100	98	97	96	95	95	94
17	107	106	104	103	102	102	101
18	115	113	112	111	110	109	108
19	122	120	119	118	117	116	115
20	130	128	126	125	124	123	122
21	138	135	134	132	131	130	129
22	145	143	141	140	139	138	137
23	153	151	149	147	146	145	144
24	161	158	156	155	154	153	152
25	169	166	164	162	161	160	159

(C) d(16)Be; K=.030; TIME = 4 WEEKS

DOSE (GY)	FRACTIONS 5	7	10	13	16	19	22
12	77	75	74	73	72	73	71
13	84	83	81	80	80	79	78
14	92	90	89	88	87	86	86
15	99	98	96	95	94	93	93
16	107	106	104	103	102	101	100
17	115	113	112	110	109	108	108
18	123	121	119	118	117	116	115
19	131	129	127	126	124	123	123
20	140	137	135	133	132	131	130
21	148	145	143	141	140	139	138
22	156	154	151	149	148	147	146

EO

Table 4

Clinical RBE for Acute Skin and Mucosal Reactions

FRACTIONS PER WEEK	4	3	2	1
Nominal weeks treatment	6	6	6	6
Dose per fraction (Gy)	0.80	1.00	1.50	2.50
Number of fractions*	25-27	20-21	13-14	7-8
Total dose (Gy)	20.0-21.6	20.0-21.0	19.5-21.0	17.5-20.0
Treatment time (days)	43-47	44-48	43-49	43-50
Low-LET Equivalent (TDF=100)	62-64	59-61	53-55	46-48
Estimated RBE ($\pm$ range)	3.04($\pm$.06)	2.92($\pm$.04)	2.67($\pm$.05)	2.51($\pm$.10)
Normalizing Constant (K in TDF formula)	.024	.025	.025	.027

*Observed minimum and maximum number of fractions yielding the standard response; all other factors were necessary consequences of these observed tolerances.

TABLE 5

NEUTRON BEAM - INTERNATIONAL STUDIES

		(a) : (b)	
1. SALIVARY TUMORS	HAMMERSMITH (21)	25 : 31	
	HOUSTON (31)	8 : 13	
	AMSTERDAM (12)	10 : 11	
	SEATTLE (12)	7 : 11	
	FERMILAB (40)	11 : 15	
	TOTAL	61 : 81	(76%)
2. SARCOMA OF BONE	MANTA (12)	6 : 7	
	CHIBA (62)	15 : 18	
	FERMILAB*	4 : 6	
	TOTAL	25 : 31	(81%)
3. SOFT TISSUE SARCOMA	HOUSTON (56)	20 : 29	
	HAMMERSMITH (21)	23 : 28	
	MANTA (12)	4 : 7	
	CHIBA (62)	5 : 7	
	FERMILAB*	3 : 6	
	TOTAL	55 : 77	(71%)
4. MELANOMA	CHIBA (62)	12 : 14	
	TOTAL	12 : 14	(86%)

(a): Local controls; (b): Cases studied. *Unpublished data

Table 6

Long-term Local Control in Locally Advanced Epidermoid Carcinoma (Randomized Studies)

	PHOTONS		NEUTRONS	
	Treated	Controlled	Treated	Controlled
Hammersmith (15 MeV)	63	12	70	53
Amsterdam (D-T)	13	7	41	22
Fermilab (66 MeV)	69	36	51	26
TOTAL	145	55	162	101
Local Control Rate	38%		62%	

Figure Legends

Figure 1 - Interdependent effects of LET (or RBE) and oxygen tension (OER) on the cellular response. Survival curves show the greater RBE (steeper slope) with neutrons and the larger OER with photons. The insert shows the values of D_0 obtained from the four curves, illustrating the relationship of RBE and OER from interaction of the four variables. (Compiled from data by Gragg et al, Ref. 28).

Figure 2 - Determination of RBE for the gastrointestinal syndrome in mice (5 day lethality). A markedly greater effect of fractionation is observed with photons compared with neutrons. The RBE is consequently larger with increased fractionation. (Compiled from data by Redpath et al, Ref. 53).

Figure 3 - Relative biological efficiency for skin damage as a function of dose per fraction. Lettering refers to human, pig, rat and mouse skin; subscripts indicate number of fractions used (after Field, Ref. 25).

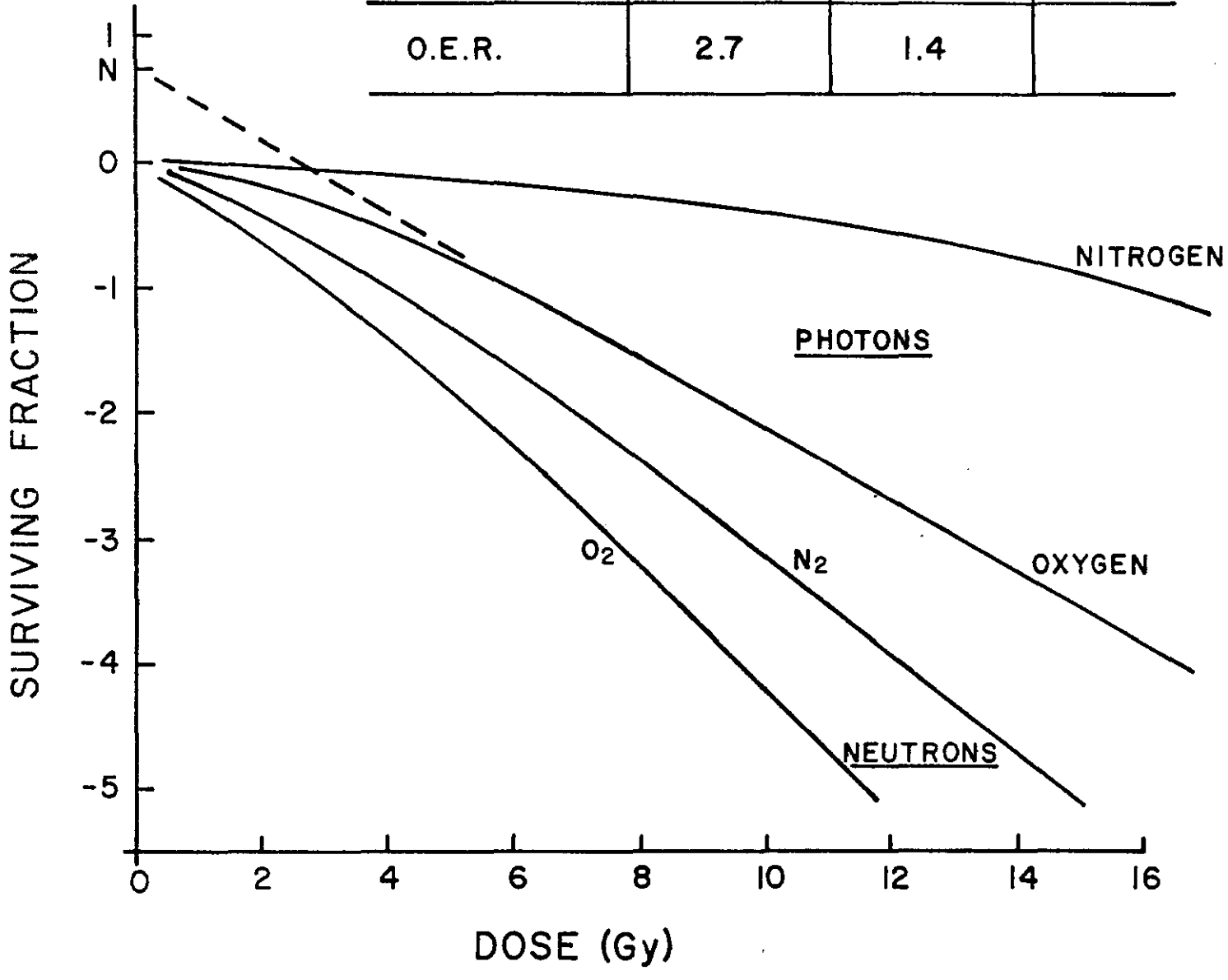
Figure 4 - RBE for various normal tissues as a function of the dose per fraction of fast neutrons produced by 16 MeV deuterons on beryllium (Hammersmith Cyclotron, after Field, Ref. 25).

Figure 5 - Ratio of fractionated dose to single dose for equal effect on pig skin, as a function of the number of fractions. The recovery factor for photons is greater than that for neutrons.

Figure 6 - Recovery rates for photons and neutrons measured in mammalian skin (human, rat, pig and mouse). Results appear to be consistent in all species studied. The slope of the fractionation parameter is 0.26 for photons but only 0.04 for neutrons. These parameters are used in calculating TDF factors for the two modalities (25).

Figure 1

ENVIRONMENT	Do PHOTONS	Do NEUTRONS	R.B.E.
OXYGEN	1.47	0.88	1.7
NITROGEN	3.94	1.22	3.2
O.E.R.	2.7	1.4	



FRACTIONS	LD-50 PHOTONS	LD-50 NEUTRONS	R.B.E.
1	9.86	4.82	2.0
3	16.11	5.99	2.7

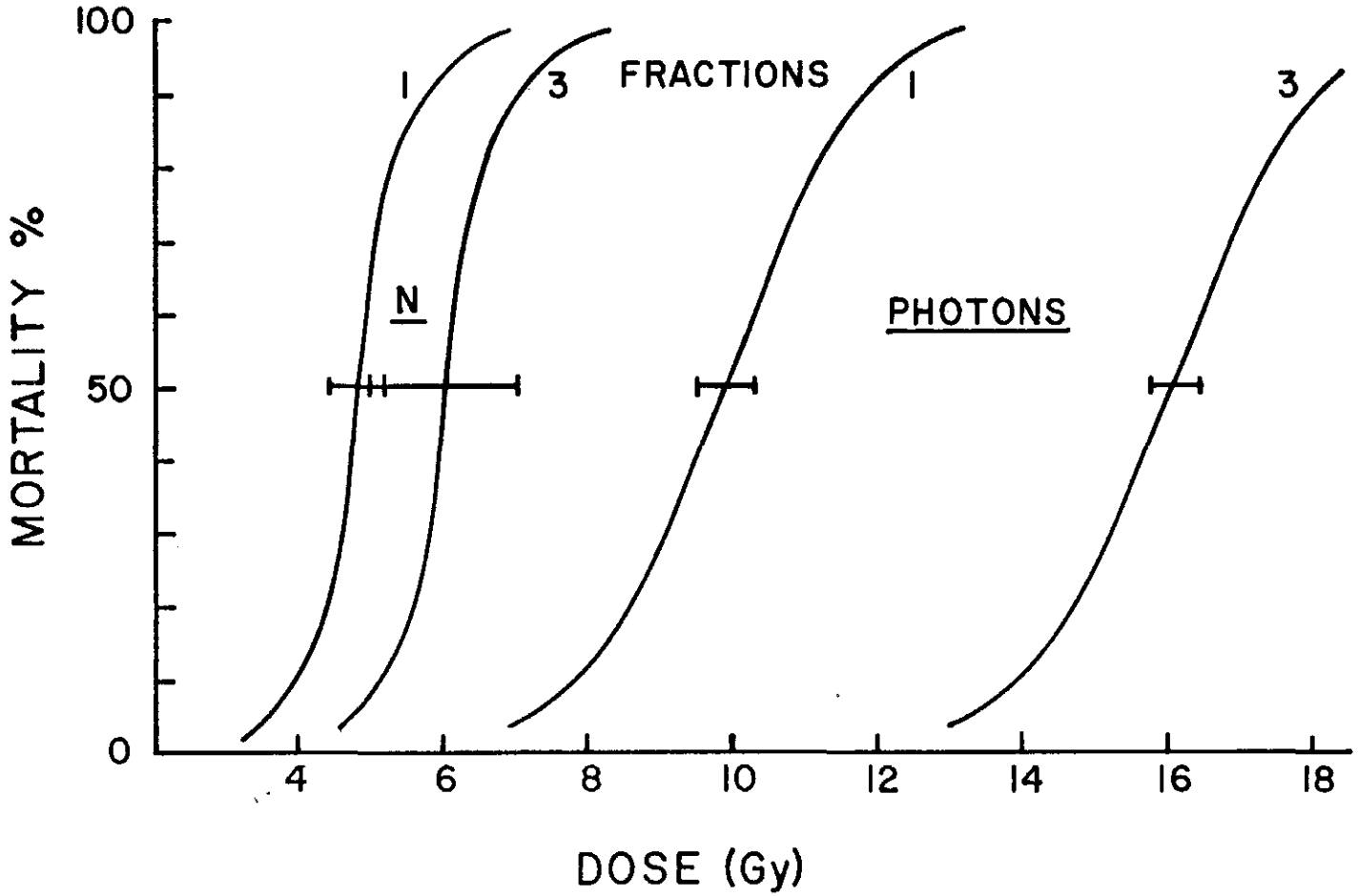


Figure 2

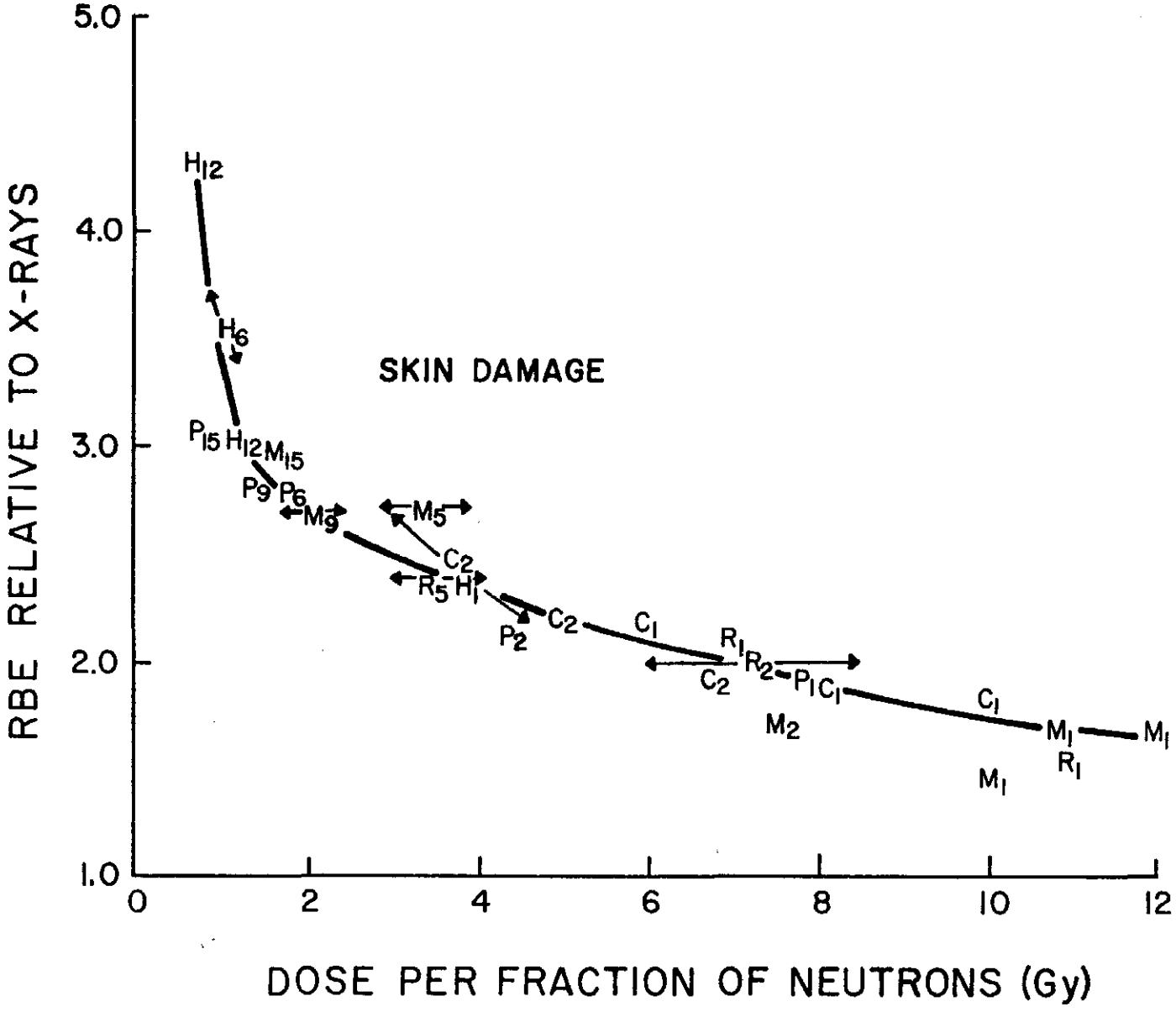

RBE RELATIVE TO X-RAYS
5.0
4.0
3.0
2.0
1.0
SKIN DAMAGE
H12
H6
P15 H12 M15
P9 P6
M3
M5
C2
R5 H1
P2
C2
C1
R1
R2
C2
P1 C1
C1
M2
M1
M1
R1
M1
0
2
4
6
8
10
12
DOSE PER FRACTION OF NEUTRONS (Gy)

Figure 3

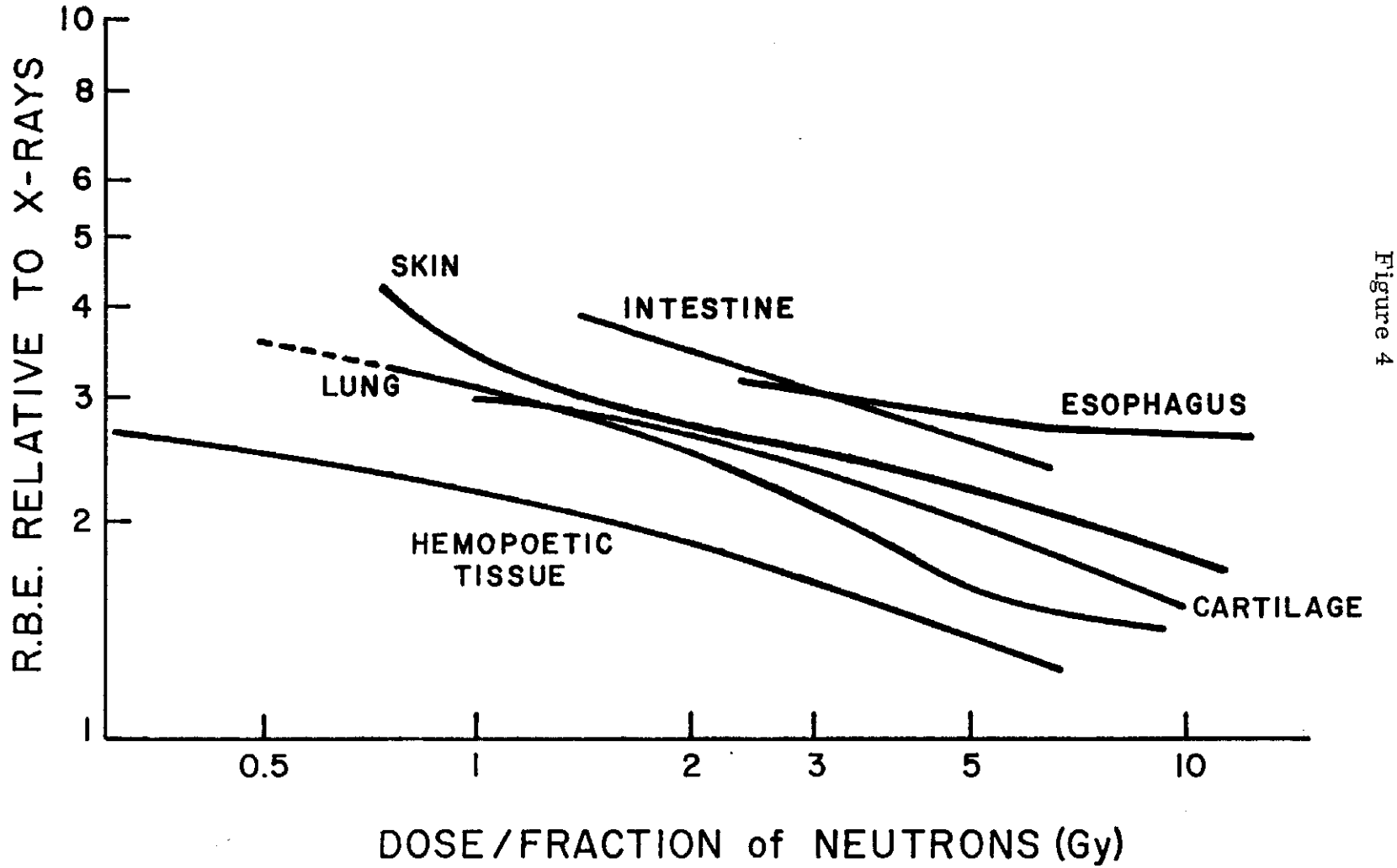

R.B.E. RELATIVE TO X-RAYS
10
8
6
5
4
3
2
1
SKIN
INTESTINE
LUNG
ESOPHAGUS
HEMOPOETIC TISSUE
CARTILAGE
0.5
1
2
3
5
10
DOSE/FRACTION of NEUTRONS (Gy)

Figure 4

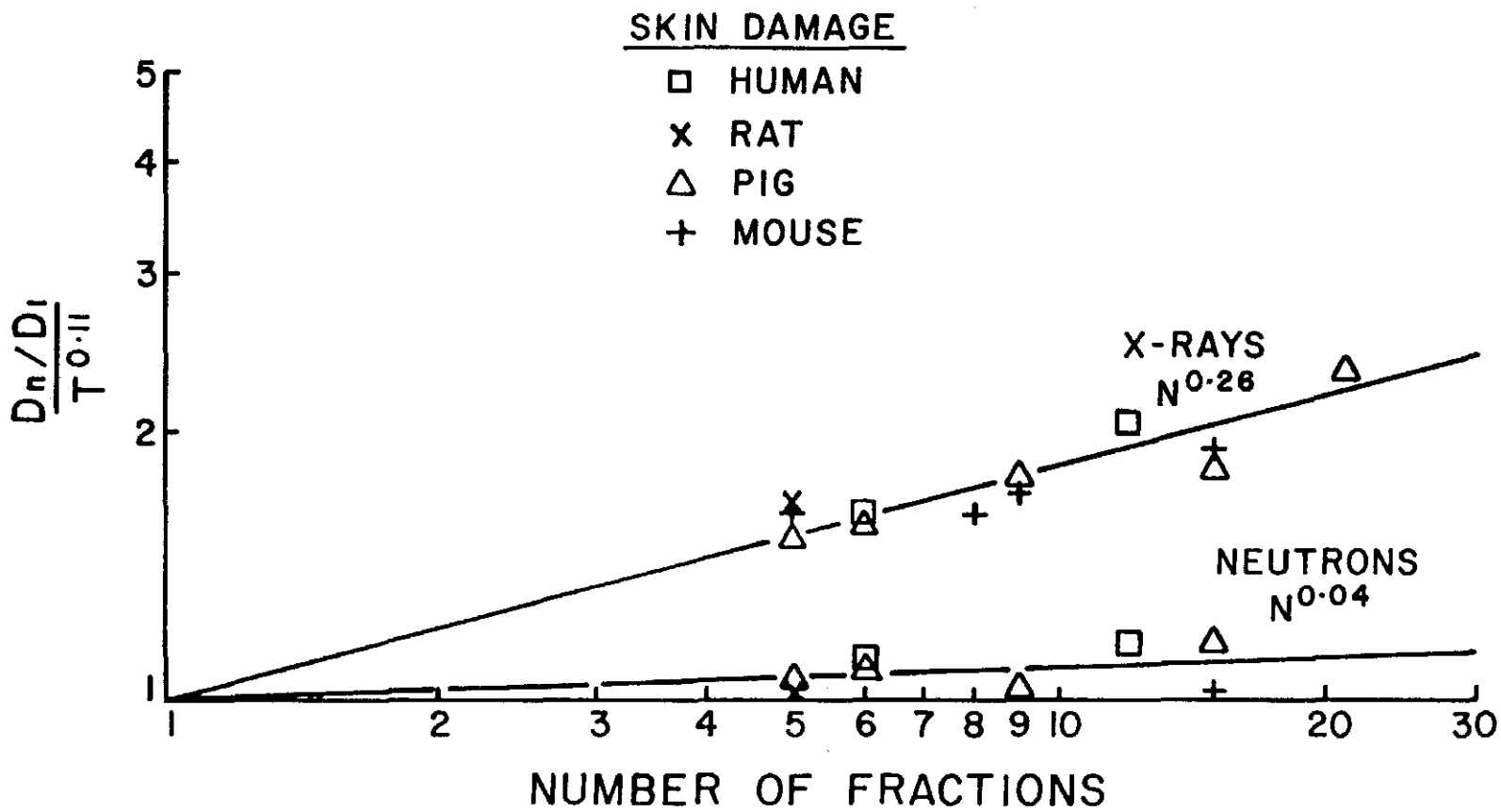
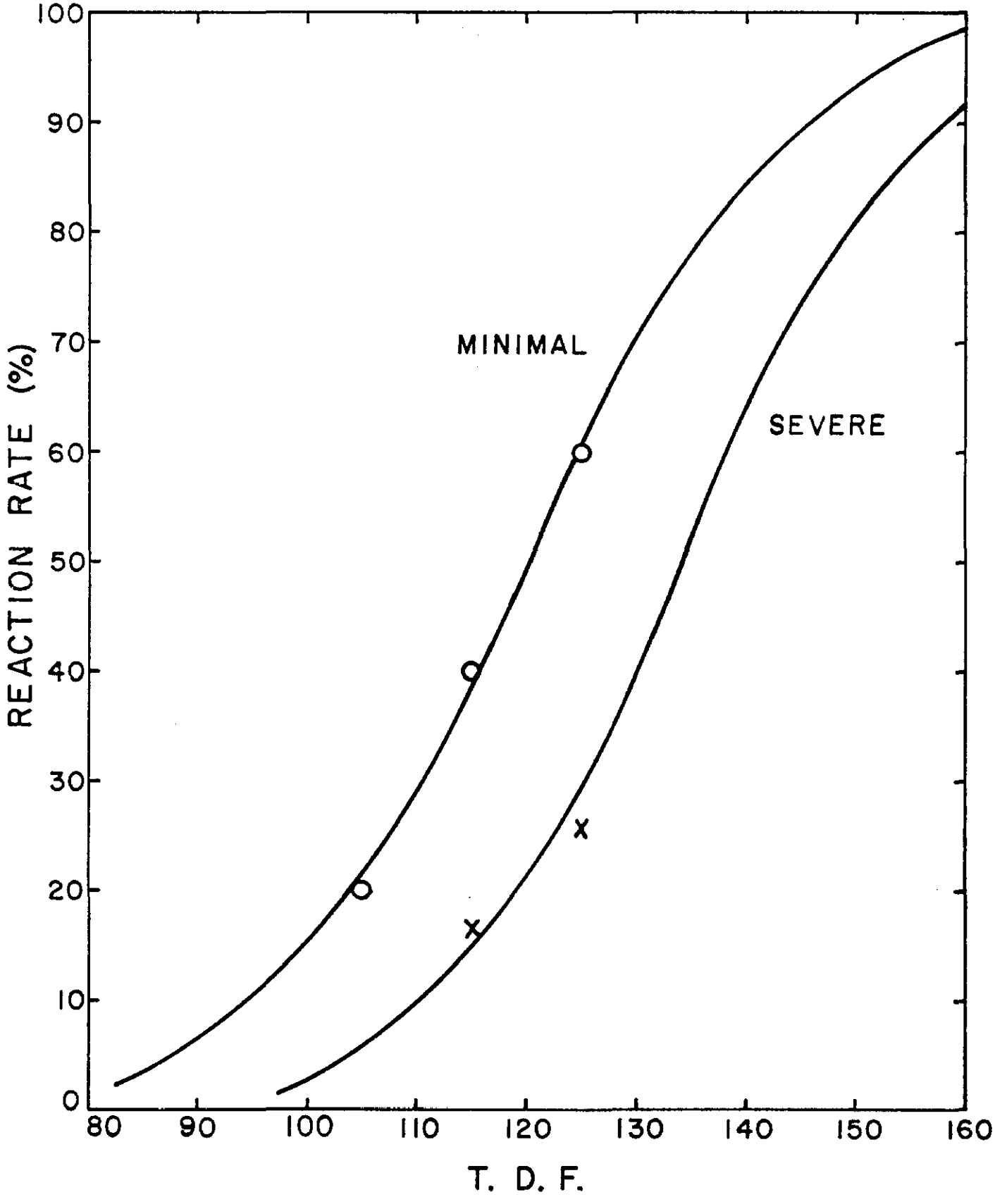

SKIN DAMAGE
HUMAN
RAT
PIG
MOUSE
$\frac{D_n/D_1}{T^{0.11}}$
X-RAYS
$N^{0.26}$
NEUTRONS
$N^{0.04}$
1
2
3
4
5
6
7
8
9
10
20
30
NUMBER OF FRACTIONS

Figure 5

Figure 6


100
90
80
70
60
50
40
30
20
10
0
REACTION RATE (%)
MINIMAL
SEVERE
80
90
100
110
120
130
140
150
160
T. D. F.