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The Potential for Heavy Particle Radiation Therapy

by

M. R. Raju
T. L. Phillips*

*Department of Radiology, University of California, San Francisco, CA 94122.

los alamos
scientific laboratory
of the University of California
LOS ALAMOS, NEW MEXICO 87545

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PREFACE

Among the functions of the Subcommittee on Radiobiology, Committee on Nuclear Science of the National Academy of Sciences/National Research Council, has been the identification of areas of science in which interchange appears to be deficient and to stimulate such interchange through sponsoring symposia or encouraging the publication of relatively brief but informative treatises in specific areas of endeavor. In recent years, the Subcommittee perceived a need in the scientific community for an informative document describing the uses of accelerator beams in radiotherapy. As Chairman of the Subcommittee at the time, I approached M. R. Raju and T. L. Phillips to inquire if, on the basis of their broad experience in this area, they would prepare such a document. I am pleased to see the material that they have assembled, which I know will fulfill very well this need as perceived by the Subcommittee. On behalf of the Subcommittee, may I thank them both for spending the substantial amount of time and effort required to provide this worthwhile service to the scientific community.

V. P. Bond, M.D.
Associate Director
Brookhaven National Laboratory
Associated Universities, Inc.
Upton, Long Island, New York

THE POTENTIAL FOR HEAVY PARTICLE RADIATION THERAPY

by

M. R. Raju and T. L. Phillips

ABSTRACT

Radiation therapy remains one of the major forms of cancer treatment. It is concerned primarily with local and regional control. Current megavoltage x-ray therapy is often successful when the cancer is small and detected early. When the cancer is locally extensive, failure is common. When x rays are used in radiotherapy, there are large variations in radiation sensitivity among tumors because of the possible differences in the presence of hypoxic but viable tumor cells, differences in reoxygenation during treatment, differences in distribution of the tumor cells in their cell cycle, and difference in repair of sublethal damage. When high-LET particles are used, depending upon the LET distribution, these differences are reduced considerably. Because of these differences between x rays and high-LET particle effects, the high-LET particles may be more effective on tumor cells for a given effect on normal cells. Heavy particles have potential application in improving radiotherapy because of improved dose localization and possible advantages of high-LET particles due to their radiobiological characteristics. Protons, because of their defined range, Bragg peak, and small effects of scattering, have good dose localization characteristics. The use of protons in radiotherapy minimizes the morbidity of radiotherapy treatment and is very effective in treating deep tumors located near vital structures. Fast neutrons have no physical advantages over ^{60}Co gamma rays but, because of their high-LET component, could be very effective in treating tumors that are resistant to conventional radiations. Negative pions and heavy ions combine some of the advantages of protons and fast neutrons.

I. INTRODUCTION

Radiation therapy, surgery, and chemotherapy are the major forms of cancer treatment. Radiation therapy and surgery are used for the local control of disease and chemotherapy for disseminated tumors (clinical and subclinical). About half of all new cancer cases receive surgery and the other half radiotherapy. Chemotherapy may be used with either form of therapy. Failure to

control or cure may occur either at the primary tumor, regional lymph nodes, or distant sites. Improvement in radiotherapy is concerned primarily with local and regional control. Radiation is not highly selective on tumor cells but affects normal cells as well. The therapist has established empirically that fractionated radiotherapy delivered five days a week over four to eight weeks is often more effective in killing tumor cells than in damaging normal tissues. Thus, the "therapeutic ratio," or ratio of tumor kill to normal tissue damage, has been improved over the years. In many cases, normal tissues retain their integrity and anatomic and functional properties. In such cases, radiotherapy becomes very attractive and often preferable to surgery, although the survival statistics of the two methods are nearly the same. Cancer of the larynx is an example. The patient usually loses his voice by undergoing surgery. With care, it is quite often possible to preserve the vocal cord and integrity of the entire larynx in radiation therapy (Moss, 1972). Radiotherapy, followed by planned surgery within two months, is a very effective treatment for certain sites.

At present, radiation therapy is often successful when the cancer is small and detected early. The choice of surgery or radiotherapy depends on the site of the tumor and the nearby normal tissues. When the cancer is locally extensive or involves a major region of the body, radiation therapy is preferred to surgery but is only successful in half, or less, of the patients. When the cancer has metastasized, the patient is rarely cured by radiotherapy (Kramer, 1972), and chemotherapy may be helpful. Local control of the disease becomes even more important with developments of immunotherapy and chemotherapy aimed to control metastases. Because these other methods can deal only with very small deposits of solid tumors, combinations of radiotherapy with chemotherapy are expected to become more important and with immunotherapy when it develops. The radiotherapist aims to destroy every tumor cell; however, in practice, the damage to normal tissues both outside the treatment volume but in the treatment beam and inside the treatment volume restricts the delivery of tumoricidal doses. Sparing normal tissues, by whatever means possible, is a key to success in radiation therapy. Thus, there are two problems: (1) decreasing the dose to normal tissues outside the treatment volume and (2) increasing the biological effect on tumor cells for a given effect on normal cells inside the treatment volume.

In the early days of radiation therapy with low-energy x rays, the skin and subcutaneous normal tissues, because of poor penetration, were the limiting factors in delivering tumoricidal doses. Therefore, radiotherapy was effective

only for the treatment of superficial tumors. With the advent of low-LET megavoltage radiation sources (x rays, gamma rays, and electrons) with their buildup and improved depth-dose, the skin and subcutaneous tissues are rarely a problem. Major weaknesses in the current megavoltage low-LET radiotherapy are the inability to define precisely the location and extent of the tumor and to avoid certain critical organs such as the kidney, lung, intestine, and spinal cord in some cases. Thus, a large volume of normal tissues suspected to contain tumor cells also has to be included in the treatment volume. Such normal tissues quite often have an appreciably greater volume than that of the tumor. The normal tissue tolerance depends on its type, the dose given, and the total volume exposed to radiation. The larger the volume, the smaller the dose that can be tolerated. Therefore, damage to normal tissues within the treatment volume is a limiting factor in delivering tumoricidal doses with conventional radiotherapy.

In spite of these problems, great progress has been made in radiation therapy in the past two decades. This progress is due to a better understanding of the biology of cancer and the radiation tolerance of normal tissues, better methods of radiation dose measurement, more careful treatment planning, and use of penetrating megavoltage radiation with improved physical distributions. Nevertheless, failure to cure is common. Suit (1969) has estimated that 175,000 cancer deaths annually occur in the United States despite treatment with radiotherapy. Nearly one-third of these deaths can be attributed to recurrence of the tumor within the treatment volume (see Table I). It should be emphasized that massive increases in the delivered or biologically effective dose are not required for large increases in local tumor sterilization. In general, the relationship between dose and percent tumor cure is a very steep one, and only a 10 to 20% increase in dose can increase the cure or control from 20 to 80%. This has been well documented in several head and neck sites by Shukovsky and Fletcher (1972). Thus, a small increase in physical dose delivery capability or a small increase in relative biological effectiveness (RBE) for tumors, compared to limiting normal tissues, can be of extreme importance.

Heavy charged particles (particles heavier than electrons), unlike x rays, deposit practically no dose beyond their sharply defined range. Thus, by using charged particles such as negative pions, protons, helium ions, and heavier ions, it is possible to confine the maximum dose to the treatment volume and to minimize the dose to normal tissues outside the treatment volume. With the exception of protons, the remainder of heavy charged particles are also densely

TABLE I. Estimate of the total number of local failures in the United States cancer population

Tumor Site	Annual Deaths (1968**)	Estimated* Number of Patients with Local Failure as Major Cause of Death	
Head and Neck	10,000	4,000	
Esophagus	5,700	3,000	
Breast	28,350	4,000	
Cervix Uterus	10,000	6,000	
Corpus Uterus	3,500	2,000	
Ovary	9,500	8,000	
Prostate	16,500	10,000	
Bladder	8,000	4,000	
Brain, CNS	7,500	7,000	
Skin	5,000	3,500	
Lung	55,000	5,000	
Lymphoma	16,500	2,000	
Total	175,500	58,500	(33%)

*Estimates made in consultation with Drs. R. Lindberg and R. Jesse (head and neck, skin), Dr. E. Montague (breast, esophagus), Drs. D. Johnson and L. Miller (prostate, bladder), Dr. J. Smith (uterus, ovary), Drs. L. Fuller and J. Butler (lymphoma), and Drs. Fuller and Lindberg (lung) (see Suit and Goitein, 1974).

**American Cancer Society figures (1968 Cancer Facts and Figures).

ionizing near the end of their tracks. In addition, there are some radiobiological reasons to expect that, by using densely ionizing particles such as neutrons, it is possible to do more damage to tumor tissues for a given damage to normal tissues. The rationale for using these radiations is to minimize the damage to normal tissues without reducing the delivery of tumoricidal doses (i.e., to increase the therapeutic ratio). This could result in improving the current cure rates in radiotherapy, while reducing normal tissue complications.

II. INTERACTION OF HEAVY PARTICLES WITH MATTER

The macroscopic and microscopic aspects of dose-distribution are important in radiotherapy, and the penetration of radiation in tissues is one of the most important factors. The biological effects depend not only on dose but also on microscopic dose-distribution. Microscopic dose-distribution (ionization density) is commonly expressed as linear energy transfer (LET)* in keV/μm.

As they pass through the medium, x rays and gamma rays are attenuated by photoelectric, Compton, and pair-production processes. Hence, the dose delivered by x rays decreases exponentially with depth except for the initial dose buildup. Fast neutrons are also attenuated exponentially as they pass through matter by elastic and inelastic collisions with atomic nuclei in the medium. Therefore, the dose deposited by neutrons also decreases exponentially with depth. The characteristic difference between the interaction of gamma rays and fast neutrons with matter is in the particles released. In the case of gamma rays, the particles released are electrons. When fast neutrons interact with matter, the particles released are protons, alpha particles, and heavy nuclei recoils.

High-energy electrons, being light, pass through matter with relativistic speed through most of their range. Hence, as a function of depth, the dose deposited by electrons remains nearly constant, then decreases rapidly near the end of the range. The decrease in dose near the end of the range is not very sharp because of considerable side-scatter and range-straggling.

When heavy charged particles such as protons, helium ions, heavy ions, and pions pass through matter, because of their sharp ranges, the dose decreases very rapidly at the end of the range. As the particles slow down, the dose deposited increases slowly with depth and then gives rise to a very sharp increase in dose near the end of the range due to the "Bragg peak" effect. The LET of heavy charged particles at depth is greater than at entrance. This difference is in contrast to the lack of difference for x rays, neutrons, or electrons mentioned above.

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*LET (linear energy transfer) was introduced by Zirkle. It is the energy transferred per unit length of the track and is usually expressed in keV/μm of unit density material. The energy lost by the particle in MeV/gm/cm^2 (dE/dx) is also used in physics. dE/dx denotes what happens to the particle, whereas LET denotes what happens to the medium. dE/dx refers to energy lost by the particle, where LET refers to energy absorbed in a specific location in the medium. In unit density material, 1 keV/μm = 10 MeV/gm cm^{-2}.

In addition to the Bragg peak effect near the end of the range, negative pions exhibit a unique phenomenon when they come to rest. Negative pions (being negatively charged) are captured by atomic nuclei in the medium, and the resulting nucleus disintegrates, yielding various particles including some short-range and heavily ionizing fragments. In addition to the Bragg peak effect, this phenomenon increases the dose at depth. The LET at the pion stopping region is also increased because of heavily ionizing fragments.

X rays and electrons are often referred to as low-LET radiations, but even these low-LET radiations deposit a small fraction of their dose at LET of about 30 keV/μm. The high-LET component extends to about 100 keV/μm for proton beams, to about 250 keV/μm for helium ion beams, to about 900 keV/μm for pions and fast neutrons, and for heavy ions is even higher. Thus, the difference between these so-called high-LET radiations is described by the relative proportion of dose in various LET intervals and the maximum LET. All high-LET radiations are really mixtures of LET (e.g., see Bewley, 1968).

III. RADIOBIOLOGICAL PHENOMENA AND THEIR MODIFICATION WITH LET

Like many branches of medicine, radiation therapy is partly an art and partly a science. As Fowler (1966) pointed out, "If therapists had waited for a fully scientific basis before treating the first patient, radiotherapy would not have started yet." Yet it has cured hundreds of thousands of patients already. However, from the beginning, there have been intense efforts to develop radiobiological techniques to form a rational scientific basis for radiotherapy. Radiotherapists have developed empirical methods for using x rays, and this empiricism has allowed for the effects of fractionation, etc. The contribution of radiobiology has been to give some understanding of the reasons for the empirical findings. Therefore, in attempting to switch to new radiations, we are faced with either developing a whole new empiricism or using our knowledge of radiobiology to attempt a logical translation of our experience with x rays to predict the best methods of using the new radiations.

Puck and Marcus (1956) developed a method for measuring mammalian cell survival as a function of dose when cells are growing *in vitro*. Hewitt and Wilson (1959) developed a technique to measure tumor cell survival for cells growing *in situ* in their natural environment (*in vivo*). Since the response of normal tissues to radiation is also of great importance, various techniques have been developed to measure the effects of radiation on the limiting normal tissues in

radiation therapy (Till and McCulloch, 1961; Withers and Elkind, 1970; Phillips and Margolis, 1972). These radiobiological techniques have been helpful in discovering and understanding some of the radiobiological phenomena relevant to radiotherapy. The major radiobiological factors which affect tumor control include the oxygen effect, recovery from sublethal cellular damage, variations of radiosensitivity as a function of cell cycle (cell age), and cell proliferation after irradiation. Although these phenomena have been very helpful, the practice of radiotherapy was developed empirically long before these phenomena were discovered. Except for cell proliferation, the magnitude of changes in response caused by these radiobiological phenomena is reduced when heavy particles are used in radiotherapy. Radiobiological techniques are essential for translating the vast amount of clinical experience developed for x rays to the use of heavy particles in radiotherapy. There is at present a rapidly growing body of radiobiological knowledge which is now beginning to affect the strategy of radiotherapy.

A. The Oxygen Effect

We know that the dose required to deliver the equivalent biological effect of x rays (low-LET radiations) is reduced by a factor of two or three in the presence of free oxygen, compared to the effect in the absence of oxygen. This phenomenon is known as the "oxygen effect." Figure 1 shows cell-survival curves measured under aerated and hypoxic (absence of oxygen) conditions (Barendsen, 1968). It can be seen that hypoxic cells are resistant to radiation, compared to oxygenated cells. The oxygen enhancement ratio (OER) is defined as the ratio of doses under hypoxic and oxygenated conditions needed to produce the same biological effect. In the case of x rays, the OER is 2.5. Many tumors appear to have an inadequate blood supply and, hence, may contain a small proportion of hypoxic cells. Powers and Tolmach (1964) experimentally demonstrated the existence of viable hypoxic tumor cells in a mouse tumor. Figure 2a shows their results concerning the surviving fraction of cells from a tumor exposed *in vivo*. The survival curve has two components: the first corresponding to oxygenated cells, the second to hypoxic cells. By extrapolating the resistant component to zero dose, it can be seen that about 2% of the viable tumor cells were hypoxic.

The presence of even a small proportion of hypoxic but viable cells in the tumor requires an increase in dose for tumor cure. This is illustrated in Fig. 2b (Fowler *et al.*, 1963). If all cells are fully oxygenated, a 75-mm-diameter tumor can be cured with 90% probability using a dose of ~ 5000 rads, but if

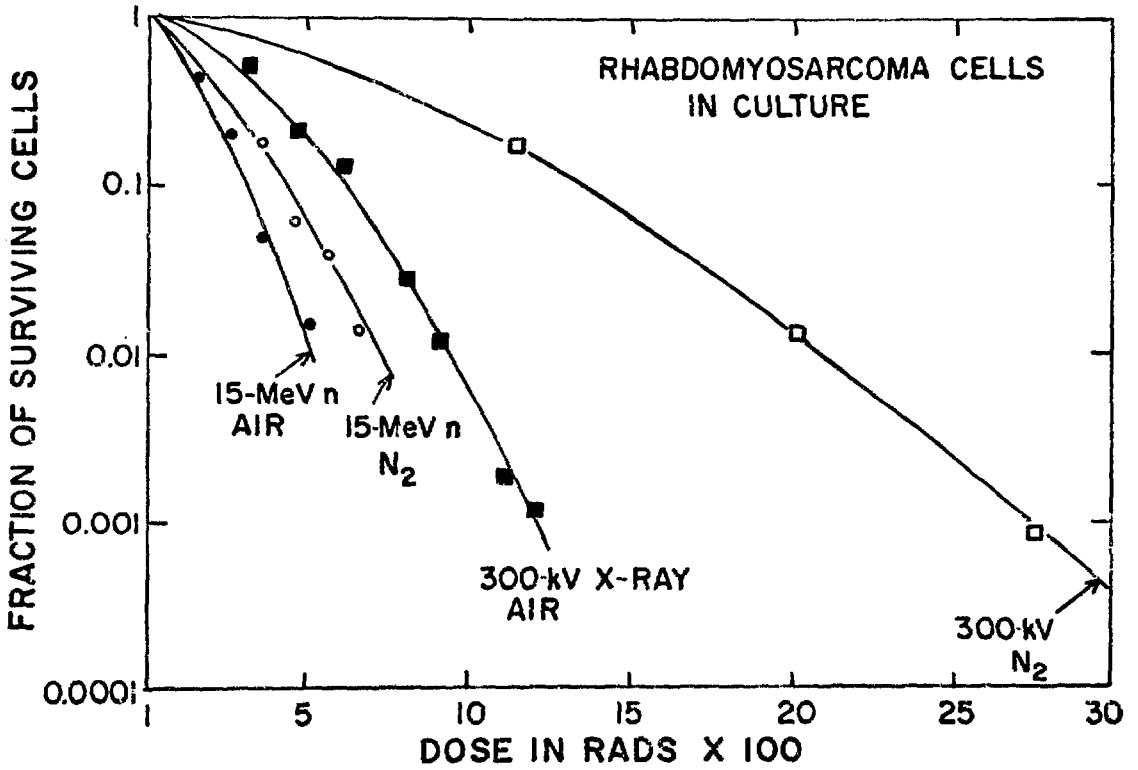

Fig. 1. Cell-survival curves under aerated and hypoxic conditions (courtesy of Barendsen, 1968).

the tumor contains 1% hypoxic cells, a tumor even as small as 5 mm in diameter cannot be cured with the same dose. Thus, the presence of hypoxic cells requires a significant increase in dose to be tumoricidal (i.e., nearly double). Normal tissues in the treatment volume may not tolerate such a high dose.

The relevance of oxygen in radiotherapy was recognized long before the oxygen effect mechanism was understood (Crabtree and Cramer, 1933). Gray (1957) postulated that hypoxia may be an important cause of failure to cure in x-ray radiotherapy. However, it has recently been shown that, in certain types of animal tumors, an increasing proportion of hypoxic tumor cells become oxygenated ("reoxygenation") during fractionated radiotherapy (Thomlinson, 1969). Thus, hypoxic cells that become oxygenated during treatment are not so resistant to subsequent fractions of radiotherapy. Therefore, it may be possible to overcome the oxygen effect by fractionation with conventional low-LET radiation alone for many less advanced stages of cancer. However, reoxygenation may not take place in advanced tumors and in certain histologic types. It must be stated also that, while it may be possible to overcome the effect of hypoxic tumor cells by making

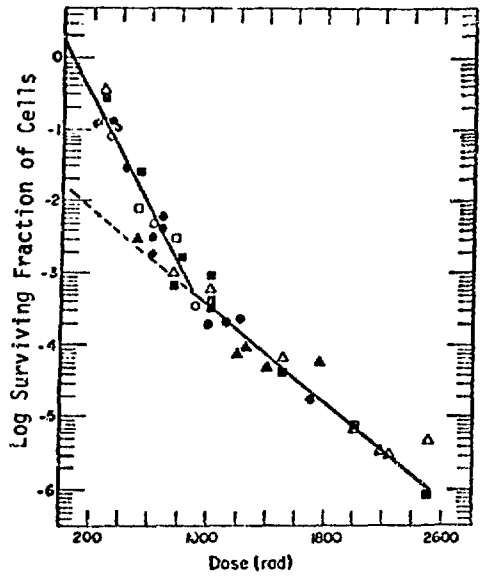

Fig. 2a. X-ray survival curve of cells of the six C_3HED mouse lymphosarcomas irradiated *in vivo*. Each symbol refers to a separate experiment (courtesy of Powers and Tolmach, 1964).

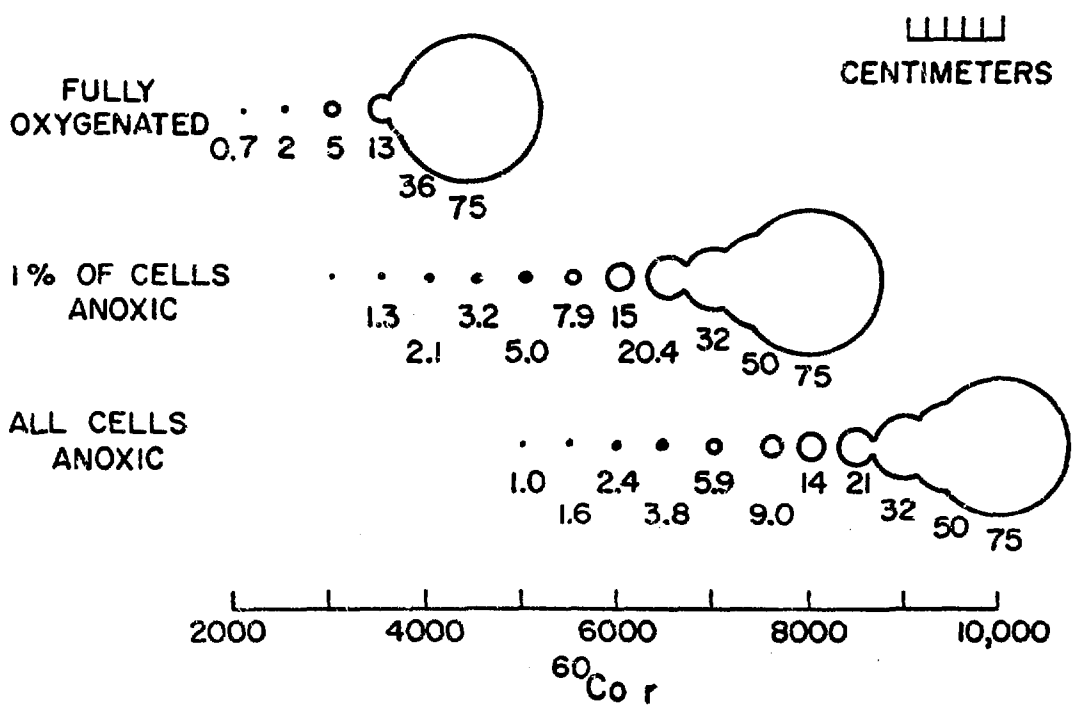

Fig. 2b. Calculated doses required to reduce the number of cells surviving in each tumor volume to 0.1 to give a 90% chance of "cure" (courtesy of Fowler and associates, 1963).

use of reoxygenation and correct fractionation, this may not be optimal therapy because, in optimizing for reoxygenation, we may have eliminated optimization for cell-cycle recovery, repopulation, etc.

It is known that the OER decreases with increasing LET (Barendsen, 1968). Except for protons, all other heavy particles, because of their high-LET, have a reduced OER. Thus, high-LET radiations may be more effective in overcoming the hypoxic cell problem where current methods are unsuccessful, and this is one of the rationales for using heavy particles in radiotherapy. It must be pointed out that, as a limiting factor in radiation therapy, hypoxic cells have been proven experimentally but have not been definitely established clinically (Kaplan, 1970).

B. Cell-Cycle Sensitivity

The generation time interval between mid-points of two consecutive mitoses has been divided into four stages: mitotic phase (M); DNA synthetic phase (S); G_1 phase; and G_2 phase. Schwartz (1914) advocated the use of multiple fractions in radiotherapy because multiple fractions increased the likelihood of irradiating tumor cells when they were in radiosensitive stages.

Terasima and Tolmach (1961) were the first to report that the radiation sensitivity of cells for x rays varies in different parts of the cell cycle. Cells in metaphase were found to be radiosensitive. Cells in the later part of S-stage were found to be most resistant. Cells at the G_1/S interface are also radiosensitive in most of the cell lines tested. Figure 3 shows cell-survival curves for cells in different stages (Sinclair, 1969). It can be seen that there are significant shape variations in the survival curves and in the radiation sensitivities of cells when they are in different stages of the cell cycle. Cells in M-phase are very sensitive, and the survival curve is exponential. Cells in late S-stage are very resistant, with a broad shoulder. Cells in other stages are in between these two extremes. However, these results may not be generally applicable to all cell lines. A hypothetical curve for hypoxic mitotic cells using a dose-modifying factor of 2.5 is also shown (Fig. 3). These results indicate that cell-cycle-related changes in radiosensitivity are nearly the same magnitude as differences between oxygenated and hypoxic cells. The magnitude of these radiosensitivity variations as a function of cell cycle is found to be reduced for neutrons but is qualitatively the same as x rays (Sinclair, 1969). For charged particles of very high LET (> 100 keV/μm), the positions of the maxima and minima can be altered in addition to the reduction in magnitude of these variations (Raju *et al.*, 1975a).

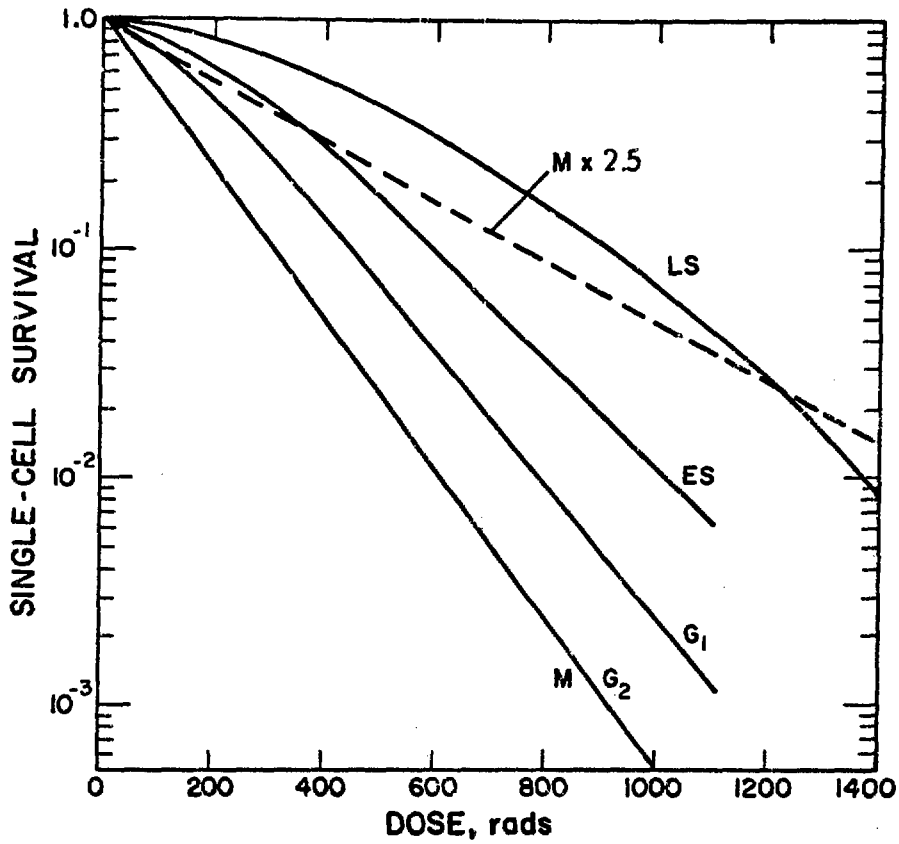

Fig. 3. Single-cell survival data for various stages of the Chinese hamster cell cycle (ES = early S, LS = late S). The broken line is a hypothetical curve for anoxic mitotic cells, assuming a dose-modifying factor of 2.5 (courtesy of Sinclair, 1969).

C. Biological Effectiveness

As early as 1938, Zirkle and Lampe reported that fast neutrons were more effective than gamma rays in producing biological effects. The relative biological effectiveness (RBE) of a test radiation (t) compared with 250-kVp x rays is defined by the ratio of D_γ/D_t, where D_γ and D_t are the doses of x rays and the test radiation, respectively, required to produce the same biological effect. The biological effects on cells in culture as a function of LET were measured by Barendsen (1968), Todd (1967), Deering and Rice (1962), and Skarsgard et al. (1967), and their results are shown in Fig. 4. Barendsen and his associates obtained particles of different LET by changing the particle velocity. The other investigators obtained different LET values by using different heavy ions of nearly the same velocity, and the heavy ion results have the following common characteristics:

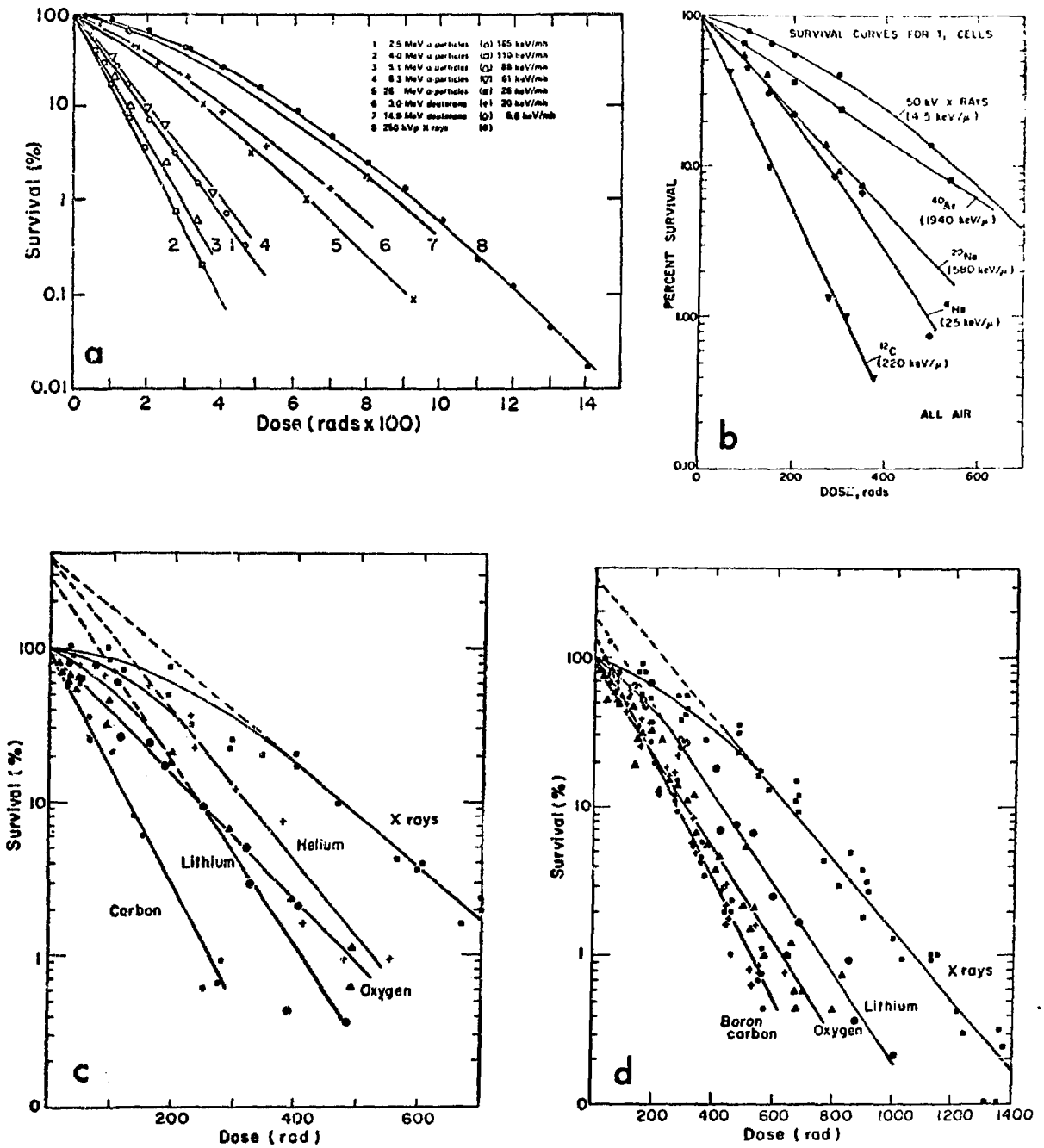

Fig. 4. (a) Survival curves of human kidney cells (T_1) for different mono-energetic heavy charged particles of different LET (courtesy of Barendsen, 1968). (b) Survival curves of human kidney cells (T_1) for heavy ions (courtesy of Todd, 1967; replotted). (c) Survival curves of HeLa cells (HeLa S3) for heavy ions (courtesy of Deering and Rice, 1962; replotted). (d) Survival curves of Chinese hamster cells (CH_2B_2) for heavy ions (courtesy of Skarsgard and associates, 1967; replotted).

(1) With increasing LET, the cells become more sensitive, with the D_o* value reaching a minimum at about 200 keV/μm.

(2) With increasing LET, the shoulder of the survival curve is reduced, and the curve becomes exponential at about 200 keV/μm for heavy ions. The maximum effect point as a function of LET was found by Barendsen and his associates to be only about 100 keV/μm when they used low-energy alpha particles. The differences in maximum effective LET values between low-energy alpha particles and heavy ions could be due to differences in microscopic energy distribution. These results indicate that the parameter LET may not be adequate to compare the biological effects of different particles, and we must take into account the microscopic energy distributions of these particles.

(3) With LET greater than these optimum values, the survival curves remain exponential but the D_o increases because more energy is deposited in the cells than is necessary to kill the cell.

There are qualitative and quantitative differences in the biological effects of high-LET radiations compared to gamma rays. The variations of RBE and OER as a function of LET are shown in Fig. 5 (Barendsen, 1968). The RBE depends upon

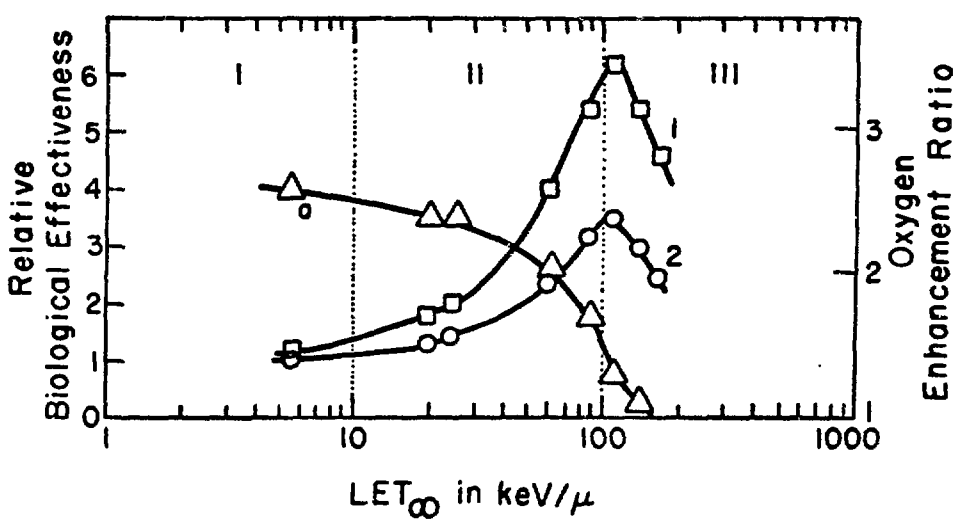

Fig. 5. Variations of RBE and OER as a function of LET of alpha particles and deuterons, derived from survival curves of cultured cells of human kidney origin. RBE curves 1 and 2 correspond to fractions of 0.5 and 0.01 surviving cells. Curve a represents the variation of OER with LET. LET regions I, II, and III represent the variations in which biological effects are minimum, maximum, and saturated, respectively (courtesy of Barendsen, 1972).

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*The dose required to reduce cell survival to 37% in the exponential region of the survival curve.

the survival level at which it is calculated because of the differences in shapes of the survival curves for high-LET particles and x rays. The RBE is large at low doses (higher survival levels). The OER is reduced with increasing LET and becomes unity at about 100 to 200 keV/μm.

D. Sublethal Damage

A typical mammalian cell-survival curve has an initial shoulder region, followed by an exponential region. The presence of a shoulder implies that the damage must be accumulated before it becomes lethal. Elkind and Sutton (1959) conducted a series of experiments in which the dose was delivered in two equal fractions, with different time intervals between doses. They found that fractionated doses were less effective than single doses and attributed this difference to the ability of cells to repair sublethal damage. This phenomenon is commonly known as "Elkind recovery" or sublethal damage repair (SLD). This phenomenon is a very common one and occurs in different degrees in almost all mammalian cells.

Figure 6 shows cell-survival curves for single and fractionated doses of x rays and alpha particles (Barendsen, 1968). It can be seen that there are significant differences in single and fractionated doses for x rays, whereas there is no difference for alpha particles. This clearly indicates that there is no recovery between exposures to high-LET particles. For particles of intermediate LET (e.g., neutrons), the recovery between exposures is smaller than for x rays (Broerse and Barendsen, 1969).

E. Potential Advantages of Heavy Particles for Radiotherapy

In principle, heavy charged particles (protons, heavy ions, and negative pions) offer advantages in improving dose localization in the treatment volume compared to megavoltage radiation. The introduction of these particles in radiotherapy reduces the damage to normal tissues outside the treatment volume. There may be intrinsic differences in radiosensitivity of tumors. Because of the high LET components, fast neutrons, negative pions, and heavy ions may have higher RBE values on some tumors that do not respond well to conventional radiations compared to limiting normal tissues. This could increase the chances of tumor cure without increasing the damage to normal tissues within the treatment volume.

The relatively slow process of reoxygenation might necessitate the use of small, daily doses of conventional radiotherapy to overcome the hypoxic cell

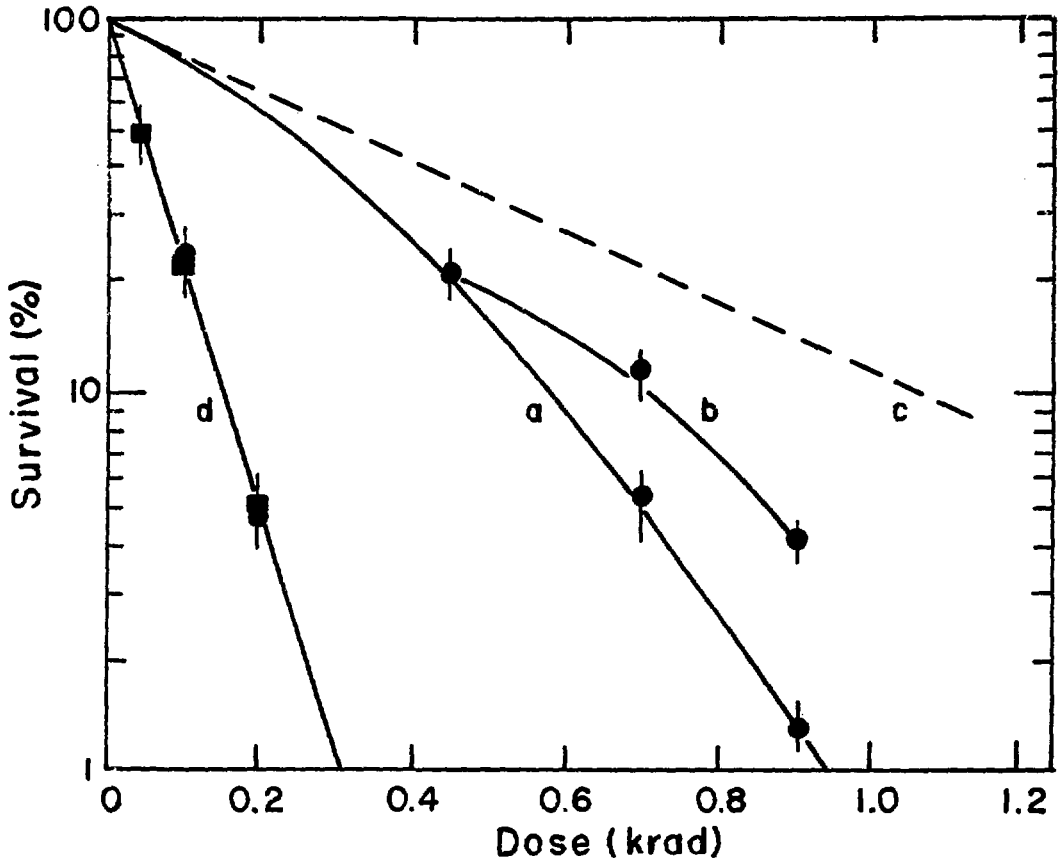

Fig. 6. Survival of cells after single and repeated exposures: (a) dose-survival curve after single doses of 200-kVp x rays; (b) dose-survival curve of cells which have received 450 rads of 200-kVp x rays 12 hr before the second doses of 250 and 450 rads; (c) theoretical dose-survival curve after repeated exposures of small doses of x rays; and (d) dose-survival curve for alpha particles [(-O-) single exposures and (-□-) two doses with 12-hr interval] (courtesy of Barendsen, 1962).

problem. Because of their reduced OER, the use of fast neutrons, negative pions, and heavy ions might partly eliminate this necessity of using small, daily dose fractions. Other treatment schedules might conceivably take advantage of other factors influencing the tumor radiosensitivity (e.g., changes in age distributions and cell proliferation) (Barendsen, 1972). Because of a smaller dependence on accumulation of sublethal damage and changes in radiosensitivity in the cell cycle, high-LET radiations (neutrons, negative pions, and heavy ions) may produce a more uniform effect on human tumors that are known to have a wide range of x-ray radiosensitivity (see Barendsen, 1974).

IV. NEUTRONS IN RADIOTHERAPY

There are three major types of neutron interactions with tissue: (1) recoiling protons from hydrogen in tissue; (2) recoiling heavy nuclei from other elements in tissue such as carbon, nitrogen, and oxygen; and (3) nuclear disintegration products. Fast neutrons of less than 5-MeV energy contribute nearly 90% of the dose through recoil protons. Recoiling protons have a range of energies up to the maximum neutron energy. The average energy of the recoil proton is nearly half of the neutron energy. The elastic collision of neutrons with heavy elements such as carbon, nitrogen, and oxygen in tissue results in recoiling heavy nuclei which contribute less than 7% of the total dose. These heavy recoiling nuclei have a very short range and exhibit high-LET, extending up to about 900 keV/μm. The contribution to dose by recoil protons is reduced with the increasing energy of fast neutrons. For example, for 14-MeV neutrons, the dose due to recoil protons is reduced to about 70% (Bach and Caswell, 1968). Neutrons with energies greater than 5 MeV produce nuclear disintegrations in their interactions with heavy nuclei. The frequency of nuclear disintegrations increases with increasing neutron energy. These reactions are known as inelastic processes and result in emission of alpha particles, deuterons, protons, and neutrons. Neutron interactions in tissue are discussed thoroughly by Auxier _et al_. (1968) and in an ICRU report (1976).

In addition to production of heavy particles, neutrons also produce gamma rays when they are captured by hydrogen nuclei. The dose contribution by this process is about 4% in air, ~ 10% at the surface, but about 20% of the total dose at depth in tissue. The presence of gamma rays complicates neutron dosimetry, and the dosimetry is commonly done by measuring the total dose using tissue-equivalent ionization chambers and by measuring one or the other component using either a photon- or neutron-insensitive detector.

The problem of delivering a well defined neutron beam for radiotherapy comparable to the x-ray beam is not trivial. This is because there is no effective absorber for neutrons corresponding to lead for x rays. Polyethylene absorbs neutrons most effectively on the basis of weight, but steel is more effective per unit thickness. Neutron collimation for 14-MeV neutrons from a d-T generator is a difficult problem because of the isotropic emission of neutrons. Compound shields made of steel and polyethylene are used for this application (Broerse _et al_., 1972). Low neutron output requires a short distance from the source to the patient. The collimating materials need not be very efficient for these

cyclotron-produced neutrons because they are emitted in a forward direction and the neutron output is not as limited as in the case of neutrons from a d-T generator. Collimation is obtained by using collimators made of borated wood (Bewley and Parnell, 1969) and other compositions as well as steel.

A. Sources of Neutrons

Cyclotrons capable of accelerating deuterons in the energy range of 16 to 50 MeV with beam currents greater than 10 μA are necessary for neutron radiotherapy in terms of dose rate and depth-dose, although 30-MeV and higher energy deuterons are required for deep tumors. Neutrons can be produced also by the $^{3}H(d,n)^{4}He$ reaction (commonly known as the DT reaction). The d-T neutron generators are relatively compact, but the technology for making a reliable machine with adequate intensity and a small enough effective source size has not yet been perfected. Brennan et al. (1974) reported that a fixed drive-in target on a 15-MeV d-T neutron generator is capable of producing a neutron yield of about $5 \cdot 10^{12}$ n/sec (10 rads/min at 125 cm SSD), and Booth and Barschall (1972) at the Lawrence Livermore Laboratory also reported this for a different design on a revolving target. The current status of d-T neutron generators for radiotherapy has been reviewed by Kelsey (1975).

Skin sparing and penetration in tissue are very important considerations in radiotherapy. Penetration in tissue for divergent beams such as x rays and fast neutrons depends on the distance from the source to the patient (commonly referred to as source-to-skin distance, SSD) and improves with increasing SSD. It is necessary to have an SSD of 100 cm or more for neutron beams to have a penetration comparable to ^{60}Co gamma rays.

Skin sparing and depth dose-distribution of cyclotron-produced neutrons with deuterons of 16, 30, and 50 MeV are shown in Fig. 7 (Hussey et al., 1974a). Significant skin sparing was observed clinically at the Hammersmith Hospital cyclotron [16-MeV deuterons on beryllium (Catterall et al., 1971)]. Skin sparing and penetration improve with increasing energy of the neutron beam (Bewley, 1971). Neutrons produced by 30-MeV deuterons have skin sparing and penetration comparable to ^{60}Co gamma rays. Neutrons produced by 50-MeV deuterons at an SSD of 140 cm have slightly better skin sparing and penetration than ^{60}Co gamma rays.

B. Early Experiences with Fast Neutrons

In 1932, Chadwick experimentally discovered the existence of neutrons. Even earlier, Dr. E. O. Lawrence conceived the principle of the cyclotron to accelerate

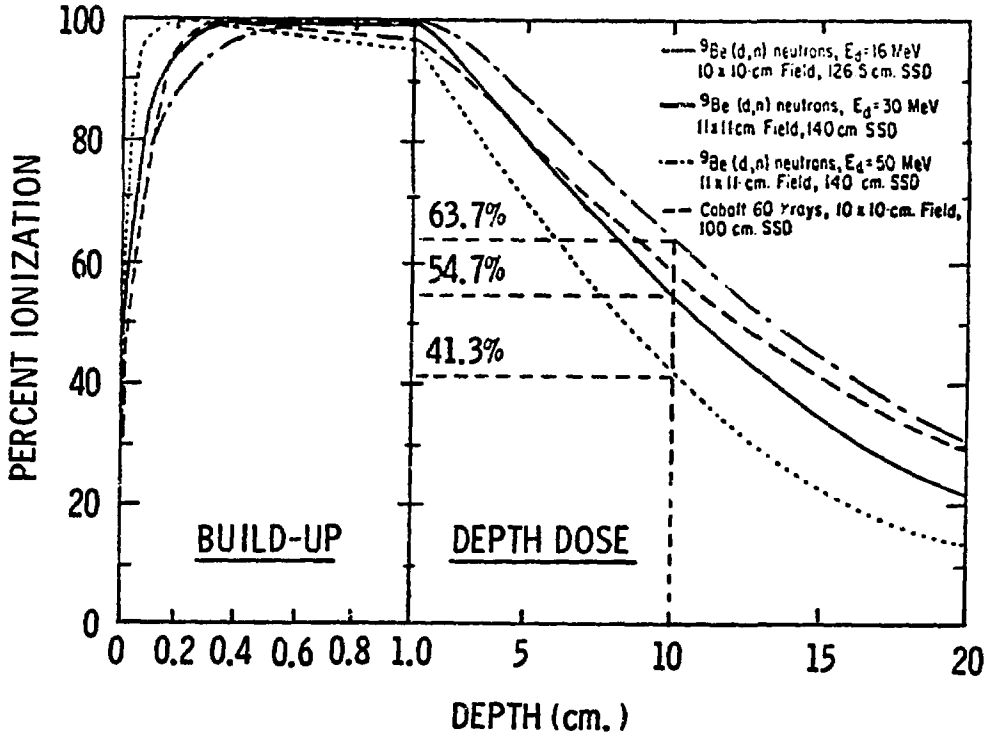

Fig. 7. Dose buildup (skin sparing) and depth dose-distribution of neutrons produced by deuterons of different energies at the cyclotron. Cobalt-60 gamma-ray data are also shown for comparison (courtesy of Hussey et al., 1974a).

heavy charged particles to higher energies. By 1936, a 37-in. cyclotron was built. Neutrons were produced by bombarding a beryllium target with 8-MeV deuterons accelerated by this cyclotron. Biomedical studies were started immediately thereafter, and a systematic study of neutron dosimetry and the comparative effects of neutrons and x rays in various biological systems evolved (Lawrence and Lawrence, 1936; Zirkle and Lampe, 1938; Aebersold, 1939). These results indicated that the action of neutrons on biological materials was more effective than x rays per unit of energy absorbed. Lawrence and his associates (1936) have also shown that, in comparison with x rays, neutrons may be more effective selectively on an experimental tumor compared to normal tissue. The first patient was treated in 1938 by Dr. Stone and his associates (Stone et al., 1940; Stone and Larkin, 1942). The rationale for using fast neutrons in radiation therapy at that time was that neutrons were found to be more effective than Roentgen rays per unit of energy absorbed by tissue; therefore, it was hoped that neutrons might be more effective in the treatment of cancer.

The 37-in. cyclotron was used initially for treating patients. This cyclotron was available one day a week for medical studies. Consequently, the patients were given single, large doses to find the erythema dose for neutrons, and its effect on the skin, mucosa, and tumor was observed. Twenty-four patients were treated. The treatment dose varied from 60 to 275 N units (1 N unit is equal to about 2.5 Roentgen units). Good tumor responses were found, and the late effects produced by neutrons were found to be similar to those of the x-ray treatments with equivalent biological doses. Dr. Stone and his associates felt that these promising results warranted an extensive and thorough trial with fast neutrons (Stone et al., 1940). In the fall of 1939, a new 60-in. cyclotron known as the "medical cyclotron" was built. This cyclotron was intended mainly for clinical applications and, hence, was available for fractionated treatment. The medical cyclotron produced a 16-MeV deuteron beam on beryllium. Patient treatment at this cyclotron continued until 1943. Two hundred and twenty-six patients were treated, but the program was interrupted by World War II. Stone presented his final results in 1948, seven years after the treatments were started at the medical cyclotron and four years after the last treatment (Stone, 1948). His results were summarized as follows:

(1) Gross and microscopic studies of mammalian tissues have shown no significant qualitative differences by neutrons and x rays.

(2) The biological effectiveness of neutrons varied greatly from one test object to another and even in the same tissue from one reaction to the other.

(3) The difference between the neutron dose required to kill cancer cells and for acute damage of normal tissues was small, this difference being even smaller for late reactions in normal tissues.

Stone concluded that ".....neutron therapy as administered by us has resulted in such bad late sequelae in proportion to the few good results that it should not be continued."

C. Current Neutron Radiobiology

At the time of the fast neutron therapy conducted by Stone, x-ray radiobiological phenomena and their modifications with fast neutrons were not well understood. As discussed before, x-ray and neutron cell-survival curves have different shapes, the x-ray survival curve having an initial shoulder and the neutron survival curve being nearly exponential. Hence, the RBE depends upon the level of biological damage used as an end point and, therefore, the dose

chosen. The survival curves for x rays and neutrons for single doses and fractionated doses are shown in Fig. 8 (Hall, 1973a). The RBE for neutrons at a surviving fraction of 0.1 is 1.5 for single doses. The RBE for neutrons increases to about 3.6 for fractionated doses. This is a direct consequence of differences in the shapes of the survival curves for x rays and neutrons. Hence, the biological effectiveness of neutrons compared to x rays increases as the dose per fraction is reduced and as the number of fractions is increased.

Because of the reduced OER for fast neutrons (~1.5 compared to ~2.5 for x rays, see Fig. 1), interest in using fast neutrons in radiotherapy was renewed again at the Hammersmith Hospital in London (Fowler et al., 1963). The Hammersmith group wanted to understand why the patients treated by Stone had such marked late effects. A systematic study using pig skin and mouse and rat foot skin was made to measure the early and late effects of fast neutrons for single and

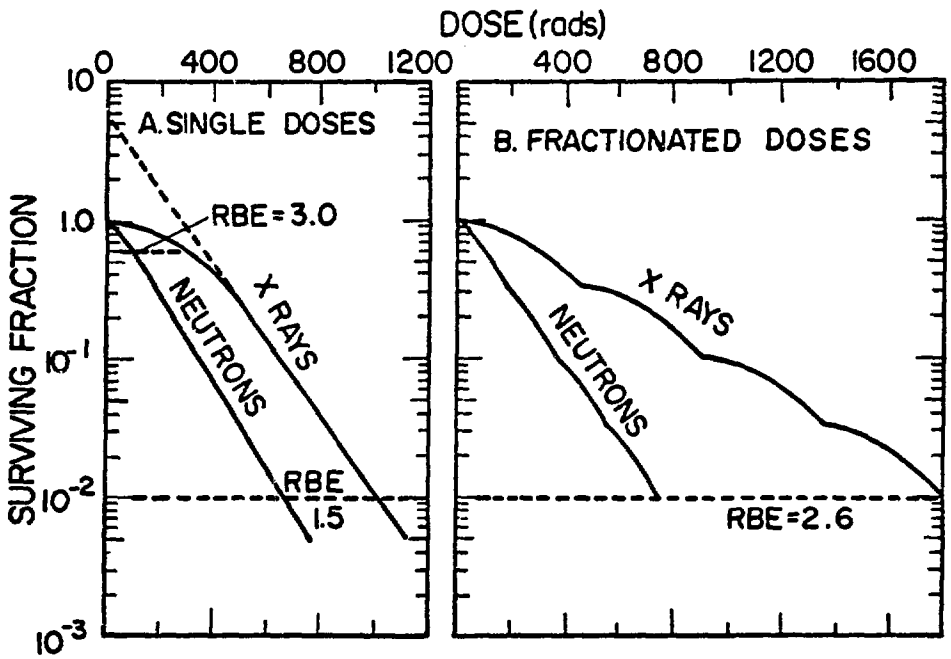

Fig. 8. (A) Single doses. Typical survival curves for mammalian cells exposed to x rays and fast neutrons. In the case of x rays, the survival curve has a large, initial shoulder; for fast neutrons, the initial shoulder is smaller and the final slope steeper. Because the survival curves have different shapes, the RBE does not have a unique value but varies with dose, becoming larger as the size of the dose is reduced. (B) Fractionated doses. This shows the effect of giving doses of x rays or fast neutrons in four equal fractions to produce the same level of survival as in (A). The shoulder of the survival curve is re-expressed after each dose fraction; since the shoulder is larger for x rays than for neutrons, this results in an enlarged RBE for fractionated treatments (courtesy of Hall, 1973a).

fractionated doses compared to x rays. They found that, if the doses of fast neutrons and x rays were matched to produce the same biological effect, the time-course of reactions for fast neutrons and x rays was quite similar (Fig. 9a,b).

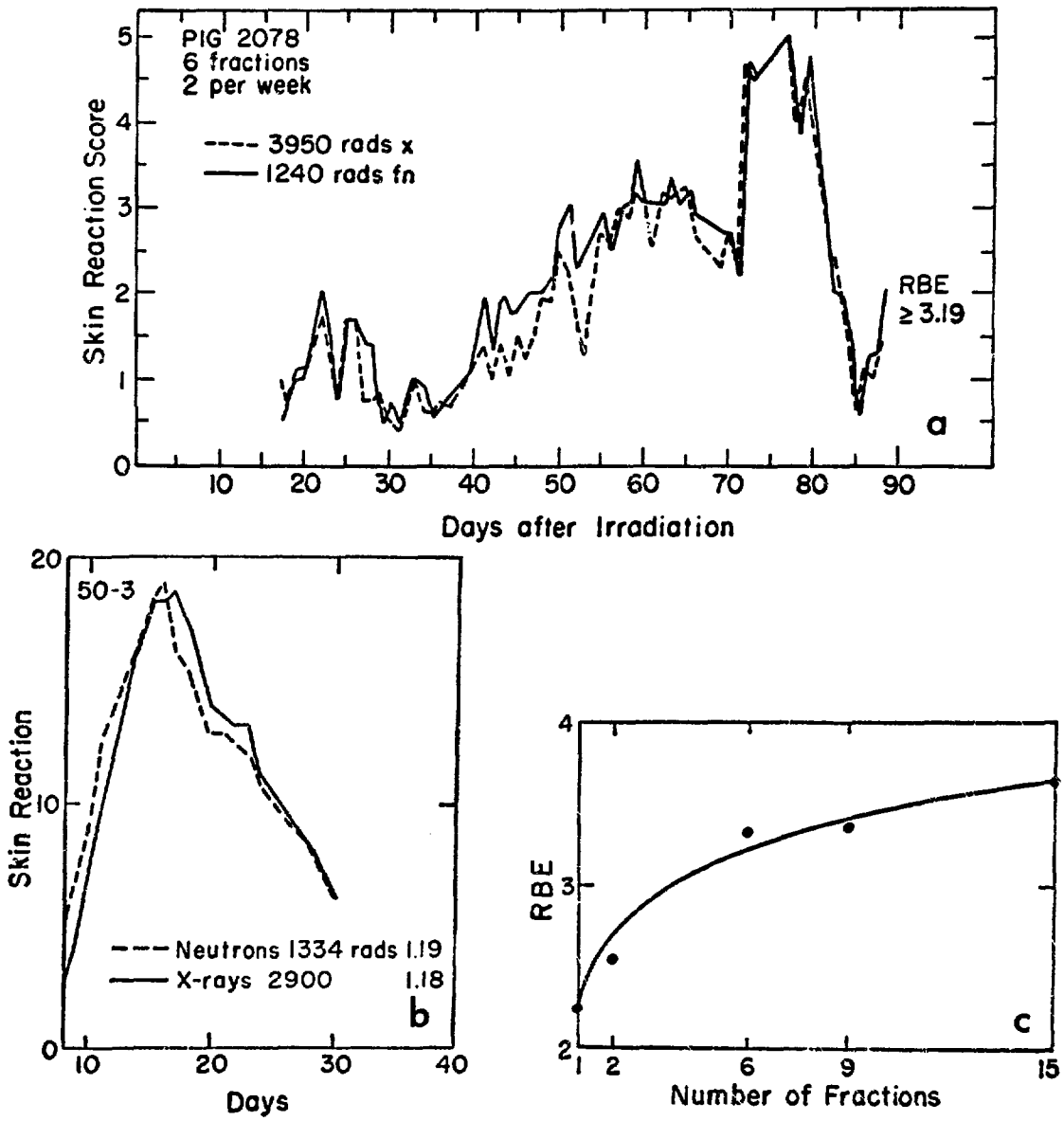

Fig. 9. (a) The average skin reaction plotted as a function of time (in days) after first exposure. These results are from an experiment in one pig (courtesy of Bewley et al., 1963). (b) Mean skin reaction vs time after irradiation of one group of mice given a fast-neutron dose of 1334 rads and one group given a 250-kVp x-ray dose of 2900 rads. The average reactions over the period 8 to 30 days are given to the right side of the doses (courtesy of Denekamp and her associates, 1966). (c) Variation of RBE of fast neutrons compared to 8-MeV x rays with the number of fractions delivered (courtesy of Bewley et al., 1967).

The reaction of pig skin after 50 days represents the long-term damage. Observations even after seven years did not show any significant difference between the x-ray and fast-neutron reactions. Observations of histologic material on some of the pigs did not show any qualitative difference between the damage produced by fast neutrons and x rays.

These workers have concluded that the biological effectiveness of fast neutrons remains the same for acute and late effects (Bewley et al., 1963). Fractionated experiments with neutrons indicated that recovery during fractionated treatment is smaller than for x rays (Bewley et al., 1967). The RBE for fast neutrons was found to increase with increasing numbers of fractions, as shown in Fig. 9c. Even for fractionated doses, when early biological effects were used to match the x-ray and neutron doses, they did not find any significant increase in late effects even seven years after fractionated neutron exposures compared to x rays. The Hammersmith group concluded that the late reactions observed by Stone and associates were because of unrecognized overdosage resulting from increased RBE for multifraction treatments of fast neutrons. As suggested by Barendsen and his associates (1963), the increased RBE for damage to normal tissues as well as tumors after fractionated doses of fast neutrons, in comparison with single large doses, can be interpreted on the basis of cellular phenomena as being due to the differences in the shapes of the dose-survival curves discussed earlier.

The early and late effects of fast neutrons compared to x rays were also studied using the mouse and rat foot as experimental models. Late reactions of radiation can be studied by measuring the deformity of the feet using an arbitrary scale. The RBE of fast neutrons for late reactions in the mouse and rat foot systems was also found to be the same as for early reactions. Figure 10 shows the results of late reactions (deformity) plotted as a function of early reactions for single and fractionated doses of x rays and fast neutrons (Field, 1969). It can be seen that deformity increases very sharply with a small increase in early reaction once a threshold for deformity is reached. The relationship between early and late reactions remains the same for x rays and fast neutrons for single as well as for fractionated doses (Hornsey and Field, 1974). These results stress the importance of accurate measurements of the early and late effects to normal tissues.

Field (1976) recently reviewed the results of early and late normal tissue damage after fast neutrons produced by 16-MeV deuterons on beryllium. He indicated that there may be a slow repair process in slowly dividing tissues, in

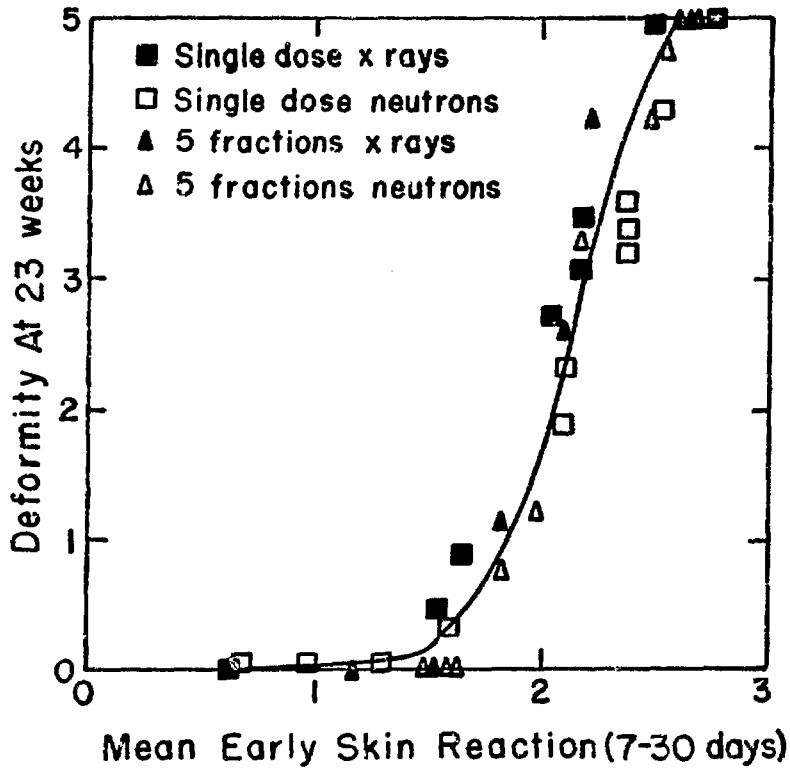

Fig. 10. Late reactions (deformity) in the rat foot plotted as a function of early reactions (courtesy of Field, 1969).

addition to the well known "Elkind repair" of sublethal damage and cellular repopulation. Slow repair seems to occur for x rays and not for neutrons. This may increase the RBE for slowly dividing tissues where the overall treatment time is increased. Broerse (1974) has reviewed the RBE values of 15-MeV neutrons for normal tissue effects.

If neutrons are to be more effective than x rays in radiotherapy, the RBE on tumors should be higher than for limiting normal tissue. For single doses, the RBE for all experimental tumor systems was found to be greater than for skin. Figure 11 shows the results of three tumor systems in comparison with normal tissues for five or more fractions (Field and Hornsey, 1974). It can be seen that the RBE decreases with increasing dose per fraction for normal tissues and tumors. Reoxygenation occurs in all of these three tumor systems. For fractionated doses, the RBE of neutrons for tumors was found to be lower than for single doses but slightly higher or equal to skin. These results indicate that fast neutrons may have a potential advantage for radiotherapy in cases of a specific combination of tumors and limiting normal tissues.

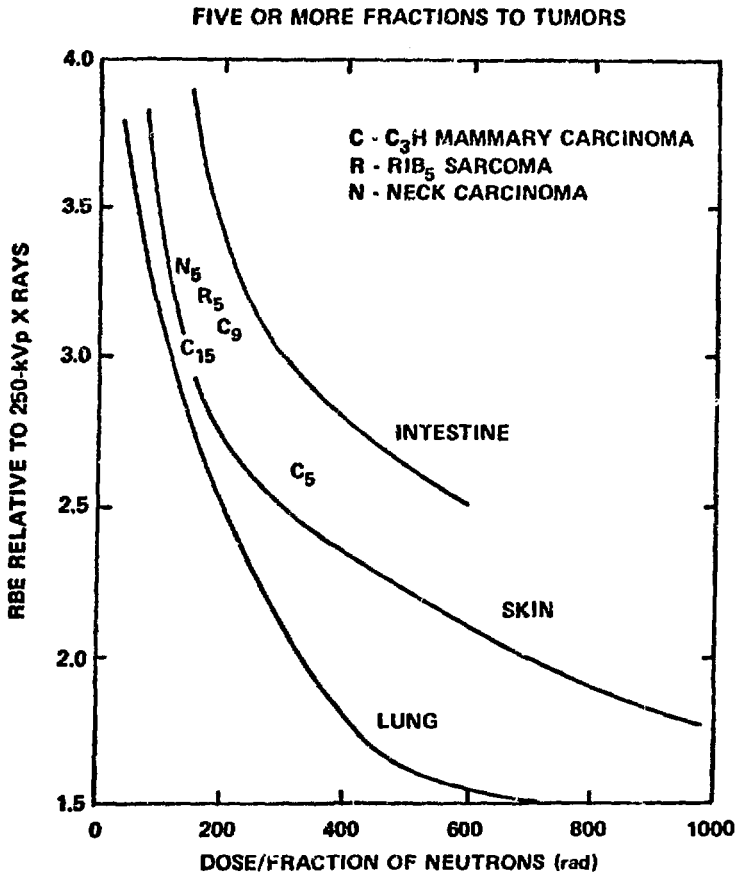

Fig. 11. Neutron (16-MeV deuterons on beryllium) RBE for five or more fractions to tumors in comparison with normal tissues. The subscripts for C, R, and N indicate the number of fractions (courtesy of Field and Hornsey, 1974).

Mammary carcinoma in mice is known to reoxygenate extensively; therefore, it was predicted that x rays would be as effective as neutrons in treating this tumor. Fowler and his associates (1972) tested the effectiveness of fast-neutron treatment compared to x rays. They found that the fractionation schedule with neutrons is less critical than for x rays. With the optimum choice of fractionation scheme (dose per fraction and time interval between fractions), x rays can be made as effective as neutrons. However, the optimum choice of fractionation with x rays requires detailed knowledge of the time-course of reoxygenation in the tumor. Because of the lack of such detailed knowledge on the time-course of reoxygenation in human tumors, Fowler and his associates (1972) concluded that neutrons might prove to have an advantage over conventional radiations even on tumors that are known to reoxygenate well.

D. Clinical Studies

Hammersmith Hospital.--Neutron radiotherapy is in progress at the Hammersmith Hospital; a total of over 500 patients have been treated. A randomized clinical trial of fast neutrons and photons in the treatment of advanced tumors of the head and neck is in progress. By the end of June 1974, 52 patients had been treated by neutron therapy and 50 by photon therapy. Nearly one-third of the photon patients were treated at the Hammersmith Hospital and the other two-thirds at participating institutions. Neutron therapy was given on Mondays, Wednesdays, and Fridays for four weeks, and a total tumor dose of 1440 rads (corrected dose of 1560 rads after intercomparison neutron dosimetry) was given in 12 equal fractions. The neutron beam was a fixed horizontal beam and, therefore, technically inferior to photon beams. Photon treatments were given by either cobalt or 6-MeV linear accelerators. The tumor doses varied from 4540 rads in 12 fractions in 28 days to 6840 rads in 30 fractions in 43 days. Thus, there was a wider spread in photon doses. The effective doses (dose x RBE) of neutrons were on the high side of the dose-distribution with photons.

The results indicated that, in spite of technical inferiority of the fast-neutron beam compared to megavoltage photons (such as a fixed horizontal beam and poor penetration), the clinical results in the neutron-treated series were superior to those in the photon-treated series in terms of tumor regression, relief of pain, and healing of ulceration. There were practically no recurrences in the fast-neutron-treated cases, whereas in the photon-treated cases, more than half of the tumors which appeared to regress completely recurred later. Some superiority of the neutron results could be due to higher effective neutron doses; however, even for cases where the x-ray doses and neutron effective doses were the same, the neutron results seemed better. It is likely that the improved results with fast neutrons were due to radiation quality differences between fast neutrons and photons (Catterall *et al.*, 1975). Recent analysis of the clinical material with a larger number of patients is consistent with the previous findings (Catterall, 1976).

Europe and Japan.--In Holland, a study of the responses of different types of lung nodules is in progress to select the types of tumors that are most suitable for neutron radiotherapy. They have found that the RBE of fast neutrons for tumor regression increases with increasing doubling time of the tumor. From these results, neutrons seem to be more effective for slow-growing tumors, as they have been found to give more uniform response in different tumors than x rays (Breur

and Van Peperzeel, 1971; Van Peperzeel et al., 1974). Breur (1976) reviewed the current status of new neutron therapy projects in Europe. At least five centers (Manchester, Glasgow, Amsterdam, Hamburg, and Heidelberg) are using d-T neutron generators, and four centers (Berlin-Buch, Louvain, Edinburgh, and Heidelberg) are using cyclotrons. In Japan, there are two medical cyclotrons in operation, one at the National Institute of Radiological Sciences, Chiba, and the other at the Institute of Medical Sciences, University of Tokyo. A third multipurpose cyclotron is under construction at Tohoku University (Umegaki, 1975).

United States of America.--In the United States, there are currently three neutron radiotherapy centers: (1) the M. D. Anderson Hospital and Tumor Institute in Houston is using the Texas A. and M. University cyclotron, which accelerates deuterons up to 50-MeV energy; (2) the Naval Research Laboratory (NRL) cyclotron in Washington, D. C., which accelerates deuterons up to 35 MeV and is being used for neutron therapy by a group of nearby cancer institutions (MANTA); and (3) the University of Washington (Seattle) cyclotron, which accelerates deuterons up to 22.5 MeV.

The OER was found to be about 1.6 for all the neutron beams mentioned above; however, the RBE for the neutron beam at the NRL cyclotron was found to be about 20% less than that at Hammersmith, and the RBE for the neutron beam used by the M. D. Anderson Hospital and Tumor Institute was about 10% less than the NRL neutron beam (Hall et al., 1974). Figure 12 shows intestinal crypt survival for different neutron energies. It can be seen that the RBE decreases with increasing energy of the neutron beam. Extensive experiments with cultured cells have also shown decrease of RBE with increasing neutron energy (Barendsen, 1968). Thus, some dose adjustment is required in clinical trials involving these three centers.

These three groups have treated about 700 cases and are now embarking on a series of joint controlled clinical trials, and the clinical results were reviewed recently (Hussey et al., 1976; Parker et al., 1976; Rogers et al., 1976). The clinical results for fast neutrons from the M. D. Anderson Hospital are not as encouraging as those from the Hammersmith Hospital. The early impressions on clinical trials with fast neutrons at the M. D. Anderson Hospital suggest that late effects are more severe for neutrons compared to x rays (Hussey and Fletcher, 1974b). These results indicate the need for great caution in the use of neutrons in radiotherapy. However, the clinical results when patients are treated with neutrons two times weekly plus 25-MeV gamma rays three times weekly are very encouraging both for better tumor control and fewer complications (Hussey et al.,

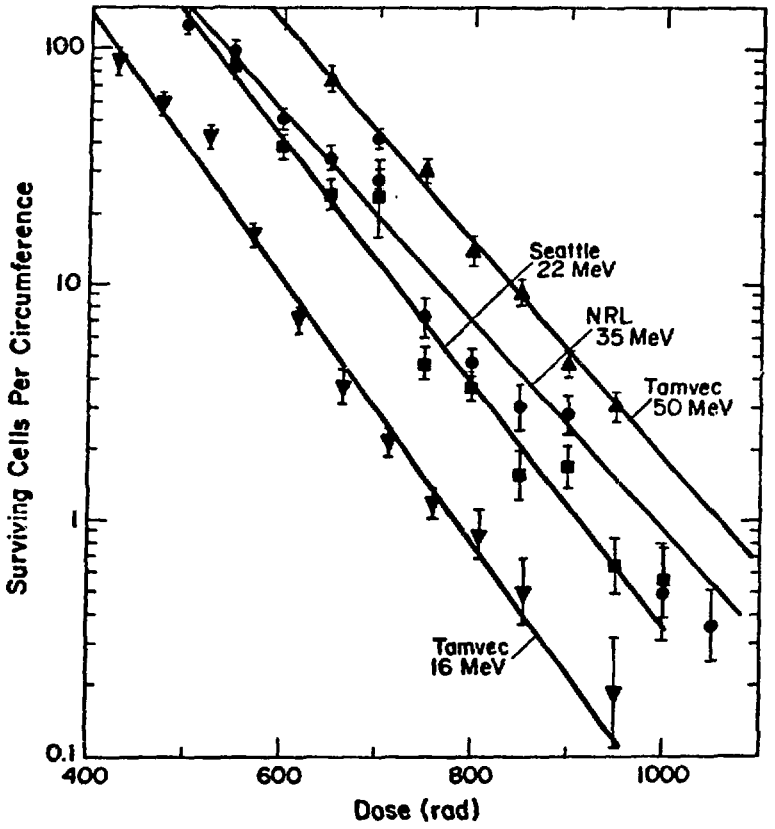

Fig. 12. Intestinal crypt cell survival for cyclotron-produced fast neutrons of different energies. Neutrons are produced by deuterons on beryllium. The data are for neutrons produced by the 16- and 50-MeV deuterons from the Texas A. and M. University variable energy cyclotron, the 22-MeV deuterons from the University of Washington (Seattle) cyclotron, and the 35-MeV deuterons from the Naval Research Laboratory cyclotron (courtesy of Withers, 1975).

1975). These favorable results could be due to better dose localization and five times weekly fractionation. There are two more neutron therapy centers in operation currently, one at the Fermi Laboratory in Chicago, Illinois, and the other in Cleveland, Ohio.

V. PROTONS AND HELIUM IONS IN RADIOTHERAPY

The use of these particles in radiotherapy was proposed by Wilson as early as 1947. A few years later, synchrocyclotrons were built which were capable of accelerating these particles to energies adequate for radiotherapy. Heavy charged particles, when passing through matter, travel in a nearly straight line and come to a stop after passing through a certain depth of absorber, depending upon their initial energy. There will be a slight deviation from a perfectly straight

trajectory because of the cumulative effect of many small-angle scatterings of heavy charged particles due to coulomb interactions with nuclei of the medium. This is known as "multiple scattering." The root-mean-square scattering angle is approximately inversely proportional to the mass of the particle; therefore, heavier particles show a smaller scattering angle. A small fraction of particles undergo nuclear interactions before they near the end of the range. The dose produced by nuclear secondaries is within 2%. The dominant process is energy loss through interactions with electrons in the medium. Secondary electrons produced by high-energy protons are of very low energy; hence, the ionization produced by the protons is confined mostly within 1 μm of the geometric path of the particle (Wilson, 1947). Proton beam dosimetry is commonly done by using parallel-plate ionization chambers and is simple because ionization is produced directly in the gas rather than in the wall of the ionization chamber. This is opposite to that of x rays or neutrons, where ionization is predominantly produced by interactions in the wall. Therefore, the thickness and atomic composition of the wall materials used in the ionization chambers are not critical.

The rate of energy loss of a charged particle is proportional to the square of its charge and inversely proportional to the square of its velocity. Thus, the rate of energy loss increases sharply near the end of the range where the dose reaches the Bragg peak and falls off very rapidly beyond the Bragg peak. The Bragg peak is very narrow for monoenergetic proton beams; however, this peak can be broadened to any desired width by using a ridge filter (variable thickness absorber). Koehler and Preston (1972) compared the dose-distribution of protons to ^{60}Co gamma rays and 22-MeV photons from a betatron. The dose-distribution comparisons are for a treatment plan for carcinoma of the uterine cervix. Four fields are employed in two opposed pairs, with their axes inclined at 100°. Figure 13 shows dose-distributions along one axis for ^{60}Co gamma rays, 22-MeV x rays, and protons. The dose to normal tissues outside the treatment volume is about 70% of the tumor dose when ^{60}Co gamma rays are used. This normal tissue dose is reduced to about 40% when 22-MeV x rays are used, and this is reduced further to about 22% when protons are used. In addition, the dose with protons can be made more uniform throughout the treatment volume including the edges. Thus, using multiport proton irradiation, the dose given to all of normal tissues can be reduced even more than can be achieved with 22-MeV x rays.

The biological effectiveness of protons was found to be nearly the same as that of conventional radiations, with the exception of a narrow zone in the final

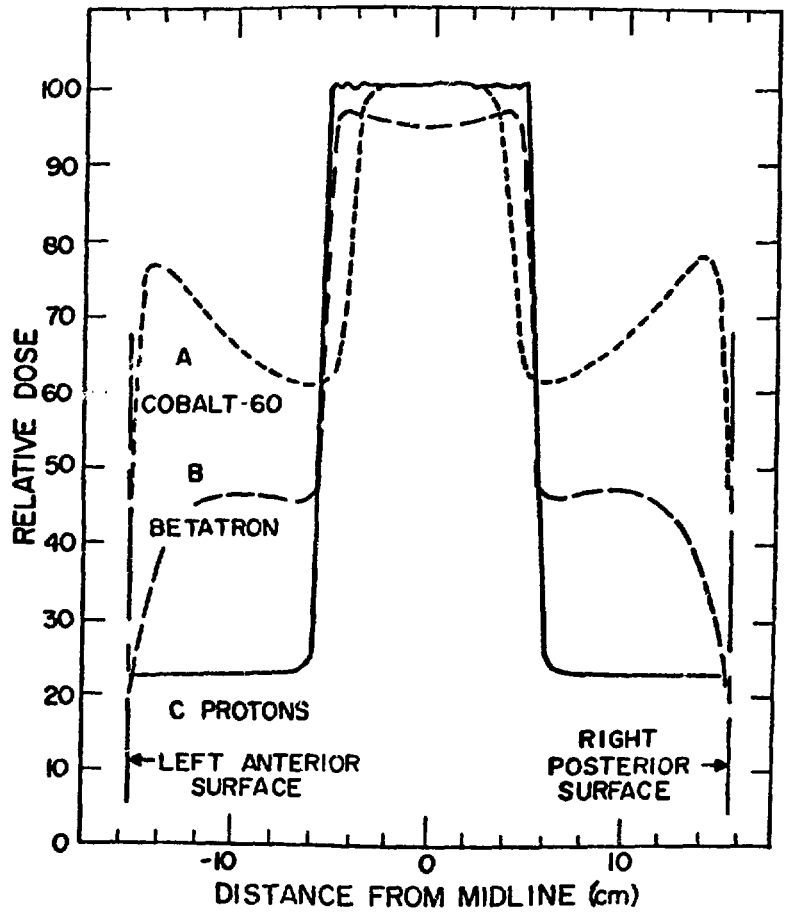

Fig. 13. Dose-distributions designed for irradiation of the uterine cervix: four fields in two opposed pairs with axes at 110°. The dose along one axis is shown: (A) for ^{60}Co gamma rays, (B) for 22-MeV x rays, and (C) for protons (courtesy of Koehler and Preston, 1972).

few millimeters of the range in which a significant increase in RBE was found. However, when the peak was broadened to cover large treatment volumes, the biological effectiveness was found to be very similar to conventional radiations. Clinical experience with protons has also established that the biological effectiveness of protons is qualitatively and quantitatively the same as conventional radiations (Stenson, 1971; Archambeau et al., 1974). Thus, the advantage of using protons in radiotherapy is to improve the dose localization in the treatment volume, while minimizing the dose to the normal tissues outside the treatment volume. Therefore, the clinical experience with megavoltage radiations can be applied directly to proton radiotherapy. Because of these dose localization characteristics, protons might improve the cure rates significantly and certainly reduce morbidity to the patient.

The fact that these particles have not been used extensively for radiotherapeutic purposes, in spite of their potential applications and the availability of machines, could be due to several reasons:

(1) The statement by Dr. Stone that ".....the late effects from the use of neutrons should serve as a warning to those proposing to use protons, multimillion volt beta rays, and multimillion volt Roentgen rays in the treatment of human cancer."

(2) In the 1950s and 1960s, high-energy physics research was very well funded and all synchrocyclotrons were operating 24 hours a day, seven days a week, with a full program on high-energy physics research.

(3) There was a lack of adequate tumor localizing and cross-sectional density measuring techniques.

However, pioneering studies by Tobias and Lawrence (Tobias et al., 1952) led to the use of protons and alpha particles for treating human diseases associated with the pituitary gland. Later, proton work was initiated at the Harvard cyclotron. A total of about 1350 patients have been treated at Berkeley and Harvard (Tobias et al., 1971a; Kjellberg, 1975). Proton Bragg peak therapy is the routine treatment of choice for most patients with acromegaly, Cushing's disease, and chromophobe adenoma. Probably because of the above mentioned reasons, only a few cases other than pituitary glands have been treated at either institution.

A limited amount of large-field radiotherapy has been done at Uppsala, Sweden, but, because of unavailability of the accelerator for extended periods of time, they used mostly large, single doses (Stenson, 1971). In general, the results were encouraging. There is currently a proton radiotherapy program in the Soviet Union using three of their existing high-energy proton synchrocyclotrons. About 250 patients have been treated with large fields (Koehler, 1974; Dzhelepov and Ruderman, 1975). Suit at the Massachusetts General Hospital recently launched a large-field radiotherapy program with protons. In 1974, Suit and Goitein proposed to use a combined treatment with protons to spare distal normal tissues and 22-MeV x rays to spare the skin. They have treated three patients where improved dose localization could be an important factor. The results were satisfactory, but the energy of the Harvard synchrocyclotron (160 MeV, range 17.5 cm in water) is somewhat limiting for the treatment of deep-seated tumors, particularly with intervening bone. Fourteen patients have been treated so far with protons using large fields and small doses per fraction (Suit et al., 1976).

Proton beams are also being used for the treatment of choroidal melanoma. Choroidal melanoma is treated currently by surgically removing the involved eye. Constable and Koehler (1974) have demonstrated that, by using protons, the choroid involved by melanoma can be irradiated while, at the same time, sparing the retina and normal tissue behind the eye. The patient treatment for choroidal melanoma was started in July 1975 at the Massachusetts eye and ear infirmary using the Harvard cyclotron. Six patients have been treated so far (Suit et al., 1976).

Koehler (1968) demonstrated the potential application of protons in radiography. Proton radiographs, compared to x-ray radiographs, are relatively insensitive to variations in chemical composition but are highly sensitive to density variations. Proton radiography offers a better means of tumor detection and internal structure than corresponding x-ray radiographs.

Helium ions have nearly the same dose localization advantages as protons. Even when their Bragg peak is broadened, there is a small but significant high-LET component for helium ions. Raju and associates (1972) found significant reductions in OER when the narrow Bragg peak was broadened to about 6 cm. These results were later confirmed by Todd et al. (1974). Raju and Jett (1974) have made a series of measurements for various dose mixtures of x rays and alpha particles from plutonium on human kidney cells in culture under oxygenated and hypoxic conditions. Figure 14 shows the variations of RBE and OER as a function of percent high-LET component (100 keV/μm). These results clearly indicate that

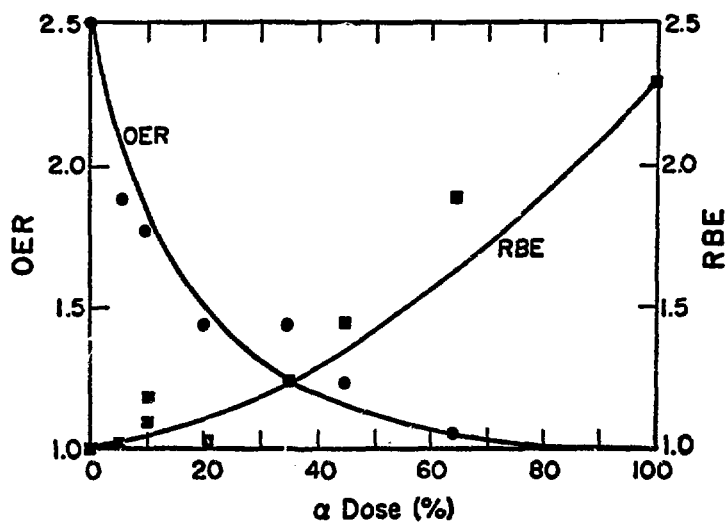

Fig. 14. Variation of RBE and OER for dose mixtures of x rays and alpha particles as a function of percent high-LET component (plutonium alpha particles) in human kidney cells in culture (Raju and Jett, 1974).

even a small high-LET component comprising about 10% of the dose is very effective in reducing the OER significantly, although the RBE may not be increased very much. Helium ion beams have potential advantages in radiotherapy because they have the dose localization advantages of protons and also because some of the hypoxic cell problem may be overcome. There are two accelerators with biomedical facilities and capabilities of producing helium ions for therapy: one at Berkeley and the other at Newport News. The helium ion beam at Berkeley is used mainly for pituitary treatment; however, a clinical trial using this beam for large-field radiotherapy is currently being organized at Berkeley by the San Francisco Bay Area Heavy Ion Association (BAHIA) and the Lawrence Berkeley Laboratory. Eight patients have been treated using a flat 25-cm-diameter helium ion beam (Castro, 1976). D'Angio et al. (1974) have treated some mycosis fungoides patients with helium ions using the cyclotron at Newport News. Radiobiology work using helium ions is in progress at Saclay, France, and is being pursued as a first step before getting into heavy ion radiotherapy (Malaise and Guichard, 1975).

VI. VERY HEAVY IONS

The use of very heavy ions (heavier than helium) in radiotherapy was proposed by Tobias as early as 1960 (for details see Tobias and Todd, 1967). Very heavy ions (VHI) could overcome the hypoxic cell problem in radiotherapy better than any other radiation and, at the same time, provide most of the dose-distribution advantages of protons and helium ions. However, Fowler (1965), on the basis of cosmic-ray data and calculations, predicted that the energetic heavy ions, because of their energetic delta rays and the production of nuclear secondaries, may lose some of the advantages of using heavy ions in radiotherapy. VHI were available at the laboratories of Berkeley and Yale in 1957. However, these had ranges less than 1 mm; thus, they restricted their studies to monolayer cultures of cells. Nevertheless, these studies provided information on biological effects at the cellular level as a function of LET (Deering and Rice, 1962; Skarsgard et al., 1967; Todd, 1967).

Penetrating beams of nitrogen ions of limited intensity have been accelerated at Princeton and Berkeley [see Science 174, 1121-1133 (1971)]. The intensity of high-energy heavy ions (0.2 to 0.8 GeV/nucleon) that could be accelerated with existing machines was restricted mainly by limitations in the injector. However, a limited number of dosimetric and radiobiological experiments have been done at both locations.

As VHI particles pass through matter, some are lost because of nuclear interactions before they approach the end of the range. For a given range of traversal, the cross section for nuclear interaction increases with increasing mass of heavy charged particles. For example, in the case of a nitrogen ion beam, nearly 4.5% of the particles are lost for each centimeter of traversal compared to 2.5% for protons. Most of the secondary particles have been found to accompany the primary beam and to stop near its vicinity. Some secondary particles travel deeper and, therefore, produce a small but undesirable exit dose; however, these secondaries are not expected to diminish the usefulness of very heavy ions in therapy (Tobias, 1973).

Tobias et al. (1971b) also discovered that some energetic heavy ions become radioactive as they pass through matter and stop near the vicinity of the primary beam. They have termed this phenomenon "auto-activation." Auto-activation can be used to visualize and match the treatment volume and the stopping region of the primary heavy ion beam. Benton et al. (1973) proposed the use of heavy ions in radiography. Radiobiological measurements of monoenergetic oxygen ion beams were also made at Berkeley (Tobias, 1973).

The biophysical properties of a 3.9-GeV nitrogen ion beam were measured at the Princeton accelerator, and the results are reported in a series of papers in Science 173, 1121-1128 (1971) and in Radiation Research 54, 12-23 (1973) and 55, 422-456 (1973). Biological measurements indicated rather large variations in OER over the narrow Bragg peak (Hall, 1973b). Hall concluded that, ".....while nitrogen ions per se are quite unsuitable for radiotherapy, ions of higher atomic number may hold promise of being very favorable."

A heavy ion facility to produce high-energy, high-intensity beams of a variety of heavy ions for physics and biomedical research is currently in operation at Berkeley. This facility utilizes the previously existing heavy-ion linear accelerator (Super Hilac) as an injector to the Bevatron. This was done with minor modifications, and the coupled facility is named Bevalac (Tobias, 1973). Only a very small part of the duty cycle (2 to 3%) is used in this mode of operation; therefore, research programs at Super Hilac are affected very little.

Heavy ion beams such as carbon, neon, and argon with ranges of about 15 cm and higher have been accelerated recently. Dose rates as high as 500 to 1000 rads/min (over small areas) were obtained. A series of physical and biological measurements were made using this beam. Figure 15 shows the cell-survival measurements as a function of depth for a neon beam modified by a ridge filter to

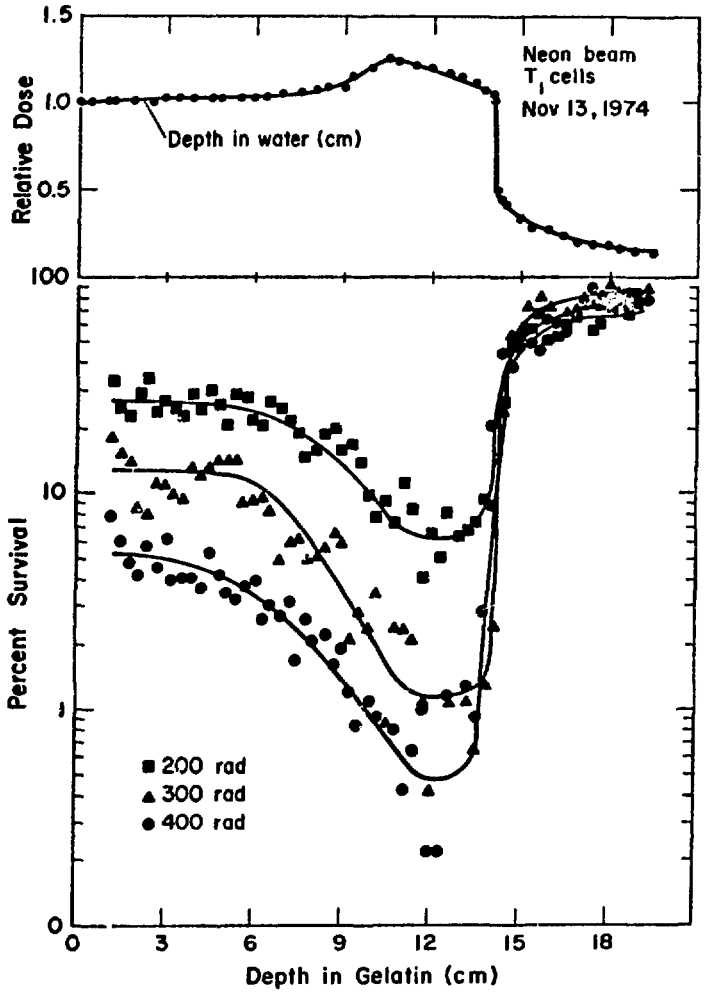

Fig. 15. Cell survival as a function of depth for a neon ion beam (Raju et al., 1975b).

give a nearly constant effective dose from 10.5 to 14 cm in depth. These results clearly indicate enhancement of cell killing in the peak region, and the effect of secondaries beyond the range of the neon ions of 15-cm range in water was rather small (Raju et al., 1976a).

Chapman et al. (1976) subsequently obtained survival curves for stationary-phase Chinese hamster cells (V79) irradiated in the plateau and in the center of a 4-cm wide peak. The peak-to-plateau ratio of RBEs and the OER at the peak center are shown in Table II. It can be seen that the peak-to-plateau ratio in RBEs is highest for carbon ions and that the OER for this peak width is comparable to fast neutrons. Carbon and neon ions may be of choice in radiotherapy if dose localization considerations are given importance. If high-LET is an

TABLE II. RBE peak-to-plateau ratios and OER at peak center

Beam	RBE Peak/RBE Plateau	OER (peak)
Helium ions (230 MeV/n, 8-cm peak)	1.15	2.3
Carbon ions (400 MeV/n, 4-cm peak)	1.60	1.7
Neon ions (400 MeV/n, 4-cm peak)	1.35	1.6
Argon ions (5 MeV/n, 4-cm peak)	0.90	-

advantage for the treatment of resistant types of tumors, argon ions may be of interest.

The acute effects of 375-MeV/nucleon neon ions at the peak (4-cm width) and plateau on the skin of the mouse leg and hamster skin were studied by Leith et al. (1975a,b). The RBE of neon ions at the plateau and peak was found to be about 1.3 to 1.8 and 2.2 to 2.4, respectively, depending upon the dose level. Otherwise the time-course of skin reaction development and subsequent healing was found to be quite similar to x rays. This suggests that skin damage and subsequent epithelial repopulation after irradiation for neon ions are not different from x rays. Fractionation experiments at the neon peak position indicated that the repair of sublethal damage was about 25% of x rays. Leith et al. (1975c) also studied the effects of neon ions at the beam entrance on the thoracic spinal cord of rats. Neon ions were found to be about 1.3 times more effective in producing paralysis compared to helium ions. However, no significant differences have appeared in latency periods for the production of paralysis after irradiation with neon ions. Woodruff et al. (1976) quantitatively measured the effects of neon ions on hamster lung at the beam entrance using morphometric methods. Neon ions were found to produce changes in cellular composition at all dose levels significantly different from x rays. It was concluded that neon ions appear to elicit a more intense early radiation response than x rays, but the long-term significance of these findings is not yet known.

The RBE for neon ions at the peak and plateau regions was measured by Phillips and Fu using intestinal crypt assay (see Leith, 1976a). At a dose of 800 rads, the RBE was 1.9 at the plateau and 2.0 at the peak (4-cm width). The RBE for neon ions is quite similar to 15-MeV neutrons.

Using rhabdomyosarcoma rat tumor, Curtis and his associates found an RBE of 1.8 at the plateau and 2.9 at the peak (4-cm width) at a dose of 1000 rads (see Phillips et al., 1976). Using the EMT6 mouse tumor, the RBE at the plateau was 2.0 and at the peak 2.5 at 1000 rads (Phillips et al., 1976). A reduced OER

and a high RBE at the plateau were also observed in a rat brain tumor (Leith et al., 1976b). The RBE values for tumors in the peak region are higher than in normal tissues and are probably due to the presence of hypoxic cells in the tumors.

VII. PIONS

Unlike other heavy charged particles of interest in radiotherapy, pions are unstable and have a mean life of 2.54×10^{-8} sec. The pion has a mass 273 times that of an electron or approximately 15% the mass of a proton. Negative pions with energies of 60 to 90 MeV (range 12 to 23 cm in tissue) are of interest in radiotherapy. When they pass through the medium, they deposit their dose mainly by energy loss phenomena (collisions with electrons) at a LET of ~ 0.3 keV/μm, although a small but significant fraction of the dose is deposited at higher LET due to nuclear interactions. As they pass through a medium such as tissue, the dose deposited by pions increases very slowly and reaches a sharp maximum near the end of the range (the Bragg peak). The LET due to energy losses of negative pions increases to about 50 keV/μm.

Near the end of the range, a pion is captured into the electron orbit of atoms heavier than hydrogen in the medium. The pion cascades down the atomic levels in a time short compared with its lifetime. During the cascade, characteristic x rays known as "pi mesic x rays" are emitted. When in its lower atomic orbit, the pion spends considerable time inside the nucleus, due to its strong interaction with the nucleus, and is captured by it. This results in a disintegration known as a "star" formation. The rest mass of negative pions (140 MeV) appears in the form of kinetic energy of nuclear fragments, except for about 40 MeV, used in overcoming the binding energy of the nucleus. Nearly 60 MeV of the remaining energy appears in the form of kinetic energy of neutrons, and the balance of 40 MeV appears in the form of kinetic energy of heavy charged particles such as protons, deuterons, tritons, alpha particles, and heavy nuclei that are absorbed locally. Soon after this phenomenon was observed in nuclear emulsions, Fermi and a few others recognized that this unique property of negative pions made them promising in radiotherapy. Fowler and Perkins (1961) made detailed calculations and advocated the potential of negative pions in radiotherapy. These calculations motivated many groups in different parts of the world (Berkeley, U.S.A.; CERN, Switzerland; and Harwell, Great Britain) to measure the physical and radiobiological properties of negative pions, although the

available intensities from the then existing machines were 100 to 1000 times less than that required for radiotherapy. Physical measurements indicated that the dose at the peak was about 2.5 times higher than at the entrance with a peak width of about 3 cm. The physical measurements were in agreement with the theoretical calculations. About 2% of stopping pions produce high-energy gamma rays. Mesic x rays or high-energy gamma rays can be used to visualize the pion stopping regions (Sperinde et al., 1970).

The RBE at the beam entrance (plateau) was nearly unity and at the peak position about 2 to 5, and the OER at the peak was about 1.6. This work has been reviewed (Raju and Richman, 1972; Raju, 1974a). Therapeutically relevant pion beams from a conventional pion channel require a large spread in energy, and the differences in biological effects at the plateau and peak are expected to be reduced for such beams. The potential application of negative pions in radiotherapy was discussed by Kaplan (1969), who emphasized the importance of dose-localization in radiotherapy. Bond (1971) also discussed the possible use of negative pions in radiotherapy.

Construction of pion-producing accelerators with special facilities for biomedical research was completed at Los Alamos, Vancouver, and Zurich (Rosen, 1966, 1972). The Los Alamos facility is already in operation with a 100-μA proton beam current (50 rads/min over $\sim 30\ cm^3$). Seven patients with skin nodules have been treated to assess the biological effectiveness of pions for skin reaction and tumor regression (Kligerman, 1976; Kligerman et al., 1976). The pion facilities in Zurich and Vancouver are in the initial stages of operation.

A large solid-angle (nearly 1 sr), 60-sectored pion channel of a novel design was built at Stanford University, and its principles of operation were proven experimentally. This is known as the Stanford Medical Pion Generator (SMPG). This design permits multiport irradiation. Because of its large solid angle, less intense particle accelerators can be used for pion production. SMPG eventually will be coupled either to a superconducting electron linear accelerator or other suitable accelerator. The advantage of SMPG, in principle, is that it reduces the tumor-to-entrance dose ratio by a factor of nearly 9 compared to two opposed fields from conventional pion channels. In addition, the dose fraction due to stars will be higher when the tumor volume is treated by SMPG compared to two opposed fields using conventional pion channels (Kaplan et al., 1973; Pistenma et al., 1976).

The recent work on pion radiobiology has been reviewed by Raju et al. (1976b).

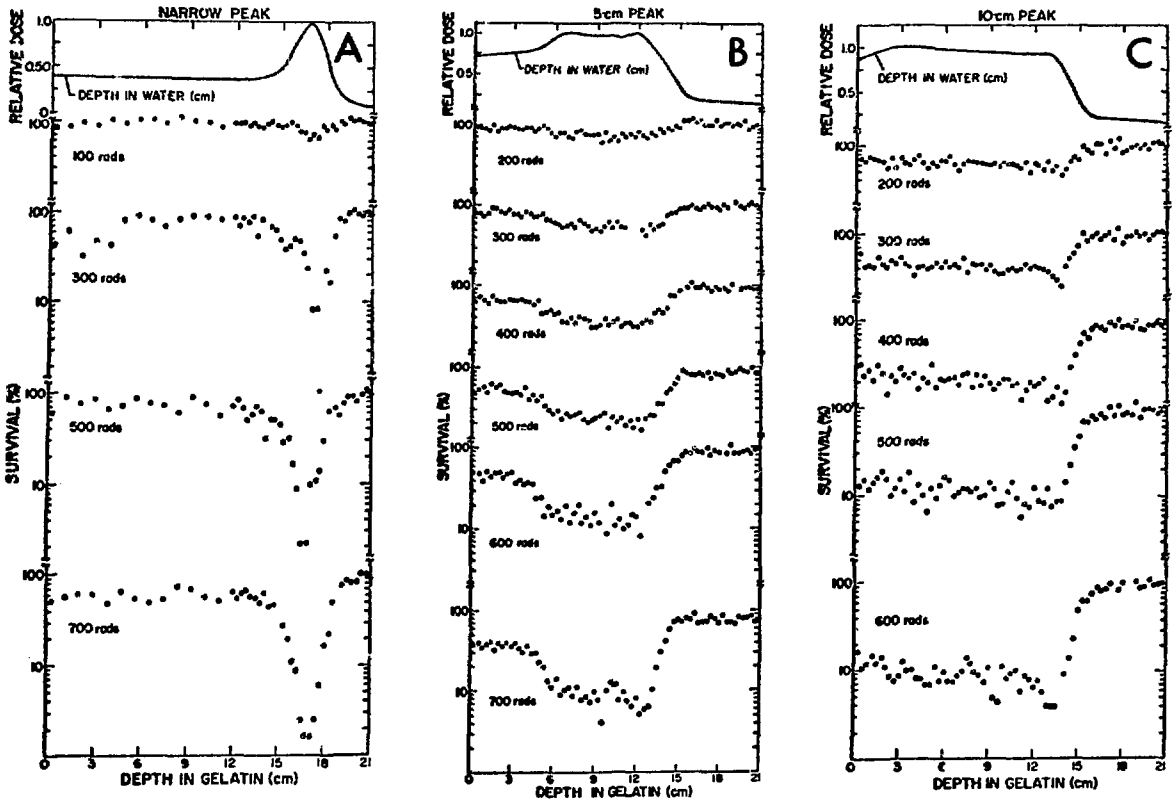

Fig. 16. Depth-dose and cell survival as a function of depth for negative pion beams: (A) narrow peak; (B) 5-cm wide peak; and (C) 10-cm wide peak (Raju et al., 1976b).

Figure 16 shows the depth-dose distribution and cell survival with depth for pion beams that are nearly monoenergetic and when the peak is broadened to 5 and 10 cm using a range shifter. It can be seen that enhanced cell killing at the peak is reduced with increasing width of the peak. When the peak is broadened, there is also a slight enhancement in cell killing with depth in the peak region due to the increasing fraction of dose from pion stars and must be taken into consideration in pion radiotherapy. The RBE ratio of peak-to-plateau is reduced from about 2.0 for a narrow peak to about 1.2 for a 10-cm wide peak. More radiobiology work needs to be done with pion beams before they can be used effectively in radiotherapy.

VIII. COMPARISON OF DIFFERENT HIGH-LET RADIATIONS

Figure 17 shows a schematic comparison of different types of radiations of interest to radiotherapy in light of their dose-distribution and high-LET advantages (Raju, 1974b). The dose-distribution advantage includes skin sparing,

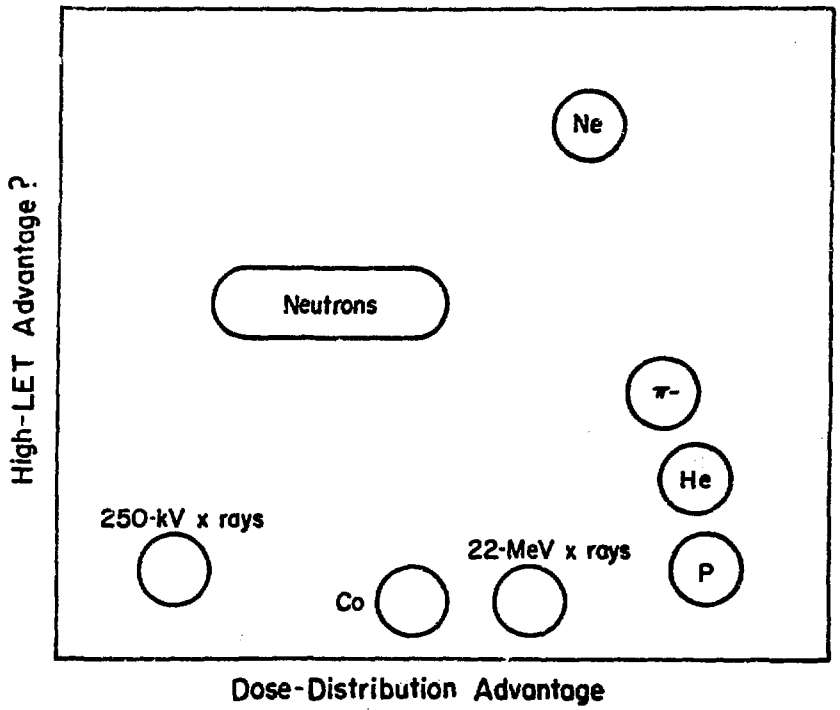

Fig. 17. Schematic comparison of different types of radiations of interest in radiotherapy. Although based on experimental results, this comparison is an oversimplification. It is recognized that the relative positions of the particles in this schematic diagram can be argued and should be used for clarity purposes only. RBE is not taken into consideration in the dose-distribution advantage (abscissa). This idea of representing the relative merits of particles was suggested by Mr. A. M. Koehler (Raju et al., 1974b).

depth-dose, and sharpness of dose-distribution. However, the biological advantages of high-LET radiations are not yet established clinically; therefore, the high-LET advantage is shown with a question mark (see Fig. 17). It should be emphasized that this comparison, although based on experimental results, is oversimplified for clarity.

All heavy charged particles have similar advantages in dose-distribution over conventional radiations but have differing LET distributions. Fast neutrons have no advantage in dose-distribution compared to megavoltage radiations but do have higher LET. It is clear from Fig. 17 that, if only physical factors of dose localization are important in radiotherapy, the particles of choice are protons or helium ions. A small increase in tumor dose can yield a large increase in tumor cure (Shukovsky and Fletcher, 1972). High-LET radiations may be more effective for the treatment of resistant tumors. This question should be answered soon from ongoing fast-neutron therapy programs.

A comparative study of heavy particles is in progress by Raju and his associates. Figures 18 and 19 show some of the preliminary results. Figure 18 shows experimental measurements of depth-dose distribution of various charged-particle beams modified to give a 10-cm wide peak. It can be seen that protons and π^- mesons have nearly similar depth-dose distribution except that mesons have a significant dose beyond the region of interest because of μ^- and e^- contamination in the beam. One would expect improved depth-dose distribution with mesons compared to protons because of star phenomena. However, the increase in dose at the peak region, because of the Bragg peak effect alone, is higher for protons than for π^- mesons. The additional dose due to stars from π^- capture compensates for this difference. With the increasing mass of the heavy ion, for a given dose at the peak, the entrance dose increases because of nucleon interactions. Figure 19 shows cell-survival measurements with depth for the beams shown in Fig. 18. Cell-survival measurements for various beams look similar except, in the case of an argon-ion beam, cell killing with depth is reduced considerably more than for other particles. This is because of saturation effects at very high LET, consistent with the results reported earlier by Chapman _et al_. (1976) and Hall _et al_. (1976). These preliminary results from the comparative study are consistent with the schematic presentation shown in Fig. 17. The OER values at the center of the 10-cm wide peak from the comparative study by Raju and his associates were found to decrease with increasing mass of the heavy ion. Preliminary OER values for x rays, protons, carbon, neon, and argon ions were about 3.0, 3.0, 2.5, 2.0, and 1.7, respectively. Thus, even for argon ions, the OER is not much different from that for neutrons. The OER values for heavy ions are much higher than anticipated. It appears that the large delta-ray penumbra associated with energetic heavy ions does not help to reduce the OER. A dense localized energy deposition is important to reduce the OER, although it is not critical for increasing the RBE. Hypoxic cell sensitizers are promising means of overcoming the hypoxic cell problem in radiotherapy (Adams _et al_., 1976). Because of possible toxic effects of these compounds on patients, it may be impossible to overcome completely the radioresistance of hypoxic cells. Thus, high-LET radiations in combination with hypoxic cell sensitizers may be necessary if we are to minimize the radioresistance of hypoxic cells in radiotherapy (see Hall _et al_., 1975; Chapman _et al_., 1976; Raju _et al_., 1976c).

The physical dose-distributions of all heavy charged particles (negative pions, protons, very heavy ions) are similar in nature; however, the

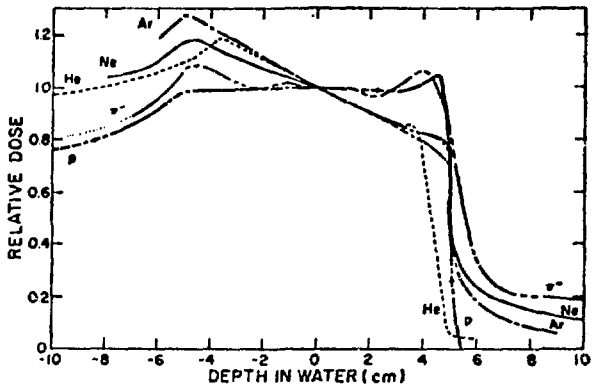

Fig. 18. Depth-dose distribution of protons, negative pions, helium, neon, and argon ions (normalized at the peak center). Recent data indicate that carbon ions are very close to those of helium and neon at the entrance but that the exit is higher even than neon ions. The exit dose depends very strongly on the energy (range) of the primary beam. Ideally, we should have used all beams with the same range for this comparative study. The ranges of carbon, neon, and argon beams used in this study were 25, 15, and 12 cm, respectively. The exit dose for argon is slightly smaller than neon because of this difference. If all heavy ion beams of the same range are used for comparison, the exit doses increase with increasing mass of the heavy ion.

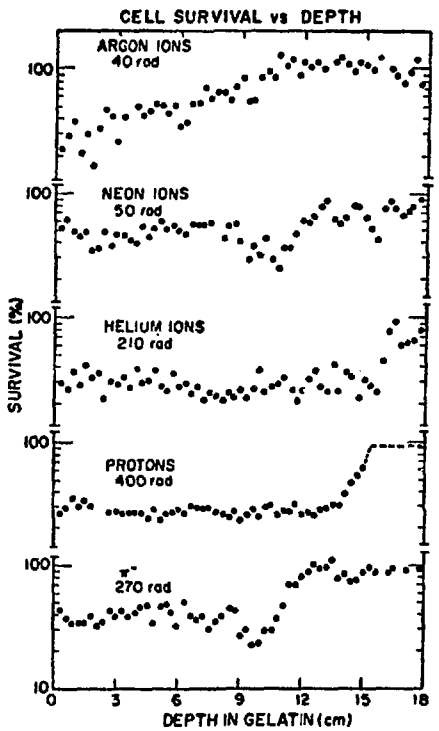

Fig. 19. Cell survival with depth for various heavy charged particle beams at doses giving approximately similar survival levels.

dose localization advantage is reduced with increasing mass of the ion. If the present neutron, proton, and helium therapy trials prove superior to conventional radiations, then mesons and very heavy ions will combine some of the advantages of dose localization and high LET. If it is found that a LET higher than that of fast neutrons is even better to treat radioresistant tumors, then very heavy ion beams such as neon and argon may be of interest.

A small fraction of high-LET radiation (~10%) is very effective in lowering the OER from 2.7 to 1.8 (Raju and Jett, 1974). Therefore, if the irreparable damage produced by high-LET radiations is found to be a disadvantage, then negative pions and lighter heavy ions such as helium, carbon, and oxygen may be useful. Combined therapy with conventional low-LET radiations supplemented with very high LET beams also may be effective.

The use of pions and heavy ions in radiotherapy provides an excellent opportunity for interdisciplinary research, including advanced developments in computer technology, high-energy physics instrumentation, engineering, and radiobiology, and for improvements in tumor diagnosis, localization, and treatment. Because of the sharp dose localization of these particles, development of better methods of tumor localization is essential. Fortunately, computerized axial tomography has been developed and should work in close cooperation with high-LET radiotherapy for increased local control of many of the tumors shown in Table I, as well as of tumors not treatable previously such as cancer of the pancreas. The availability of neutrons in five centers in the United States and protons, helium ions, heavy ions, and negative pions in four centers makes possible a systematic study of the benefits of these particles in clinical radiotherapy. It is essential that these facilities be employed at the earliest date in a properly controlled clinical trial.

In conclusion, heavy particles have potential applications in improving radiotherapy. In addition to improvements in cure rates and reduction of complications to the patient, the use of heavy particles in radiotherapy will aid in improving our knowledge in tumor radiation biology and tumor localization techniques. This, in turn, could improve x-ray radiotherapy results. A well-coordinated national effort in heavy particle radiotherapy research is a further step in improving cancer management.

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