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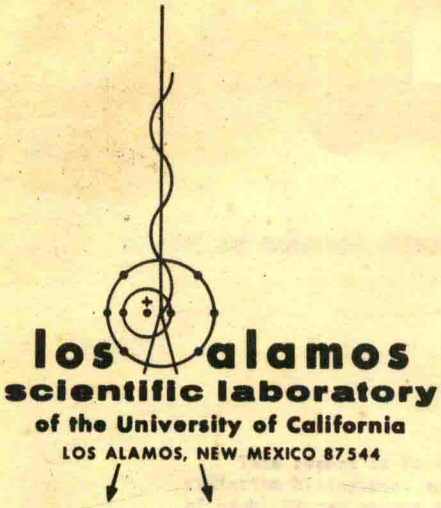

Physical and Biological Aspects of High LET Radiations with Reference to Radiotherapy*

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M. R. Raju

*Supported in part by the Division of Biomedical and Environmental Research.

This material was presented as an invited review paper at the Twentieth Annual Meeting of the Radiation Research Society held in Portland, Oregon, May 14-18, 1972.

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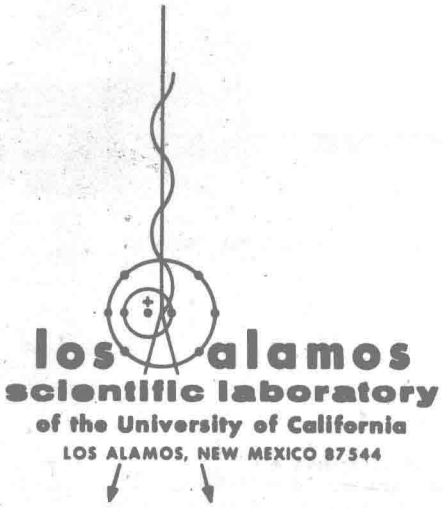

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PHYSICAL AND BIOLOGICAL ASPECTS OF HIGH LET RADIATIONS WITH REFERENCE TO RADIOTHERAPY

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ABSTRACT

This report is presented for a mixed audience such as physicists, radiation biologists, and radiation therapists interested in the use of high LET radiations in radiation therapy. The particles covered are protons, heavy ions, negative pions, and fast neutrons. The following topics are covered: current progress and limitations of conventional radiations in radiotherapy, the rationale for the use of high LET radiations in therapy, interaction of different types of radiations with matter, physical aspects of high LET particles, biological effects as a function of LET, radiobiology and radiotherapy of high LET radiations, clinical implications of better localization, and comparison of dose and effective dose-distributions for the particles covered. It was concluded that these radiations are complementary and do have potential application in radiotherapy.

INTRODUCTION

Nearly 50% of all cancer patients can benefit from radiation therapy at some point in the course of their disease. A tumor volume consists of normal tissues and quite frequently important normal structures as well. The greatest advantage of radiation therapy in cancer treatment lies in the possibility of sterilizing the tumor while leaving normal tissues within the treatment volume in a satisfactory anatomic and functional state. If the patient could survive without those normal tissues within the tumor-suspected volume, we would not need radiation therapy; surgery could do the job.

In radiation therapy, the therapist aims to destroy every tumor cell. Hence, the chance of curing a tumor depends on its size. Large tumors are not as curable as small tumors. The tolerance of normal tissues, within and surrounding the treatment volume, to radiation limits the dose necessary to kill all tumor cells. With the advent of high-energy x-ray generators, the limiting normal tissues are mostly within the treatment volume. In therapy, since the normal tissue tolerance limits delivery of a tumoricidal dose to the patient, a maximum tolerable dose is given which, hopefully, gives the best chance of destroying the tumor.

Significant progress has been made in radiation therapy over the past two decades. This progress is mainly due to better understanding of the biology of cancer, better dosimetry, and use of high-energy radiations in therapy. In spite of these developments, failure to cure is still common. Suit[1] has estimated that, of 175,000 cancer deaths occurring in the United States despite treatment with radiotherapy, nearly 58,000 can be attributed to local or regional failure. Cure failure is due generally to the inability to give tumoricidal doses without undue reactions to normal tissues within the treatment volume.

Gray[2] postulated that hypoxia may be an important cause of conventional radiotherapy cure failure. Many tumors appear to have an inadequate blood supply and, hence, may contain a small proportion of hypoxic cells. Powers and Tolmach[3] demonstrated that hypoxic cells occur in experimental animal tumors and that even a small percent of hypoxic tumor cells change the ratio of cell survival-to-dose considerably. For conventional radiation, the dose required to sterilize hypoxic cells is about three times greater than that for oxygenated cells. The ratio of doses required to produce a given

effect under anoxic and oxygenated conditions is called "oxygen enhancement ratio." The presence of hypoxic but viable cells in the tumor requires an increase in tumoricidal dose. This is illustrated in Fig. 1. As you can see, if all cells are fully oxygenated, a 75-mm diameter tumor could be cured with a dose of about 5000 rads, but if the tumor contains 1% hypoxic cells, a tumor of even 5-mm diameter cannot be cured with the same dose. Thus, the presence of hypoxic cells requires significant increase in tumoricidal dose, but normal tissues may not be able to tolerate such a high dose. However, it is known that in certain types of animal tumors and, therefore, probably in human tumors as well, an increasing proportion of hypoxic cells of the tumor become oxygenated during fractionated radiotherapy (see Thomlinson[4]). Thus, hypoxic cells that are 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 radiations alone for some less advanced stages of cancer. This very well could be the reason for the success obtained in the early stages of cancer. However, reoxygenation may not take place in advanced tumors. The radiation resistance of hypoxic cells, when

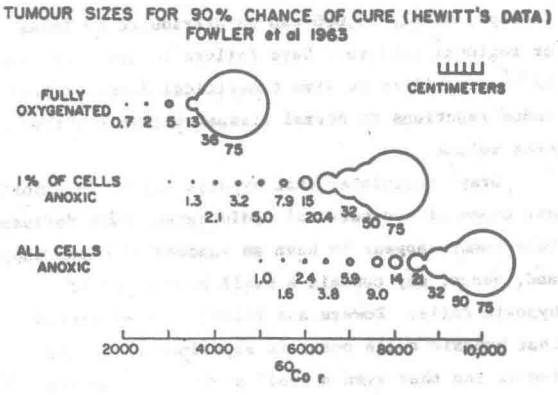

Fig. 1. Doses necessary to reduce the surviving number of tumor cells to 0.1 (i.e., 90% probability of cure) for different size tumors in oxygenated hypoxic and anoxic conditions.

compared to oxygenated cells, is reduced with increasing ionization density or LET. Thus, high LET radiations may be more effective in overcoming the hypoxic cell problem where current methods are not successful. In human tumors, there is evidence for and against the presence of hypoxic but viable cells (see Fry *et al.*[5]). It must be pointed out that hypoxic cells, as a limiting factor in radiation therapy, are so far proven radiobiologically but not clinically (Kaplan[6]).

Fast neutrons were the first high LET radiation to be tried clinically. This fast neutron trial by Dr. Stone was done only six years after the discovery of neutrons. The neutron therapy lasted for about five years, from 1938 to 1943. At that time, the rationale for using fast neutrons for radiation therapy was that they were more effective than roentgen rays per unit of energy absorbed by tissue. Therefore, it was hoped that they might be more effective in the treatment of human cancer. It was not known then that the relative biological effectiveness (RBE) of neutrons might vary with dose level. Even the reduction in oxygen effect for fast neutrons was unknown at that time; neutron therapy was premature. Dr. Stone and his associates did very careful work. Their excellent documentation was recently evaluated in light of current knowledge of radiobiology of neutrons and found to be very useful in understanding their results. From Dr. Stone's presentation of his results in the famous Janeway Memorial Lecture,[7] I quote "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; 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."

It is rather unfortunate that Dr. Stone's conclusions psychologically discouraged everyone with respect to use of these new radiations. Drs. Gray, Fowler and their associates at Hammersmith Hospital should be congratulated for curbing some of these fears with their careful studies of the radiobiology of fast neutrons. As some of you know, fast neutrons are now being tried therapeutically at Hammersmith Hospital, and results to date are very

encouraging. There is now considerable interest in the use of high LET radiations in radiation therapy.

The rationale for use of radiations (protons, helium ions, heavy ions, π^- mesons, and neutrons) is that they may provide a better differential between normal and malignant tissues in the treatment volume and, in addition, that some of the radiations have superior dose localization characteristics.

INTERACTION OF DIFFERENT TYPES OF RADIATIONS WITH MATTER

Figure 2 shows a schematic representation of different types of radiation interactions with matter as they pass through a medium such as tissue. Microscopic distributions of dose by different radiations, both at the entrance as well as at a depth of say 15 cm, are also shown when the total dose is roughly the same. X-rays, as they pass through the medium, are attenuated due to photoelectric, Compton, and pair-production processes. Hence, the dose delivered by high-energy gamma rays decreases exponentially with depth except for initial build-up. Fast neutrons are also attenuated exponentially as they pass through matter due to elastic and inelastic collisions with nuclei in the medium. Therefore, the dose deposited by them also decreases exponentially with depth. The characteristic difference between the interaction of gamma rays and fast neutrons is that particles released when fast neutrons interact with matter are protons, alpha particles, and heavy recoils and, in case of gamma rays, the particles released are electrons. The microscopic dose-distribution by x-rays at the entrance as well as depth is the same, and it is sparse as represented by the many thin lines. For fast neutrons, the microscopic dose-distribution at the entrance as well as at depth is also the same, but it is more dense as represented by a few thick lines. The width of the thin lines schematically represents the density of ionization (that is, LET).

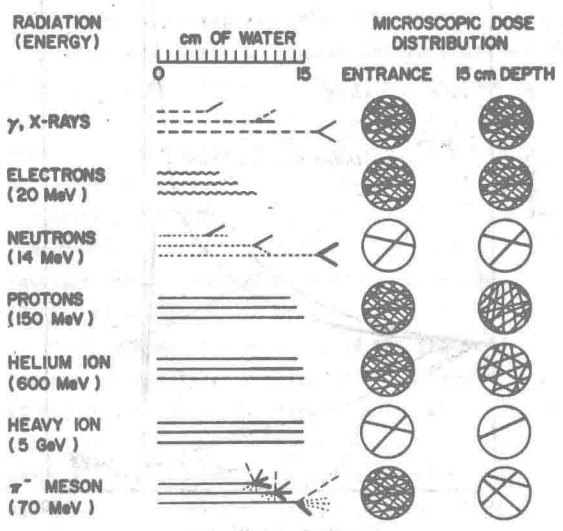

Fig. 2. Schematic representation of interaction of radiations with matter such as tissue.

When high-energy electrons pass through matter, most of the electrons come to a stop near the end of the range. Electrons, being light, travel with relativistic speed through most of their range; hence, the dose deposited by them, as a function of depth, remains nearly constant and then decreases rapidly near the end of their range. The decrease in dose near the end of their range is not sharp because of considerable range straggling. The microscopic dose-distributions at the entrance and at depth are the same and are sparse.

When heavy-charged particles such as protons, helium ions, heavy ions, and pions pass through matter, most of them also come to a stop near the end of the range. There are significant variations in velocity of these particles as they pass through matter; therefore, the dose deposited by them increases slowly with depth and gives rise to a sharp increase in dose near the end of the range due to the Bragg peak effect. The microscopic distributions of heavy-charged particles at depth have higher ionization density when compared to that at the entrance.

In the case of protons, helium ions, and pions, the microscopic dose-distributions at the entrance are very nearly the same as that of conventional radiations, as shown in Fig. 2. In addition to the Bragg peak effect, when the pion comes to rest it is captured by nuclei in the medium, and the resulting nucleus disintegrates itself into short-range and heavily-ionizing fragments. This phenomenon increases the dose at depth in addition to the Bragg peak effect, and ionizing density at

the pion stopping region is increased because of these heavily-ionizing fragments. For heavy ions, the microscopic dose-distribution is higher both at the entrance as well as at depth. The characteristics of all these heavy-charged particles (protons, helium ions, heavy ions, and pions) are all qualitatively similar but quantitatively different from one another. With increasing mass of the particle, range straggling becomes reduced and, hence, stops at nearly the same plane in depth as shown in Fig. 2.

In radiation therapy, one of the important physical parameters is the sharpness of the beam. This is usually called the "penumbra." With a sharp beam, the normal tissues adjacent to the outer edge of the beam will not be damaged. Sharpness is very good for all heavy particles, and with increasing mass of the charged particle the sharpness gets even better. The edges of the beam are fuzzy for photons and fast neutrons. These beams can be visualized as steam coming through an orifice. With increasing energy of the photons and fast neutrons, the edge of the beam can be compared to steam discharged with increasing pressure; hence, the fuzziness gets reduced. Charged particle beams can be visualized as liquid jets.

The term high LET is a convenient one to use but does not say much. I would like to stress the fact that all radiations under therapeutic situations, including so-called conventional low LET radiations, have a wide spectrum of LET values. Low LET radiations deposit a relatively small fraction of dose at an LET ~ 30 keV/μ. For proton beams, the high LET component extends to about 90 keV/μ; for helium ion beams, the high LET component extends up to about 200 keV/μ; for pions and fast neutrons, the high LET component extends to about 900 keV/μ; and for heavy ions, it is even higher. Thus, the difference between these so-called high LET radiations is the relative dose fractions in various LET intervals and the maximum LET. Thus, all these high LET radiations are really a mixture of wide spectra of LET. This may turn out to be fortunate for radiotherapeutic purposes, as mentioned by Dr. Rossi.[8]

High LET components for all these beams are due to low-energy, heavy-charged particles such as protons, helium ions, and heavy ions. Proton beams, helium ion beams, and heavy ion beams are their own carriers in order to give high LET at depth just by the slowing-down process. Fast neutron and pion beams can be considered as carriers to give rise to low-energy, heavy-charged particles.

Figure 3 shows the depth-dose distribution of different particles. Only proton depth-dose distributions are shown as representative of all heavy-charged particles, since the depth-dose distributions of all heavy-charged particles are qualitatively similar. This narrow peak is due to the monoenergetic proton beam; however, for radiotherapeutic applications, this peak can be broadened to any desired width. The dose at the peak, compared to the dose at the entrance, is reduced with increasing width of the Bragg peak but is never smaller than at the entrance. In addition, the dose beyond the range of interest is negligible. Thus, the depth-dose distribution can be broadly classified in two categories: one in which the dose decreases with depth except for initial build-up and the second in which the dose increases with depth due to the Bragg peak effect. The latter

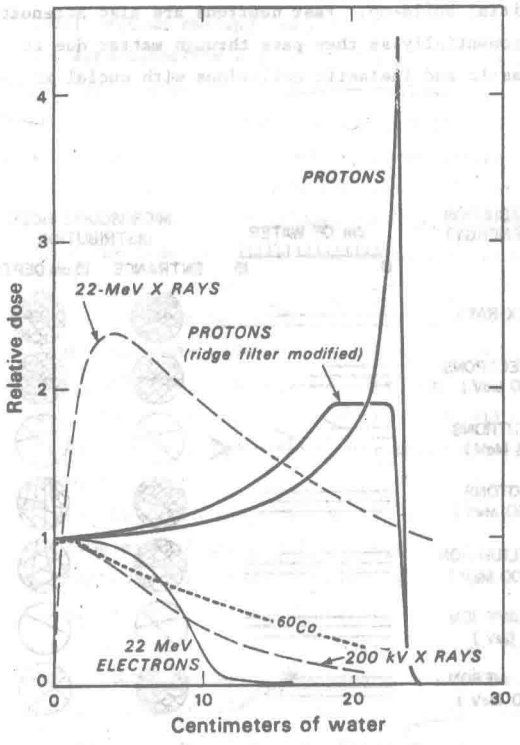

Fig. 3. Depth-dose distributions of protons, electrons, x-rays, and gamma rays.

type will be of potential value for therapeutic application of deep-seated tumors.

PHYSICAL ASPECTS OF HIGH LET PARTICLES

Protons, Helium Ions, and Heavy Ions

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. Deviation from a perfectly straight trajectory is accounted for by the cumulative effect of many small-angle scatterings of heavy-charged particles due to interactions with nuclei of the medium. This is called "multiple scattering." The root mean squared scattering angle is approximately inversely proportional to the mass of the particle. Hence, heavier particles show a small scattering angle. A small fraction of particles undergo nuclear interaction before they near the end of the range, but the dominant process is the energy loss through interactions with electrons in the medium. 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. There the dose reaches a peak, known as the "Bragg peak." The dose falls off very rapidly beyond the Bragg peak.

As heavy-charged particles pass through matter, some of them are lost to nuclear interactions before they reach near the end of the range. In case of protons, for example, nearly 2.5% of particles are lost for each centimeter of traversal in tissue. With increasing mass of heavy-charged particles, the cross section for nuclear interaction increases. Nearly 4.5% of nitrogen ions are lost to nuclear interactions for each centimeter of traversal (Tobias *et al.*[9]).

For protons, the dose beyond the region of interest is practically zero. With increasing particle mass, because of increase in nuclear interactions, the dose beyond the region of interest increases. The depth-dose distribution of protons and helium ions is very nearly the same. Figure 4 shows the depth-dose distribution of the nitrogen ion beam at Berkeley. As you can see, the Bragg

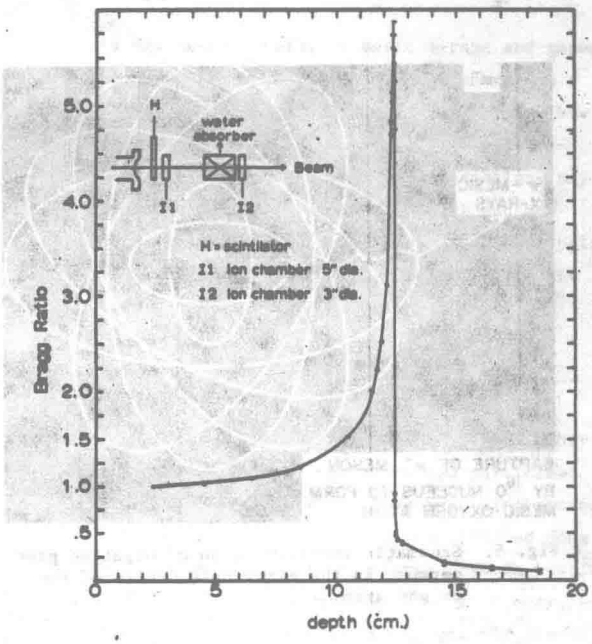

Fig. 4. The apparatus used to obtain the Bragg ionization curve. The Bragg ionization curve for 278-MeV/nucleon ^{14}N beam in water.

peak is very sharp, and the dose at the peak is quite high. The dose beyond this peak is due to nuclear secondaries produced by the beam.

Pions

Pions, unlike other heavy-charged particles, are unstable and have a mean lifetime of 2.54×10^{-8}/sec; hence, nearly half of them decay in flight to muons, then to electrons, before they reach the experimental area. A pion has a mass 273 times that of an electron, or approximately 15% of the mass of a proton. Pions, their mass being low compared to protons, scatter nearly three times as much as protons. Negative pions, being heavy particles when compared to electrons, have the usual Bragg curve and, in addition, the unique property of getting captured by a nucleus of the medium when they come to rest.

Figure 5 shows the capture of pions in the electronic orbits of an oxygen atom. The pion cascades down the atomic levels in a time that is short compared with its lifetime. During the cascade, characteristic x-rays are evident; they are called

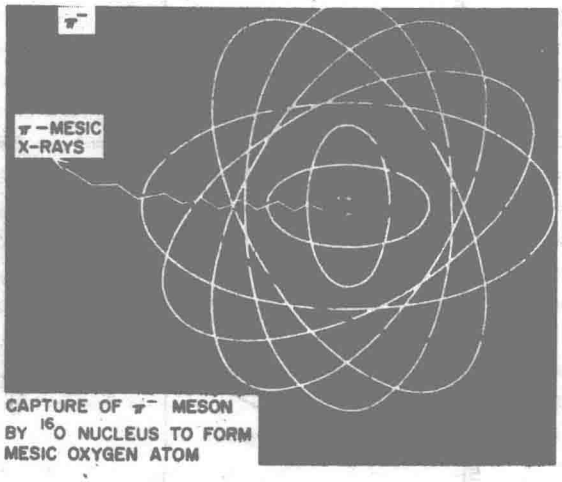

Fig. 5. Schematic representation of negative pion capture in the electronic orbits of the oxygen atom.

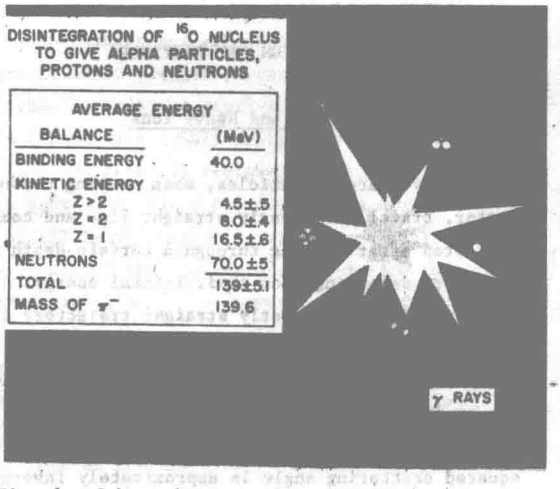

Fig. 6. Schematic representation of negative pion capture in an oxygen nucleus and disintegration of oxygen nucleus.

"pi mesic x-rays." The pion, when in the lower atomic orbit, spends a considerable fraction of time inside the nucleus and, hence, is absorbed by the nucleus. Therefore, the rest mass of 140-MeV pions appears in the form of kinetic energy of nuclear fragments except for about 40 MeV, which is used in overcoming the binding energy of the nucleus. Figure 6 shows such a catastrophic event schematically. For each disintegration, nearly 70 MeV appears in the form of kinetic energy shared by three neutrons: one proton of 16 MeV average energy, one alpha particle of 8 MeV average energy, and a heavy recoil of 4 MeV average energy. These particles cover a wide range of energy spectra.[10]

The capture reactions in carbon, nitrogen, and oxygen -- the main constituents of tissue -- are quite similar in their yield of protons, alpha particles, and heavy recoils and their mean energies. About 2% of stopping pions produce high-energy gamma rays, and these gamma rays are also of special interest and will be discussed later.

Low-energy pions decay much faster than high-energy pions. A distance of about 5 to 10 meters between the pion-producing target and the experimental area is generally required to allow the necessary shielding against the intense flux of neutrons and gamma rays produced in the target and to accommodate the magnetic system needed to direct the pions of desired energy to the experimental area. Figure 7 shows the percent of original pions remaining in the beam after it has traveled about 5 to 10 meters. As you can see, nearly 75% and 50% of pions in the energy range of interest to radiotherapy (50 to 80 MeV) decay in flight in drifting to a distance of 10 and 5 meters, respectively.

Figure 8 shows the depth-dose distribution of the π^- and π^+ beams. The increase in dose for the π^- beam over the π^+ beam is due to star events.[11] Detailed depth-dose distributions of pions have been calculated recently at the Oak Ridge National Laboratory using the Monte Carlo technique. In general, the experimental measurements are in good agreement with theoretical expectations. The LET at the peak of depth-dose distribution is quite similar to that of fast neutrons except that the LET here extends to much lower values than in the case of neutrons. It must be pointed out that, with increasing width of the Bragg peak, the percent high LET contributions to the dose for π^- mesons is decreased.

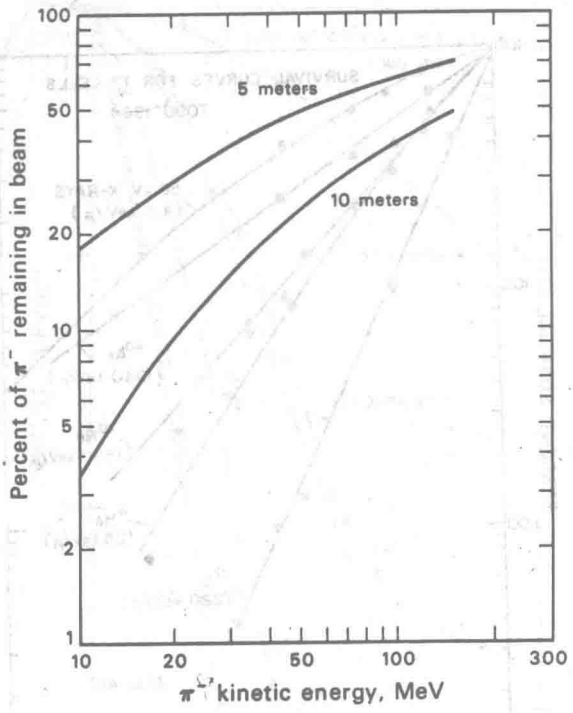

Fig. 7. Percentage of original negative pion flux remaining after a 10- and 5-meter drift.

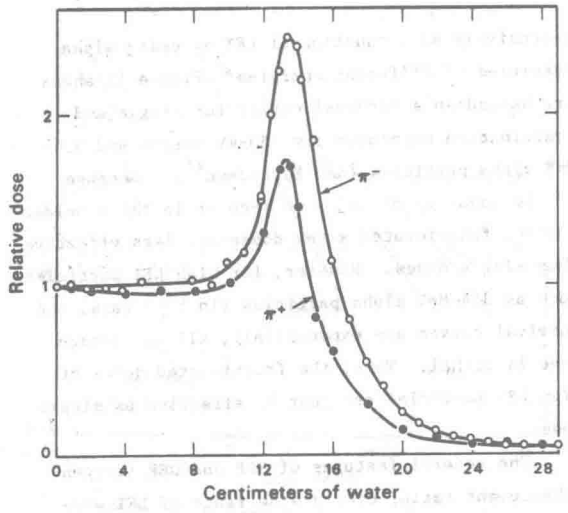

Fig. 8. Depth-dose distribution of 65-MeV π^- and π^+ beams ("pure") in water.

As discussed before, pi mesic x-rays and gamma rays are also emitted from the region where the π^- beam stops and produces stars. The dose contribution due to x-rays and gamma rays is small; however, a significant number of these radiations may be detected outside the exposed patient and may provide a good method of observing the pion stopping region externally. Experimental results indicate that, in principle, this can indeed be done.

Fast Neutrons

When fast neutrons interact with tissue, they release highly-ionizing, heavy-charged particles; most of the dose is contributed by recoiling protons from hydrogen in tissue. Hence, the absorbed dose in fatty tissues is about 15% higher than in muscle. The energy of these protons has a range of energies extending up to maximum neutron energy, but the average energy is nearly half that of neutron energy. Nearly 10% of the absorbed dose is due to recoiling heavy nuclei in tissue. These are the most dominant processes for fast neutrons below 5 MeV. Nuclear disintegrations occur at energies higher than 5 MeV, resulting in emission of protons, deuterons, alpha particles, or neutrons. These disintegrations are called "inelastic processes" and contribute as much as 30% of the dose for 14-MeV neutrons (see Bewley[12]).

The depth-dose distribution of heavy-charged particles depends on the width of the peak. For comparison of depth-dose distribution of different particles, the width of the peak is assumed to be 5 cm located at a mean depth of 10 cm. Figure 9 shows the depth-dose distribution of different particles. It can be seen that the depth-dose distribution of all heavy-charged particle beams is similar. Mesons have the most favorable depth-dose distribution; however, there will be some dose beyond the peak because of possible contaminants in the beam. Heavy ions also will have some residual dose beyond the peak because of the considerable number of nuclear secondaries produced by the beam in traversing the medium. It must be noted that the advantage of heavy-charged particles is that the dose deposited and LET in the region of interest are always higher than at the entrance. The LET at entrance is lowest for π^- mesons among heavy-charged particles and highest for heavy ions. At the peak, among heavy-charged particles, the LET is lowest for protons;

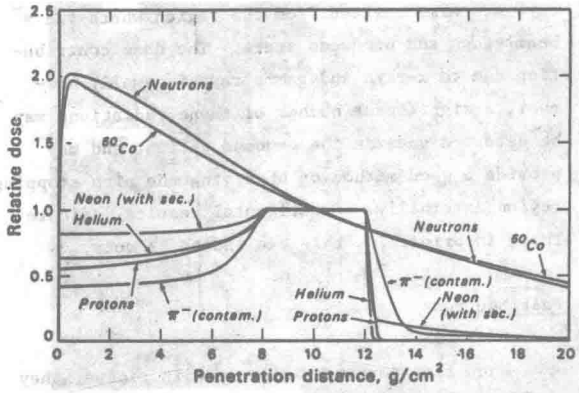

Fig. 9. Central axis depth-dose distributions of ^{60}Co gamma rays, 14-MeV neutrons, protons, helium ions, neon ions, and negative pions.

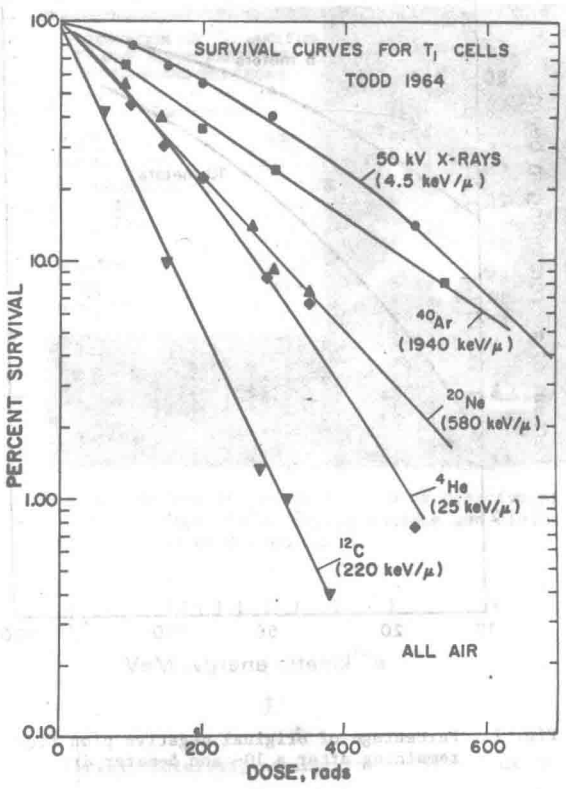

Fig. 10. Survival curves of human kidney cells (T_1) for x-rays and heavy ions.

then follow alpha particles, π^- mesons, and heavy ions. For neutrons, the LET remains nearly the same at both entrance and peak and is slightly higher than π^- mesons at the peak.

BIOLOGICAL EFFECTS OF HIGH LET RADIATIONS

The particles discussed so far cover a wide range of LET values. Let us discuss briefly biological effects as a function of LET. Figure 10 shows survival curves of human kidney cells exposed to x-rays and heavy ions.[13] As you can see, the x-ray curve has a shoulder and, with increasing LET of the particles such as helium and carbon, the shoulder decreases slowly and finally disappears for carbon ions at a LET value of about 220 keV/μ. With further increase in LET, the survival curves remain exponential, but the RBE is reduced because of depositing much more dose than is necessary to kill the cells. Because of this dose saturation, the RBE is nearly the same for argon ions of about 2000 keV/μ as that for 50 kV x-rays. Figure 11 shows the survival curves for x-rays, helium ions, and carbon ions in the presence of air and nitrogen. These results are again from Dr. Todd's work. As you can see, with increasing LET the oxygen enhancement ratio is decreased and is very nearly one for carbon ions.

Dr. Barendsen has studied biological effects extensively as a function of LET by using alpha particles of different energies. Figure 12 shows Dr. Barendsen's survival curves for single and fractionated exposures for 250-kV x-rays and 3.4-MeV alpha particles (see Barendsen[14]). Because of the capacity of cells to recover in the shoulder region, fractionated x-ray doses are less effective than single doses. However, for high LET particles such as 3.4-MeV alpha particles (in this case, the survival curves are exponential), all the damage done is lethal. Thus, the fractionated doses of high LET particles are just as effective as single doses.

The general features of RBE and OER (oxygen enhancement ratio) over a wide range of LET were summarized by Barendsen[14] and are shown in Figure 13. In the LET region below 10 keV/μ, denoted by I in the figure, the survival curves exhibit a

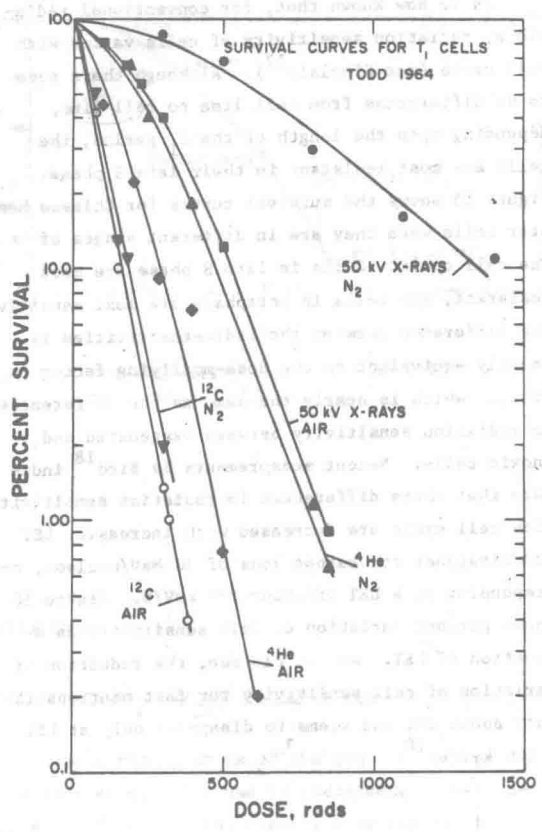

Fig. 11. Survival curves for human kidney cells (T_1) for x-rays and heavy ions under oxygenated and hypoxic conditions.

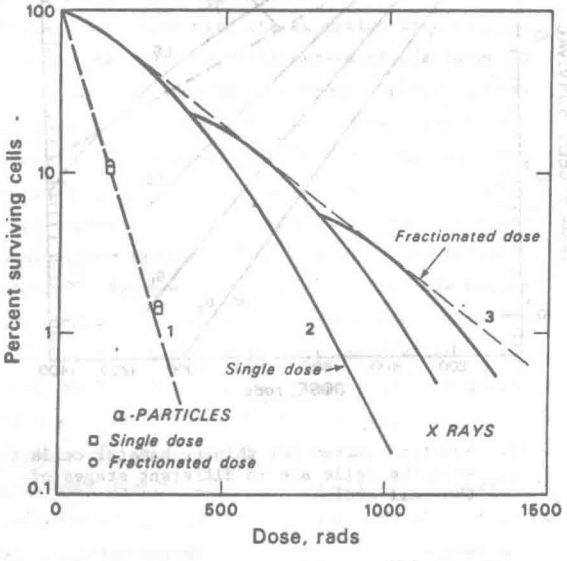

Fig. 12. Survival curves of human kidney cells (T_1) for single and fractionated doses of x-rays and 3.4-MeV alpha particles.

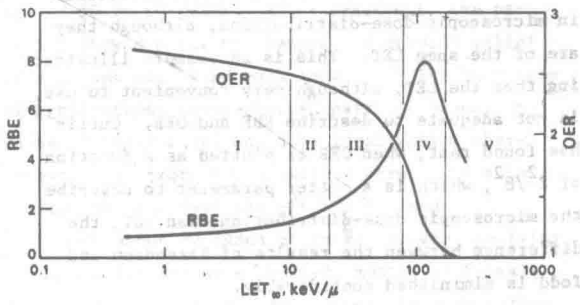

Fig. 13. RBE and OER as a function of LET, measured for damage to the reproductive capacity of cultured cells (T_1).

shoulder. The RBE and OER are relatively constant in the LET region and are nearly the same as for conventional radiations used in current radiotherapy. The LET range from 20 to 80 keV/μ is denoted as region III. In this region the survival curves tend to be exponential because the damage is produced predominantly by single particles rather than the accumulation of many single events, as in region I. The biological effects in region III are relatively independent of dose rate and dose fractionation. The RBE increases sharply, and the OER decreases with LET in this region. In region V, corresponding to LET greater than 160 keV/μ, the survival curves are strictly exponential. The RBE in this region decreases with increased LET because of saturation. The OER in this region remains close to unity. Regions II and IV can be described as transition regions.

Barendsen's estimates of the variation of RBE and OER with LET were based on his studies of human kidney cells irradiated with an alpha particle beam. The velocity of alpha particles was adjusted to yield the desired LET. The RBE was found to peak at about 110 keV/μ, and the OER approached unity at about 200 keV/μ. However, using the same cell line system as Barendsen, Todd obtained a range of LET by using different heavy ions but keeping the velocity constant. Todd found that the RBE peaked at about 220 keV/μ and that the OER approached unity at a much higher LET than that obtained by Barendsen.

This difference was attributed to the difference in microscopic dose-distributions, although they are of the same LET. This is an example illustrating that the LET, although very convenient to use, is not adequate to describe RBE and OER. Curtis[15] has found that, when OER is plotted as a function of Z^2/β^2, which is a better parameter to describe the microscopic dose-distribution than LET, the difference between the results of Barendsen and Todd is diminished considerably.

Barendsen found that the OER remained essentially the same for neutrons of different energies starting from fission to 14 MeV. However, using leukemic cells, Dr. Berry found that the OER decreased with decreasing neutron velocity. He has recently made measurements of OER as a function of LET using the same particles that Dr. Barendsen did using leukemic cells. Figure 14 shows the results of OER as a function of LET for both human kidney cells, measured by Barendsen, and for P388 murine leukemia cells, measured by Dr. Berry.[16] Dr. Berry concluded that this difference in LET response could correlate well, perhaps fortuitously, with the variation of OER he found with his cell system for different energy neutrons. Although the LET at which the oxygen effect disappears and RBE peaks depending on the microscopic dose-distribution and cell system used, the general trend of variation of RBE and OER with LET is still valid.

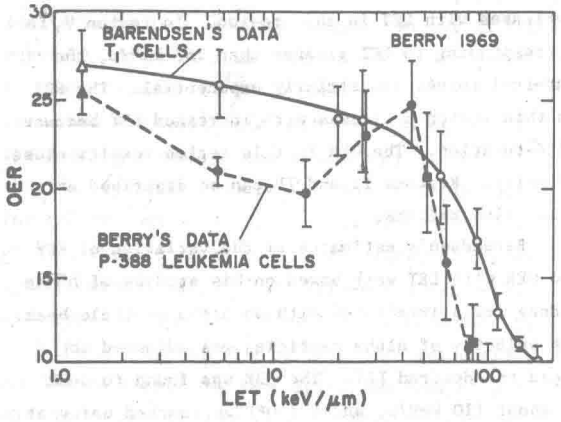

Fig. 14. OER as a function of LET for T_1 cells and leukemia cells.

It is now known that, for conventional radiations, radiation sensitivity of cells varies with cell cycle (see Sinclair[17]). Although there seem to be differences from cell line to cell line, depending upon the length of the G_1 period, the cells are most resistant in their late S phase. Figure 15 shows the survival curves for Chinese hamster cells when they are in different stages of the cell cycle. Cells in late S phase are most resistant, and cells in metaphase are most sensitive; the difference between the radiosensitivities is roughly equivalent to the dose-modifying factor of 2.5, which is nearly the same as the differences in radiation sensitivity between oxygenated and anoxic cells. Recent measurements by Bird[18] indicate that these differences in radiation sensitivity with cell cycle are decreased with increasing LET and disappear for carbon ions of 10 MeV/nucleon, corresponding to a LET of about 200 keV/μ. Figure 16 shows percent variation of cell sensitivity as a function of LET. As you can see, the reduction of variation of cell sensitivity for fast neutrons is only about 20% and seems to disappear only at LET > 100 keV/μ.[18]

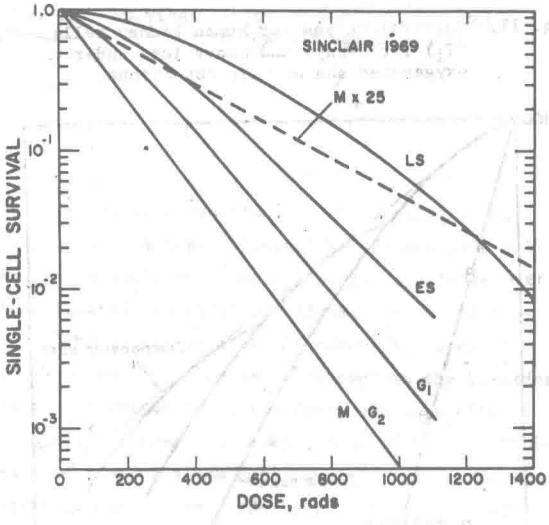

Fig. 15. Survival curves for Chinese hamster cells when the cells are in different stages of the cell cycle.

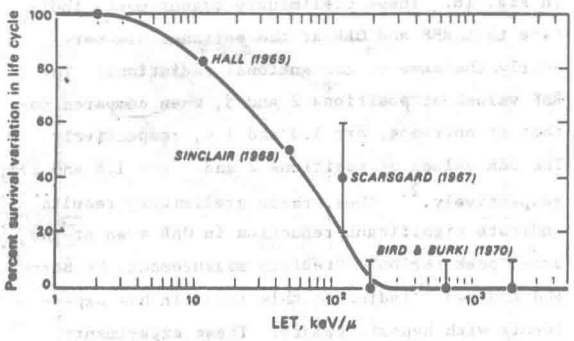

Fig. 16. Percent variation of cell sensitivity as a function of LET.

RADIOBIOLOGY AND RADIOTHERAPY OF HIGH LET RADIATIONS

Proton Radiobiology and Radiotherapy

Even before protons of the required energy were available, their use in radiotherapy was suggested by Wilson,[19] the present Director of the National Accelerator Laboratory. Pioneering studies by Tobias and Lawrence led to their use for treating human disease.[20] The biological effectiveness of protons was found to be nearly the same as conventional radiations with the exception of a narrow zone in the final few millimeters of the range in which a significant RBE was found. However, when the peak was broadened to cover large treatment areas, the biological effectiveness was found to be very similar to conventional radiations. Clinical experience with protons also established the equivalence of protons with conventional radiations.[21] Because of the similarity of the biological effects of protons to conventional radiations, clinical experience of conventional radiation could be used for protons. Nearly 1000 patients have been treated so far at Berkeley, Harvard, and Uppsala.[22] These treatments were primarily of the pituitary gland. Clinical results of acromegalic patients are so good that acromegalic treatments at Berkeley and Harvard are now routine. Acromegalic patients, when untreated, develop abnormal growths of the extremities, and most of them die before the age of 50 to 60 years. After treatment, the patients showed striking changes and gradual relief of symptoms and lived much longer.[23] For this type of application, heavy-charged particle beams, because of their excellent dose localization characteristics, protected sensitive structures such as optical chiasma near the pituitary gland.

Only about 60 cases of large targets involving malignant disease were treated, mostly at Uppsala. Treatment of relatively fewer patients with malignant disease led many people to believe that it is very difficult to apply proton beams to large targets and that they display no advantage over conventional radiations. I believe that the reason for not using these beams in the past was due mainly to the warning by Dr. Stone. In addition, most of the proton accelerators were used extensively 24 hours a day, 7 days a week, for physics research, and very little time was available for biomedical use. As mentioned before, the dose localization characteristics of protons are strikingly better than any other conventional therapy. Russian researchers recently have started radiotherapy work with protons at three locations and are planning to provide other facilities as well.

Helium Ion Radiobiology and Radiotherapy

The Berkeley cyclotron was modified in 1956. With that modification, the energy of the proton beam was 730 MeV and helium ions was 910 MeV. As you know, physicists are always trying to get higher and higher energies, and this creates problems for biomedical use. Since the energy of 730-MeV protons is too high for therapeutic application, helium ions have been used. Helium ion beam therapy has been applied mainly to pituitary irradiation of patients.

When a narrow Bragg peak is broadened to cover large treatment volumes, it is felt that the high LET component will be diluted and may not be useful in overcoming the hypoxic cell problem (see Fowler[24]). Figure 17 shows the modified dose-distribution of the high-energy helium ion beam. The width of the peak is about 6 cm of water. As marked in Fig. 17, human kidney cells are exposed at the positions marked 1, 2, and 3 in atmospheres of oxygen and nitrogen, and the results are shown

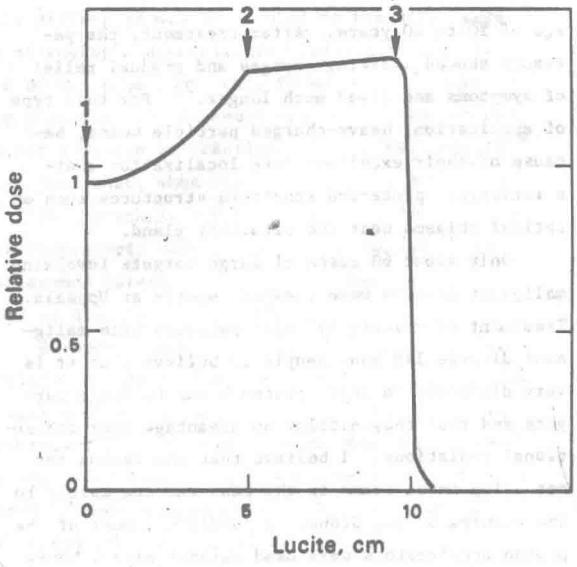

Fig. 17. Modified depth-dose distribution of a 910-MeV helium ion beam showing the three exposure positions.

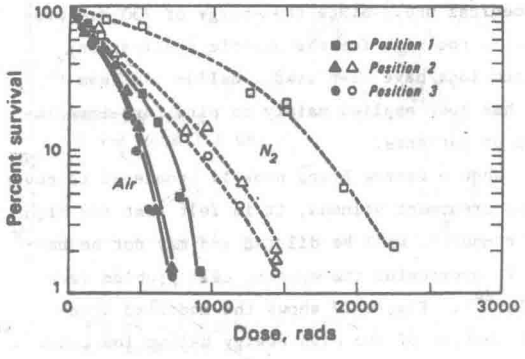

Fig. 18. Survival curves for T_1 cells exposd under aerobic and anoxic conditions at the three positions marked 1, 2, and 3 in Fig. 17.

in Fig. 18. These preliminary measurements indicate that RBE and OER at the entrance are very nearly the same as conventional radiations. The RBE values at positions 2 and 3, when compared to that at entrance, are 1.3 and 1.4, respectively. The OER values at positions 2 and 3 are 1.8 and 1.7, respectively.[25] Thus, these preliminary results indicate significant reduction in OER even at the broad peak region. Previous measurements by Berry and Andrews[26] indicated this trend in his experiments with hypoxic tumors. These experiments should be repeated several times, and it may worthwhile to repeat them for high-energy protons also.

A sophisticated human positioner was recently constructed and is being used with helium ion beams at Berkeley. They recently have treated some lung metasases, and the results are encouraging.[27] Two other helium ion facilities, one at Newport News, Virginia, and the other at Philadelphia, Pennsylvania, are being proposed for therapeutic use.

Radiobiology of Heavy Ions

The use of heavy ions in radiotherapy was proposed by Dr. Tobias many years ago on the basis of their dense ionization characteristics that could overcome the hypoxic cell problem better than any other radiation, while minimizing the variation of cell sensitivity as a function of cell cycle. Todd has done extensive work on the effect of low-energy heavy ions (10 MeV/n) on cells in culture. The range of these heavy ions is less than 1 mm in tissue.

Heavy ions of energies of therapeutic interest only very recently have been accelerated at the Princeton Particle Accelerator and the Bevatron at Berkeley (see Science[28]). Nitrogen ions have been accelerated at these locations to energies that have the necessary ranges for therapeutic application. Some preliminary physical and radiobiological measurements have been made at both Berkeley and Princeton. Figure 19 shows cell survival as a function of depth as measured by Todd at Princeton. As you can see, dense ionization at the peak is very effective in bringing cell survival to a very low level.

Figure 20 shows cell survival for hamster cells as measured by Hall for x-rays at the narrow peak of

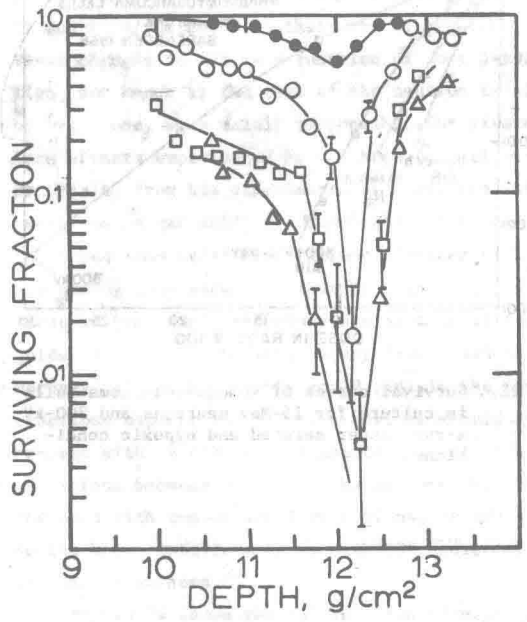

Fig. 19. Cell survival as a function of depth for the nitrogen ion beam.

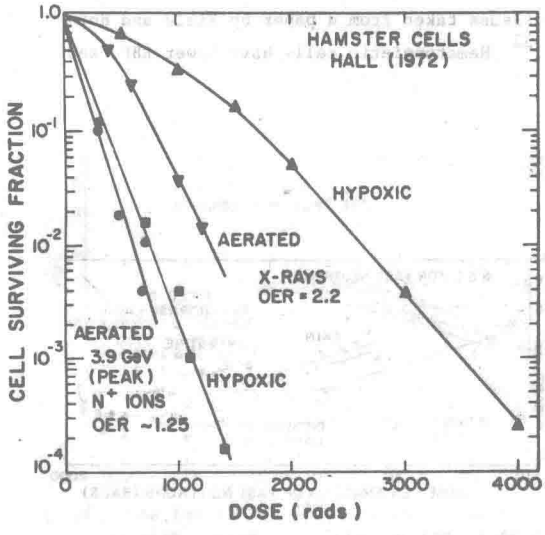

Fig. 20. Survival curves for x-rays and 3.9-GeV nitrogen ions at the peak of the depth-dose distribution under aerated and hypoxic conditions.

the 3.9-GeV nitrogen ion beam. The RBE and OER at the peak were found to be 3.0 and 1.25, respectively. Similar measurements, with quite similar results, were also made at Berkeley. Some measurements on mouse skin and tumor were also made at Princeton. It must be pointed out that, when this narrow peak is broadened, the RBE decreases and OER increases. Because of this fact, more work needs to be done with broad peaks.

Although the accelerator at Princeton is no longer in operation, the program with heavy ions at Berkeley is expected to continue. They plan to couple the heavy ion linear accelerator and the Bevatron so that heavy ions, possibly up to iron, can be accelerated to energies with ranges of 10 to 15 cm in tissue.

Pion Radiobiology

The potential application of π^- mesons in radiotherapy was recognized by Fermi and a few others soon after pions were discovered experimentally. Fowler and Perkins[10] made detailed calculations of pions, which generated more interest. Most of the radiobiology of pions was done at Berkeley and some at CERN, and some work is being done currently in England.

The current sources of π^- mesons are not sufficiently intense by a factor of 100 to 1000 to use in radiotherapy; however, some limited experiments were done. Figure 21 shows survival curves measured at the peak of depth-dose distribution at Berkeley with π^- mesons and ^{60}Co gamma rays. RBE and OER at the peak, calculated at the 10% level, are 3.0 and 1.6, respectively.[29]

Radiobiological measurements of π^- mesons are restricted to a few systems because of low dose rate. The beam used has a contamination amounting to about 15% of the dose at the peak. Most biological measurements are made only at the beam entrance and at the peak of the depth-dose distribution. The RBE at beam entrance is very nearly the same as for conventional radiations, and OER is expected to be the same as for conventional radiations. Depending on the biological end point and the system used, RBE at the peak is in the region of 1.4 to 5.0; OER values at the peak of the depth-dose distribution are in the region of 1.5 to 1.9. For a pure pion

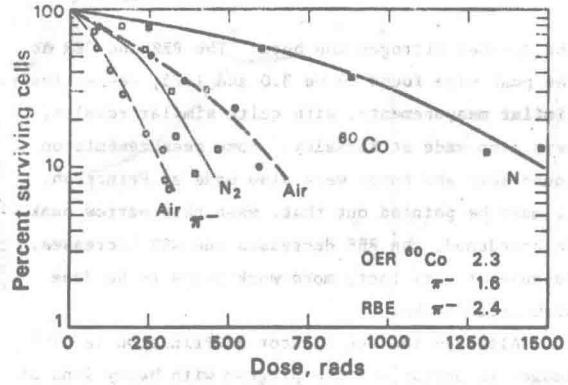

Fig. 21. Survival curves of human kidney cells in culture (T_1) for negative pions at the peak of the depth-dose distribution and for ^{60}Co gamma rays under aerated and hypoxic conditions.

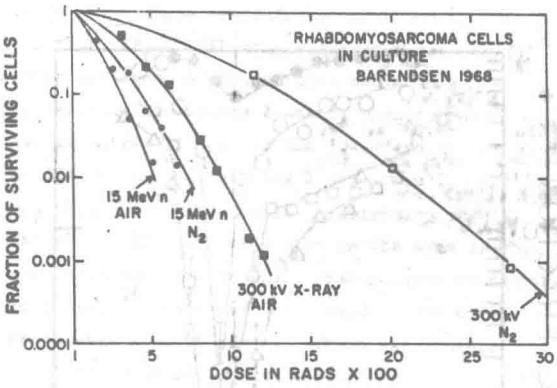

Fig. 22. Survival curves of Rhabdomyosarcoma cells in culture for 15-MeV neutrons and 300-kV x-rays under aerated and hypoxic conditions.

beam, RBE values at the peak will be slightly higher and OER slightly lower; however, these values change according to the width of the peak [i.e., with increasing width the RBE decreases and OER increases (see Raju and Richman[30])].

Pion facilities with intensities adequate for therapy are being built at Los Alamos, New Mexico; Vancouver, British Columbia; and Zurich, Switzerland. Therapeutic facilities are being built at all three accelerators (see Rosen[31]). Also, a pion facility using the Stanford superconducting electron LINAC is being built.

Neutron Radiobiology and Radiotherapy

On June 22, 1970, a meeting was held at Rijswijk, The Netherlands, on fundamental and practical aspects of the application of fast neutrons in clinical radiotherapy. Excellent proceedings of this meeting were published in the May 1971 issue of the European Journal of Cancer. Some of the biological aspects of fast neutrons will be mentioned briefly to indicate the potential of all these radiations together.

Figure 22 shows survival curves of Rhabdomyosarcoma cells in culture for 300-kV x-rays and 15-MeV fast neutrons as reported by Barendsen and associates.[14] The shoulder for fast neutrons is small. The RBE and OER for fast neutrons are about 2.0 and 1.5, respectively. Because of differences in shoulders for x-rays and fast neutrons, when the doses are fractionated RBE increases with decreasing dose per fraction.

Figure 23 shows plots of neutron RBE as a function of dose per fraction for different types of tissues taken from a paper by Field and Hornsey.[32] Hematopoietic cells have lower RBE, and

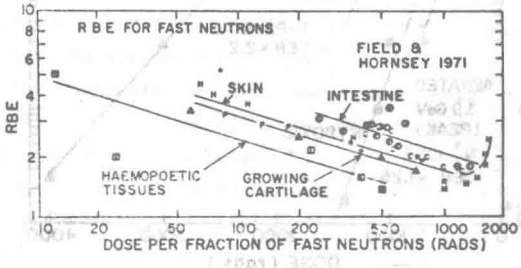

Fig. 23. RBE for fast neutrons in different tissues as a function of dose per fraction.

intestinal crypt cells have higher RBE. This could be due to differences in their repair capacity. These changes in RBE as a function of dose per fraction, not known at the time of the neutron trials by Dr. Stone, were mainly responsible for severe late effects experienced by Dr. Stone's patients. Dr. Field, from his experiments on early and late reactions on rat skin, concluded that late reactions developed from irradiated tissues increase with increasing dose much more sharply than early reactions so that early reactions are an insensitive guide for determining late injury (see Field and Hornsey[32]). Although this could explain the severe reactions experienced by Dr. Stone, we should still proceed with caution in therapeutic use of high LET radiations because of limited experience with them compared with conventional radiations, in addition to the known interference by high LET radiations in recovery processes.[33]

Figure 24 shows the RBE as a function of dose per fraction for normal tissues and tumor tissues from the work of Broerse and Roelse.[34] RBE for tumors is higher than for normal tissues. This differential is of great importance in radiation therapy. The differential could be due to the presence of hypoxic cells.

After having studied the radiobiology of fast neutrons extensively at Hammersmith Hospital, some of the problems encountered by early fast neutron

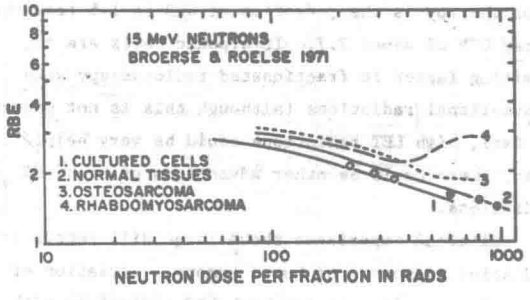

Fig. 24. RBE for 15-MeV neutrons for cultured cells, normal tissues, and tumors as a function of dose per fraction.

trial are better understood. The Hammersmith group established that fast neutron therapy is not harmful to the patient. Therapeutic studies at Hammersmith started in July 1971. For the most part, superficial tumors such as head and neck, oral cavity, etc., have been treated at Hammersmith. Hence, the limited penetration of the neutron beam is not a limitation. One hundred fifty patients have been treated there so far. They obtained an RBE of 2.9 for fast neutrons on human skin -- in agreement with previously measured RBE values using animals. Dr. Catterall reported that tumors treated so far with neutrons showed a variable response not qualitatively different from conventional therapy. There were no recurrences inside the treated field (see Catterall *et al.*[35]). Results of these treatments are very encouraging, but it is too soon to make a firm judgment because the observation period was two years or less.

Because of limited penetration of 7-MeV fast neutrons at the Hammersmith Hospital, there may be some limitations in treating other deep-seated tumors such as those in the abdomen, pelvis, etc. However, when high-energy neutrons are used in therapy, it may be possible to treat these deep-seated tumors. At present, there are plans to use high-energy neutrons generated by 40- to 50-MeV deuterons on beryllium at both the Texas A & M cyclotron and the cyclotron at the Naval Research Laboratory in Washington, D. C.

I would now like to say a word about neutron capture therapy and the use of californium implants, similar to radium implants, for therapeutic application. Neutron capture therapy was used for the treatment of brain tumors. The rationale for this therapy is that tumor tissue in the brain loses its capacity for rejecting foreign substances. Hence, when a compound containing elements having a high cross section for thermal neutrons such as ^{10}B is injected into patients, it will be concentrated in tumor tissue. When this patient is exposed to thermal neutrons from a reactor, the reaction products from the ^{10}B low-energy alpha particle and lithium recoil are generated in tumor cells. This principle, although very interesting, did not work too well because the ^{10}B compound was also found in fine blood capillaries and caused severe damage there. This treatment was tried in the late 1950's