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THE NEW PARTICLES AND THEIR APPLICATION IN MEDICINE

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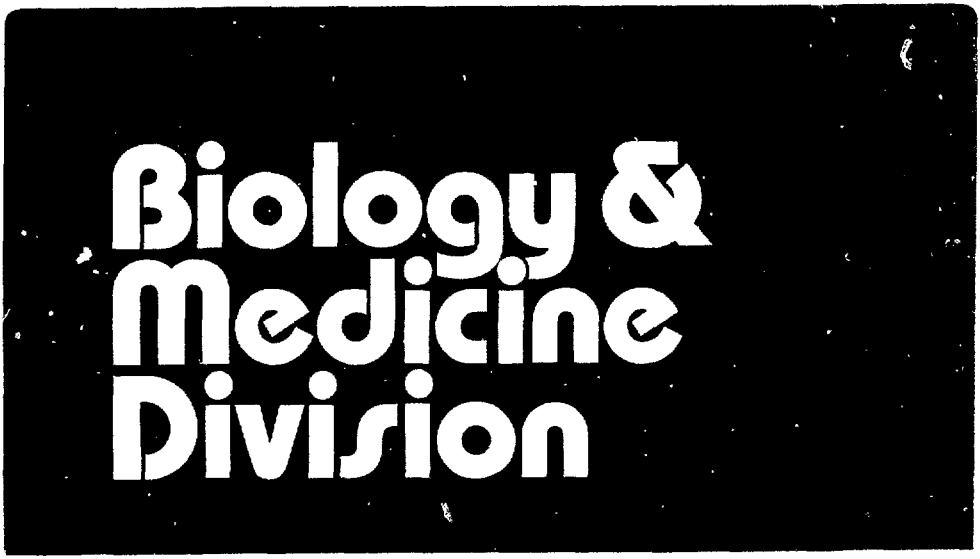

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THE NEW PARTICLES AND THEIR APPLICATION IN MEDICINE

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INTRODUCTION

In recent years there has been increasing interest in the use of "new" particle beams for various medical applications. The particles being used, fast neutrons, protons, helium ions, negative pions, and heavy ions, have in fact been known and studied by nuclear and high-energy physicists for over forty years. They are new only in the sense that, until recently, the medical community has had little experience with them in the clinic. One of the particles, the neutron, is not really new even to radiotherapy. In the late thirties Stone et al. treated 226 patients using cyclotron-produced neutrons (1940), but they discontinued therapy five years later because of unexpected severe late reactions (Stone, 1948). It was not until the sixties that it became generally recognized that neutron irradiation is relatively more effective compared to x-rays at the lower doses per fraction used in therapy than at the higher single doses commonly used in animal and cell experiments. This difference in effectiveness becomes even more important at the lower doses encountered in radiation protection, and it is interesting that it played an inhibiting role in the early days of particle radiotherapy (Brennan and Phillips, 1971). This paper will review the applications of these "new" particles to clinical medicine, primarily in the areas of tumor radiotherapy and diagnostic radiography.

APPLICATIONS IN TUMOR RADIOTHERAPY

Physical Dose Distributions of Charged Particle Beams

A basic problem facing the radiotherapist is how to deliver a tumoricidal dose while limiting the damage to normal tissues so that the patient can recover and continue to live in relative comfort. Several ways are being employed to try to accomplish this. Among these are multiport and rotational therapy, combined chemo- and radiotherapy, and the simple and standard procedure of fractionating the total dose into small daily doses over perhaps a five or six week period. The latter procedure is advantageous presumably because the normal tissue can recover between doses to a greater extent than the tumor tissue, thus allowing a larger overall dose to be given to the tumor before net normal tissue damage becomes intolerable.

The ideal beam for radiotherapy would deposit the entire dose within the tumor volume and none to the normal tissue. No beam or particle type has been found that will do this, but charged particle beams approach this ideal much more closely than the standard beams used in the clinic today (e.g., ^{60}Co gamma rays, ortho- and megavoltage x rays, and megavoltage electrons). The reason for this is a direct result of the difference in the physical processes by which heavy charged particles slow down in matter as compared with those processes which slow down electrons and cause the absorption of electromagnetic radiation. For all charged particles heavier than electrons, the dominating energy-loss process is the ionization (and excitation) of the atoms of the medium into which the charged particles penetrate. The rate of energy loss by this process increases as the particles slow down. This causes an increase in energy deposition, hence absorbed dose, near the end of the particle's range. Examples of the dose vs. depth characteristics of helium, carbon, neon and argon ion beams are shown in Fig. 1 for two different ranges (Lyman and Howard, 1977). Note the sharp peak at a depth in water corresponding to the range of the particle. The small residual dose beyond the peaks of the carbon, neon, and argon beams is from the secondary fragments created by a small fraction of the primary particles undergoing nuclear interactions and fragmenting into lighter and thus more penetrating ions. Note also the flatness of dose in the so-called plateau or shallow region of the curve near the surface.

Because the peaks of these beams are so sharp and narrow, they are not useful for treating the extended and often irregular tumors encountered in the clinic. Thus, these unmodified beams are generally modified for clinical application by the introduction of a variable thickness absorber sometimes called a "ridge" filter to spread the peak region. These absorbers move

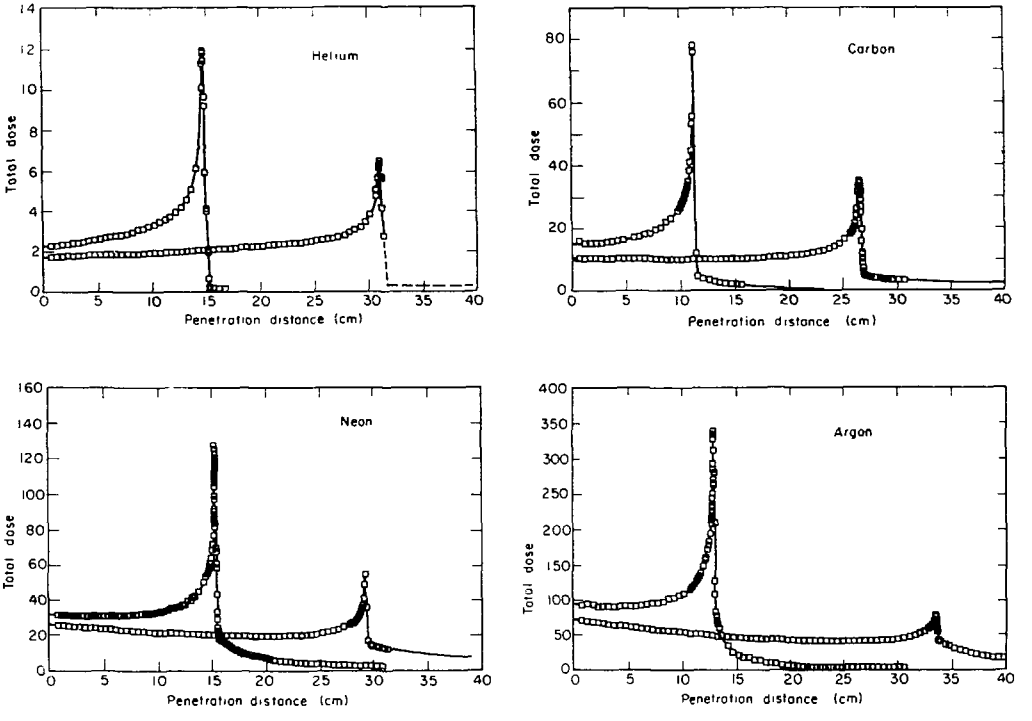

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Fig. 1. Depth vs. dose curves for helium, carbon, neon, and argon ion beams. Beams of two different ranges are shown in each panel. The energies of these beams are in the range of several hundred MeV/nucleon. Reprinted, by permission, from Lyman and Howard (1977).

in the beam to provide a varying thickness to any point as a function of time, thus effectively providing that point with doses from different positions in the dose vs. depth curve. The peak is thus spread through a broad region which is determined solely by the design of the filter. Figure 2 shows an example of a peak spread to 4 cm (Lyman and Howard, 1977). The peak-to-plateau dose ratio decreases from over 4:1 to less than 1.5:1. The subject of treatment planning with particle beams will be covered in another chapter. Figure 3 is a treatment plan for a pancreatic tumor designed with a carbon beam (a) compared to one designed with a Clinac 18 (b) (G. T. Y. Chen, private communication). The Clinac 18 plan is a four-port plan and is considered an optimum plan for this site using conventional beams. The carbon plan is a two-port plan using wedge compensation. It is clear that the spinal cord and right kidney (to the lower left

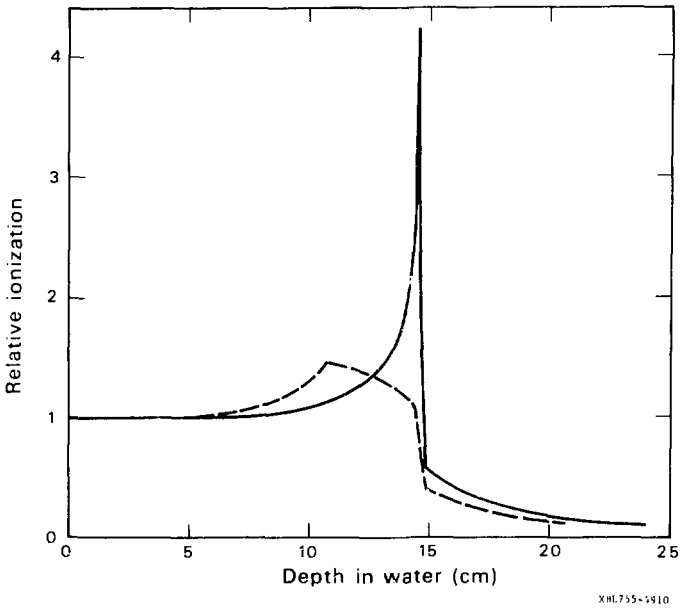

Fig. 2. The effect on the depth vs. dose curve of the introduction of a variable absorber or "ridge filter" into an unmodified beam. The sharp peak is broadened (in this case to 4 cm) and the peak-to-plateau dose ratio is significantly decreased. Reprinted, by permission, from Lyman and Howard (1977).

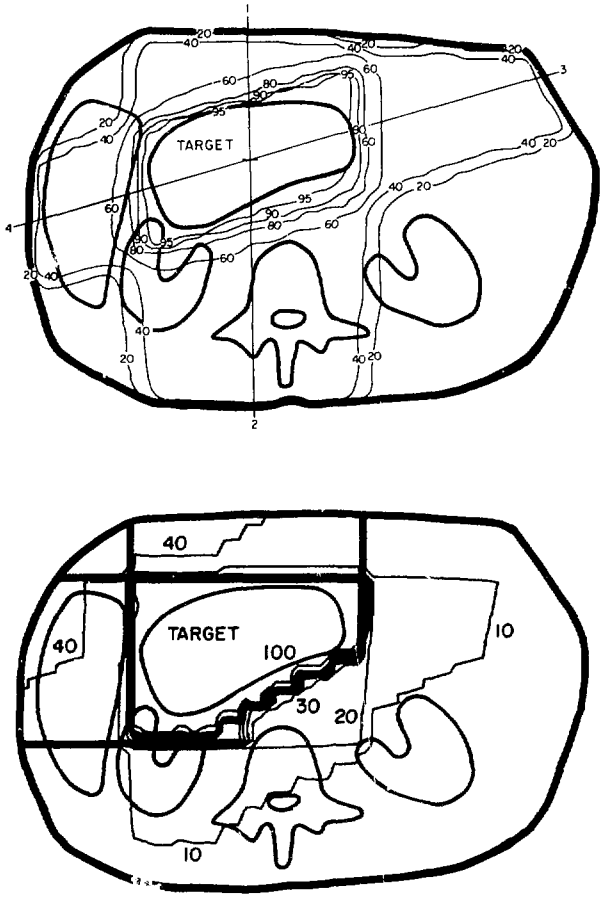

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Fig. 3. A comparison of treatment plans for a pancreatic tumor developed with photons from a Clinac 18 and with carbon ions. Inspection of the exposure levels outside the target volume shows that considerably less dose is deposited in the normal tissue for the carbon plan than for the photon plan. Reprinted by permission from G. T. Y. Chen.

of the target volume) receive considerably less dose in the carbon plan.

Heavy ions have been used as an example of charged particle beams in the above discussion, but the qualities of proton, helium-ion, and pion beams differ only slightly from heavy-ion beams. Proton and helium-ion beams have negligible secondary radiation, and potentially will provide the sharpest delineation of dose within a volume. Thus, inhomogeneities within the tissue itself become a major consideration when planning treatments, and will probably be the factor limiting the accuracy with which a given amount of radiation can be deposited within a specified target volume (Goitein, 1977).

The energy deposition from a negative pion beam is complicated by the inevitable nuclear interactions that the pions undergo as they are captured by the nuclei of the atoms in the region where they come to rest. Pion beams are secondary beams; that is, they must be created by the bombardment of a target material by a primary beam of other particles, such as protons or electrons. The pions are "radioactive" in the sense that they have a well-defined lifetime ($\tau = 2.6 \times 10^{-8}$ sec) and may decay into a muon and a neutrino. If they survive until they come to rest, negative pions will always be captured in a Bohr orbit, creating a pi-mesic atom. The total rest energy of the pion (140 MeV) is available to break apart the nucleus and give the various nuclear fragments kinetic energy. These fragments have a short range and the heavier ones, including alpha particles, have quite high rates of energy loss and contribute significantly to the absorbed dose. Negative pion beams are contaminated by muons, which result from the direct decay of the pions in flight, and electrons from gamma rays, which result mainly from neutral pion decay in the target. The various components in a negative pion beam are shown schematically in Fig. 4 (Curtis and Raju, 1968). The "star" contribution is caused by the nuclear disintegrations mentioned above. The peak in ionization is not as high as the heavy-ion peaks because typical momentum spreads for pion beams, including the one chosen for this calculation, are much larger than for the heavy-ion beams. Thus, in a sense, this pion beam is already slightly spread. Note the small muon peak beyond the pion peak. The electrons form a more or less uniform background. Design of the beam itself can alter the relative proportion of pions, muons and electrons.

A comparison of experimental data of the dose vs. depth curves for all the "new" particles is shown in Fig. 5 (Raju et al., 1978). All the curves were normalized to the center of the modified peak region. All charged particle beams were modified to give peak regions 10 cm in depth. The reason the carbon beam shows more dose beyond the peak region is because it

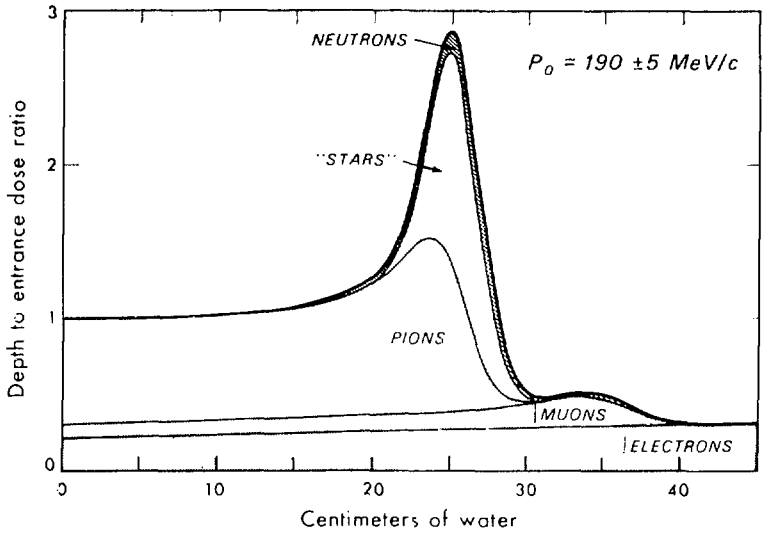

Fig. 4. A calculated depth vs dose curve for a negative pion beam showing representative values for the contributions to the total dose of pions, muons, electrons, and the "stars" or nuclear fragments from the capture interactions as the pions come to rest. Reprinted, by permission, from Curtis and Raju (1968).

was a higher energy beam (i.e., more penetrating) than the neon beam, and so more fragmentation occurred.

High LET, Relativistic Biological Effectiveness and the Oxygen Effect

The highly ionizing nature of the pion and heavier ion beams in the peak region produce not only an increased dose but also an enhanced biological effect. The quantity that is a measure of the average rate at which a particle loses energy is its dE/dx value or LET (linear energy transfer). In general, except for very high LET, biological effects increase with increasing LET.

It is important now to define another term, the relative biological effectiveness or RBE. It is used to compare the biological effectiveness of a given beam or radiation to that of

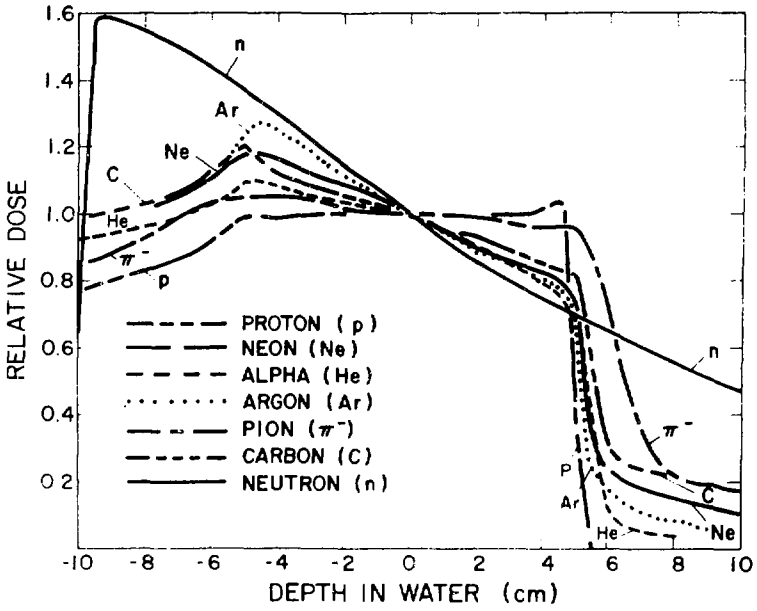

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Fig. 5. A comparison of experimentally obtained depth vs. dose curves for proton, neutron, pion, helium, carbon, neon, and argon beams, normalized to unity at the center of the spread peak dose region. Reprinted, by permission, from Raju et al. (1978).

a standard radiation, usually 250 kV x rays. It is the ratio of absorbed dose of the standard radiation to the absorbed dose of the radiation in question necessary to cause equal biological effect. That is,

$$RBE = \frac{Dose_{standard}}{Dose_{high\ LET}} ,$$

where both doses produce the same response. Thus, the RBE depends not only on the particle type and type of end point selected, but also on the magnitude of the effect selected.

A typical dependence of RBE on LET is shown in Fig. 6 (Hall, 1978). Here we see three regions: one where the ionizations are random at low LET, one where the RBE is maximum and the ionizations are optimal for the particular effect, and one at very high LET where the RBE decreases with LET, in the so-called saturation or overkill region.

Now we turn to another problem facing the radiotherapist, that of cells within tumors that do not respond well to conventional radiation. Hypoxic cells are more radioresistant than well-oxygenated cells (Barendsen et al., 1966), and some tumors contain pockets or regions away from blood vessels where there are hypoxic cells. It has been conjectured that it is the surviving hypoxic cells that in some cases cause the failure of local tumor control (Gray, 1961). The sizes of tumors that have a 90 percent chance of cure if given a dose of ^{60}Co gamma rays are shown in Fig. 7 for three different fractions of hypoxic cells, 0, 0.1 and 1.0 (Fowler et al., 1963). Clearly, a considerably larger dose is necessary to "cure" a tumor with hypoxic cells than one of the same size with no hypoxic cells.

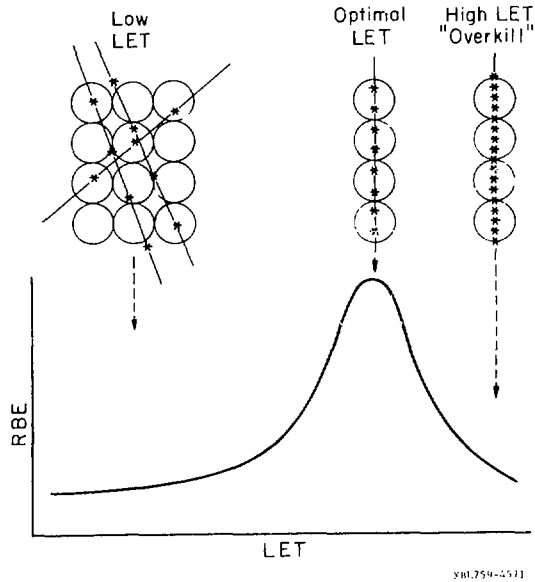

Fig. 6. A typical dependence of RBE on LET: an initial increase is followed by a maximum and then a decrease at even higher LET. Reprinted, by permission, from Hall (1978).

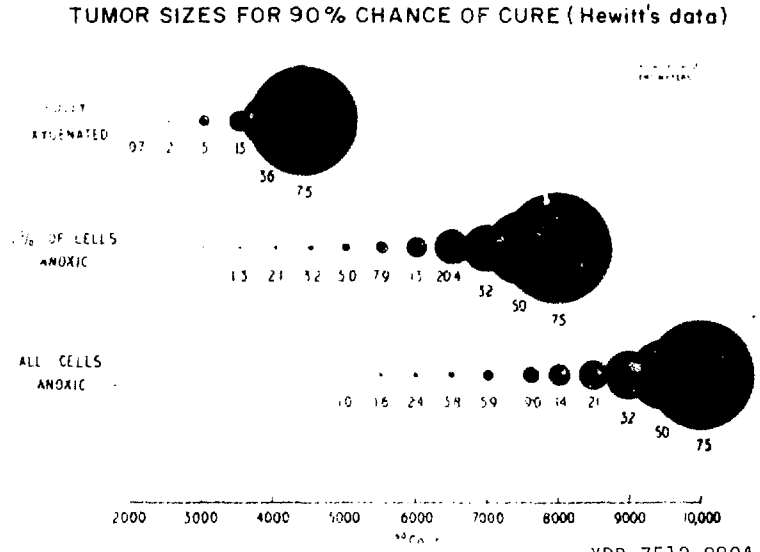

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Fig. 7. Calculated doses required to reduce the number of cells surviving in each tumor volume to 0.1, to give a 90 percent chance of "cure." Upper row of tumors with cells fully oxygenated, middle row with 1 percent hypoxic cells, and the bottom row with all cells hypoxic. Reprinted, by permission, from Fowler et al., (1963).

Since high LET particles have an increased capacity to kill cells, independent of their oxygen status (Barendsen et al., 1966), high LET beams of neutrons (Fowler, 1967; Fowler et al., 1963) pions (Fowler, 1965; Richman et al., 1966), or heavy ions (Lawrence and Tobias, 1967; Tobias and Todd, 1967) have been suggested to treat tumors with large fractions of hypoxic cells. Unfortunately, the hypoxic fraction of cells in human tumors cannot be accurately determined at present.

Experimental data, however, have been accumulating on animal tumors. Some of the more recent data will be reviewed in later lectures. Barendsen and Broerse (1969) performed a classic experiment with a rhabdomyosarcoma in a rat. They found evidence of the presence of hypoxic cells in the tumor, and then studied the extent to which a 14 MeV neutron beam could cut down the oxygen effect. The results are shown in Fig. 8. The survival of cells after irradiation in situ and subsequent cell dispersion,

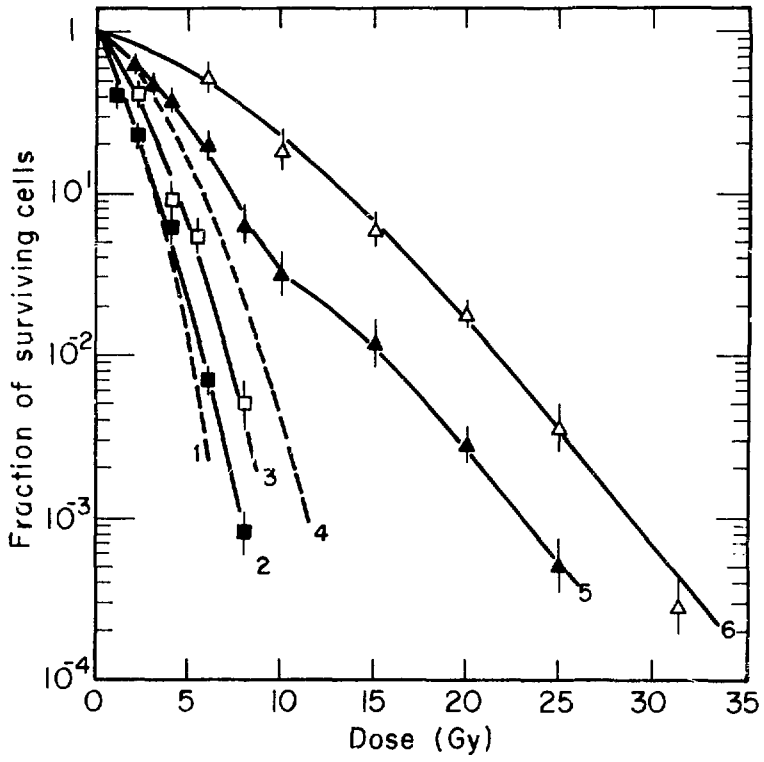

Fig. 8. Survival of R-1 rhabdomyosarcoma tumor cells irradiated in rats with neutrons (curves 1, 2, 3) and x-rays (curves 4, 5, 6). The dashed lines, curves 1 and 4, show results of cells irradiated in vitro. Curves 2 and 5 show results of tumors irradiated in vivo with subsequent excision, cell dispersion, and plating, and curves 3 and 6 show results obtained for hypoxic populations. The break in curve 5 at about 10 gray is evidence of an hypoxic fraction of about 15 percent. Reprinted, by permission, from Barendsen and Broerse (1969).

trypsinization and plating is shown for x-irradiated tumors in both air-breathing (curve 5) and asphyxiated animals (curve 6). The latter curve is representative of an hypoxic cell

population. Note the distinct break in curve 5, clearly indicating the existance of two populations of cells with different radio-sensitivities. Curves 2 and 3 are for neutron irradiated tumors. Their position on the graph shows not only a rather large RBE (~3.0) for this end point relative to 300 keV x rays, but also a significant decrease in the oxygen effect for the neutron beam.

A quantity used to measure the extent to which the oxygen effect is decreased is the oxygen enhancement ratio or OER. This is defined as the ratio of absorbed dose necessary to produce a given effect in hypoxic cells to that necessary to produce the same effect in oxygenated cells. Thus, the OER is large (i.e., between 2.5 and 3.0) for x rays and decreases with increasing LET, becoming close to one for high LET radiations (Barendsen et al., 1966).

Another quantity used to evaluate the relative radio-resistance of hypoxic cells is the oxygen gain factor or OGF, which is defined as the ratio $OER_{x\ ray}/OER_{high\ LET}$. It is a convenient quantity for comparing results from different cell lines and in different laboratories and beams. Large OGF values denote a large reduction of the oxygen effect. A comparison of OGFs for the "new" particles is shown in Fig. 9 (Raju, 1979).

EVALUATING THE PARTICLES FOR THERAPY

This is a very difficult subject because criteria for evaluating beams vary widely. Two separate evaluations of the particles will be presented here. The first, Fig. 10, plots the "physical" or dose vs. depth advantage along the ordinate and the "biological" or possible low OER advantage along the abscissa (Raju, 1978). The various particle beams are placed rather subjectively in positions relative to each other. The number of dollar signs is a rough estimation of the cost involved in implementing any of the modalities for patient treatment. The second evaluation, Fig. 11, presents the relative biologically effective dose between peak and plateau vs. OER (C. A. Tobias, private communication). Here large values of the abscissa and small values of the ordinate are advantageous. It appears that heavy ions compare quite favorably with the other modalities.

APPLICATION TO DIAGNOSTIC RADIOLOGY

Charged particle beams are being used to image structures in the body that are difficult to image with more conventional techniques. The sharp, well-defined range of charged particle beams suggested that they might be used to image structures with slightly different densities within the body. As we have seen, the energy deposited by these beams is maximum in the stopping

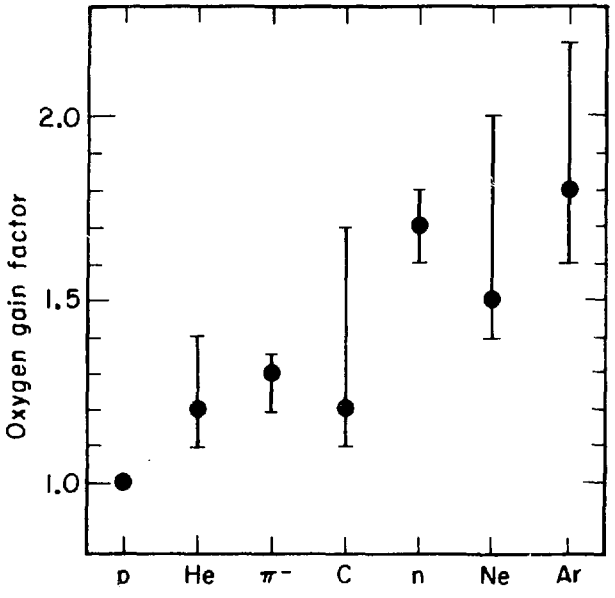

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Fig. 9. A comparison of oxygen gain factors experimentally determined for the various particles throughout the peak region. The spread of values reflect the fact that beam quality (and therefore the effect of oxygen on cell survival) varies throughout the spread region. Reprinted, by permission, from M. R. Raju (1979).

region. Imaging with proton beams has been accomplished and shows promise for diagnosing tumors of the breast and brain (Steward and Koehler, 1973, 1974). Helium ions have also been used to obtain axial tomographs of the human brain (Crowe et al., 1975). The heavier ions are being used to image the breast, abdominal region, and extremities (Sommer et al., 1978). The stopping points of heavy ions such as carbon and neon ions can be accurately recorded on stacks of plastic sheets placed behind the specimen, because the high LET nature of the particles renders the plastic preferentially etchable near the positions where the

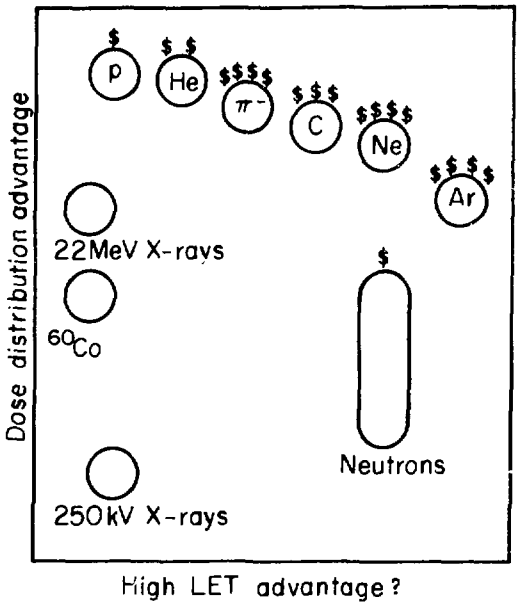

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Fig. 10. An attempt to compare the therapeutic advantages of the various particles. The advantage due to a favorable dose distribution is plotted against a possible advantage due to an increased LET (e.g., high RBE and low OER). Particles in the upper right, are assumed to be the most advantageous for therapy. The number of dollar signs give a rough indication of the relative expense of implementing the various modalities in the hospital environment. Reprinted, by permission, from M. R. Raju (1978).

particles come to rest. The large mass of the ions keeps scattering and straggling very low. Thus, the position of the plastic sheet in which the particle stops is a sensitive measure

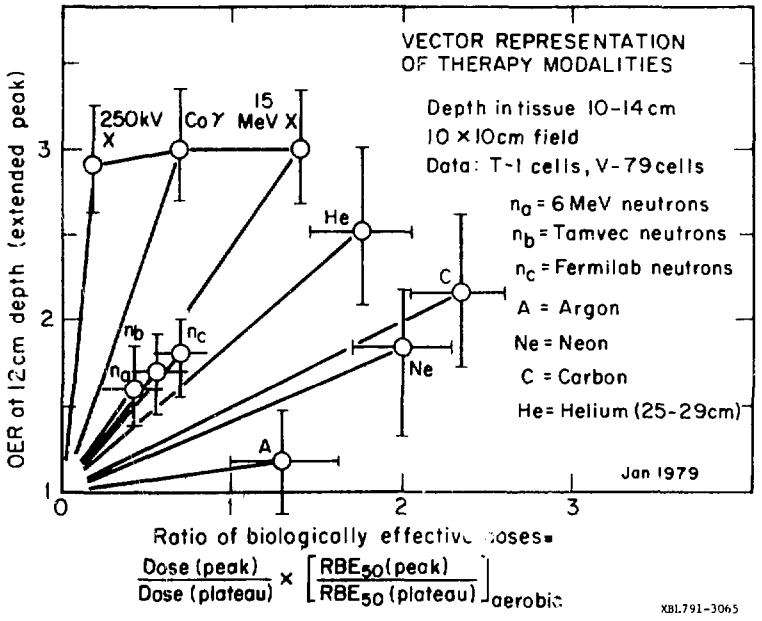

Fig. 11. Another attempt to graph the relative merits of the various particles. Here the OER is plotted against the ratio of "biologically effective" dose at the peak to that at the plateau. Here the more therapentically advantageous particles lie in the lower right-hand region of the figure. Reprinted, by permission, from C. A. Tobias.

of the range, and therefore the average density through which the particle passed. If an object of slightly higher density is traversed, the particles will stop in a different plastic sheet, as shown in Fig. 12. Thus, two images of the object will be seen on different sheets, one the negative of the other. Figure 13 compares an x-ray of a human foot and a computer reconstructed neon-ion radiograph of that foot made from a composite of all the exposed plastic sheets. Considerably more soft tissue detail is seen in the radiograph, including such structures as the Achilles tendon. The dose to the patient from the neon ions was estimated to be between 100 and 200 millirad.

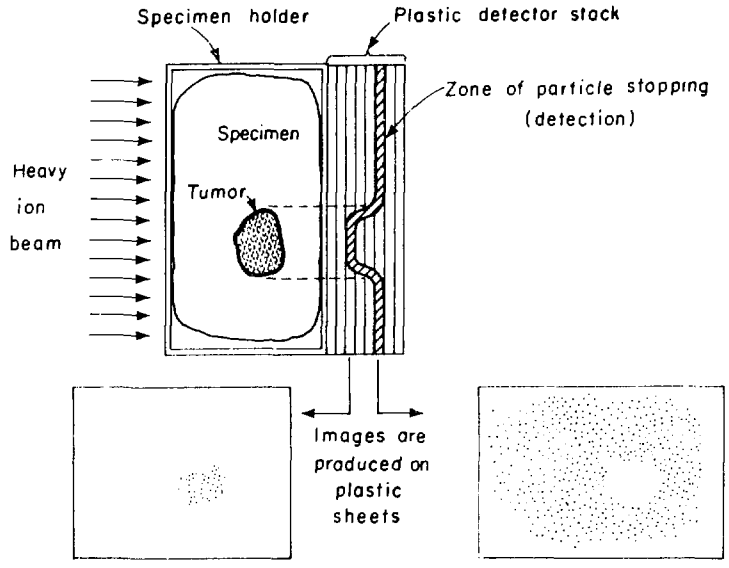

Fig. 12. The concept of heavy-ion radiography. Heavy particles penetrating a region of higher density will stop in different plastic detector sheets than the particles on either side. The plastic sheets in which the particles stop show etchable tracks. Reprinted, by permission, from Sommer et al. (1978).

APPLICATION TO NUCLEAR MEDICINE

All the new particle beams can be used to make radioisotopes, which can then be used in most of the standard techniques of nuclear medicine. However, there is another potential use of at least the heavy ion beams. A portion of the heavy-ion beam particles undergo nuclear fragmentation, and some of these high energy fragments are radioactive, for instance, ^{11}C or ^{19}Ne. These fragments can be focussed into a second beam and allowed to penetrate the body, coming to rest, for example, inside a blood vessel. The subsequent positron decay produces annihilation gamma radiation that can be detected in an appropriately designed counter array. The rate of decay of radioactivity after the beam has been turned off measures not only the usual decay of the isotope but also the flow rate of the blood carrying the isotope

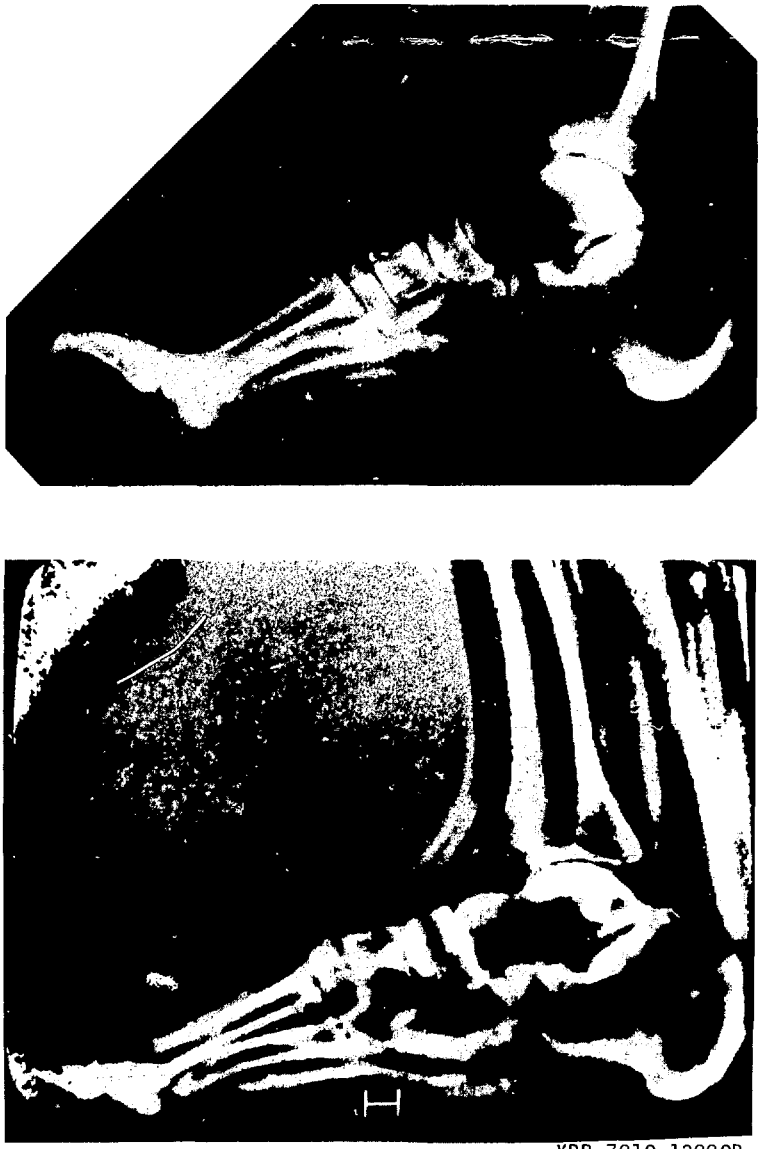

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Fig. 13. A comparison of a conventional x-ray and a computer reconstructed heavy-ion radiograph of a human foot. Soft tissue details are more evident in the heavy ion radiograph than in the x ray. Reprinted by permission from C. A. Tobias.

away from the stopping site. Studies of such noninvasive techniques for measuring blood flow are presently underway (Chatterjee and Tobias, 1977).

CURRENT MEDICALLY ORIENTED PROJECTS INVOLVING PARTICLE BEAMS

The new particles are presently being used in the therapeutic and diagnostic applications discussed above. Neutron therapy machines can be found in nine different countries: Belgium, East Germany, England, Japan, The Netherlands, Poland, Scotland, the United States and West Germany; several of these countries have both cyclotrons and d-t generators. Clinical trials are underway with varying degress of success (Dutreix and Tubiana, 1979). The most encouraging results have been with tumors of the head and neck, salivary glands, cervical lymph nodes, and soft tissue sarcomas (Catterall, 1979). Good results have been obtained treating gynecologic tumors with mixed high and low LET beams (two fractions of neutrons and three fractions of high energy x rays per week) (Peters et al., 1979). The results on brain tumors, on the other hand, have been rather discouraging.

Proton beams are being used in Sweden, the United States, and the Soviet Union. In the United States, patients are given boost therapy (i.e., proton irradiation in addition to conventional therapy) for prostatic carcinoma and other sites where dose localization is important. Proton beams are also being used to treat patients with chorodial melanoma (Gragoudas, 1978), and the results are quite encouraging.

A randomized trial of carcinoma of the pancreas is underway with a helium ion beam in the United States (Castro, 1979). This was initiated after an earlier pilot group of 41 patients showed an encouraging response. Of 34 evaluable patients, 10 either are now without cancer or at least showed local control of the tumor.

Pion programs are underway in three countries: Canada, Switzerland, and the United States. A clinical program is in progress in the United States (Kligerman, 1979) and will be started in the other two countries in the near future. The results so far are encouraging.

Initial patient studies are in progress using carbon, neon, and argon beams in the United States (Castro, 1979), but it is too early to assess the efficacy of these beams.

Proton, carbon, and neon beams are being used for radiography. Results have indicated that there are definite details on

the particle radiographs that cannot be seen on the best CT scans or xerographs. There have been at least two cases where a malignant region in a breast was identified on a particle radiograph and not seen by conventional means (C. A. Tobias, private communication).

CONCLUDING REMARKS

In conclusion, we see that the age of new particles in clinical medicine has arrived. There is tremendous activity within these programs all over the world. Much of the progress in tumor localization, dose delivery, computerization of treatment planning, and patient immobilization has been to a considerable extent motivated by an attempt to solve the many problems involved in particle therapy.

Finally, along with the potential these high LET radiation modalities hold for increased tumor cure rates and decreased failures in local tumor control, there are also the responsibilities of protecting the patient and personnel from the increased biological effect of any residual high LET radiation. It is then with the excitement of knowing that we are reviewing here a rapidly growing field important to radiation protection, tumor diagnosis, and therapy that I open the discussion of these subjects, and hope the papers to be presented here will stimulate further interest in the field.

ACKNOWLEDGEMENTS

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