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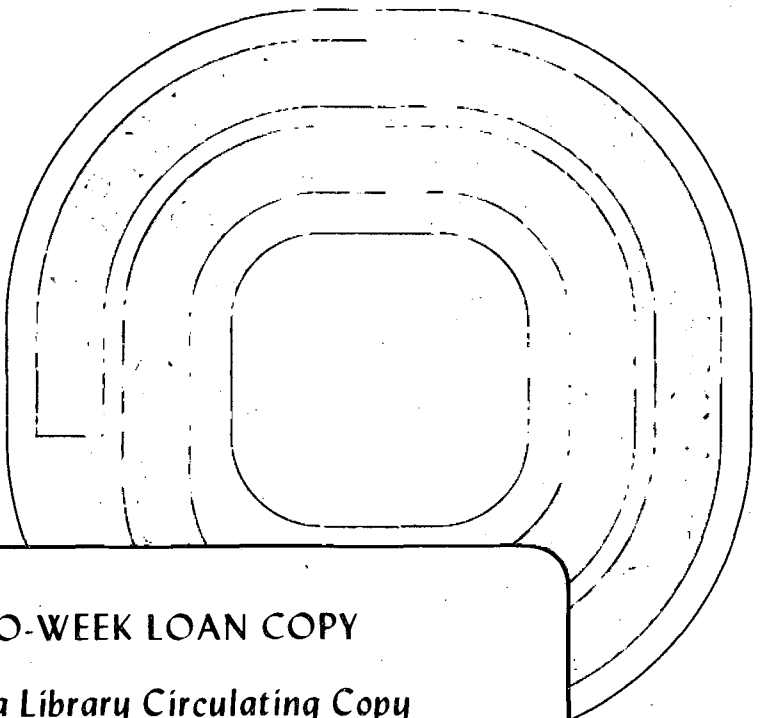

DISCLAIMER

SOME CONSIDERATIONS OF PHYSICAL AND BIOLOGICAL FACTORS IN RADIOTHERAPY WITH HIGH-LET RADIATIONS INCLUDING HEAVY PARTICLES, PI MESONS, AND FAST NEUTRONS

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During recent years a variety of high-LET radiations from accelerators have become available for radiotherapeutic investigations or for radiobiological studies that may lead to full-scale radiotherapy. These include protons and heavier accelerated particles (1-10), Pi mesons (11-14), and fast neutrons from accelerators (15) -- the latter having already been tried thirty years ago (16,17). In addition, fast neutrons produced from the transuranium isotope, Californium-252, have been suggested for use in interstitial therapy (18,19).

There are important radiobiological and physical factors that favor consideration of high-LET radiations for therapy. Factors that are often mentioned include a much-improved distribution of linear energy transfer (LET) and depth-dose, and thereby a greater efficiency in delivering a tumoricidal dose to the chosen treatment volume; a reduction in the protection afforded anoxic cells; a more equal probability of cell-killing by the radiation regardless of the state of cell division; and a greater proportion of irreversible damage (less repair). In spite of acknowledged advantages, however, decisions to use some high-LET radiations in radiotherapy may be difficult to make; the machines required are expensive, the time used is costly, and a number of years of intensive study with patients is required before significant results are available for judging the efficacy of a given particle in therapy. But the promise of heavy particles as effective therapeutic agents demands that their properties be further investigated. In this chapter we shall attempt to evaluate some of the properties of these various radiations.

Radiation therapy for tumors is usually applied because it is known that by judicious use of radiation it is sometimes possible to cause regression of tumors permanently, or for an extended period of time, without undue injury to normal tissues. There are many parameters that must be taken into account when radiation therapy is applied. Some of these have nothing to do with radiation per se, but are by

necessity true for all forms of radiation therapy. One such important requirement prior to administering therapy is a knowledge of the exact location of tumor cells in the patient's body. Much progress has been made in the field of tumor localization, particularly with the sophisticated use of radioisotopes and γ-ray scintillation cameras or other imaging devices. However, when metastatic cells are present the accuracy and efficiency of diagnostic studies remain uncertain, at best, because there is always the possibility that a few undetected cells have migrated to various parts of the body where they can start metastatic tumor proliferation. Therefore, when radiation therapy fails, the blame should not necessarily be ascribed to the particular form of radiation used. It should be recognized that such failure may be caused by our inability to determine adequately the extent and distribution of tumor tissue. For this important reason, diagnostic procedures need much further development. Gamma-ray cameras, new radioactive compounds localizing in tumors, and other diagnostic developments utilizing radioisotopes hold much promise in this area, and it is possible that x-ray roentgenographic techniques will also be further developed.

Another difficulty arises from the fact that frequently the patient becomes a candidate for radiation therapy when his disease is already in an advanced stage -- when the tumor mass has already become very large or when it has invaded critical regions of the body. Consequently, treatment has to be carried out under less-than-optimal conditions, and it is then exceedingly difficult to compare the results obtained using different radiations.

Advances in cellular radiobiology have allowed quantitative estimation of radiation effects, and certain comparisons in this chapter will be made on a cellular basis. However, there is much evidence to suggest that the answer to the question of tumor radiosensitivity is far more complex

than just an understanding of the sensitivity of the individual tumor cell; the interaction between neighboring cells is important, and the host resistance to tumor cells is also a factor that can change with radiation.

DEPTH-DOSE DISTRIBUTION

The radiations discussed clearly fall in two classes; those with exponential absorption curves in tissue, and those with ionization peaks (Bragg peaks). X rays, gamma rays, and fast neutrons have exponential absorption curves, except for a small transition region in each near the radiation beam's entrance into the body.

Gamma Rays and Neutrons

Typical absorption curves for Co^{60} gamma rays, 15-MeV neutrons, Pi mesons, and some charged particles as they might be used for therapy are shown in Figure 1 (20, 21). Fission neutrons and 3-MeV neutrons are not shown; these radiations are so rapidly absorbed by tissue that their use in the form of external beams for treating deep-lying tumors is relatively impractical* 15-MeV neutrons, usually produced by the (d,T) reaction in linear accelerators operating at 0.6 MeV, have comparable depth absorption curves to Co^{60} gamma rays, but protect the skin less effectively. Neither type of radiation has a low "exit dose", and thus all tissue structures in the path of the beam are exposed; gamma rays are absorbed somewhat more in bone than in soft tissue, whereas fast neutrons are absorbed somewhat less. From the point of view of depth dose, therefore, one would choose more penetrating neutrons in the range of 15- to 20-MeV mean energy. However, up to the time of writing this review, no (d,T) generators have been built that can produce the desired minimal intensity of 10^{13} neutrons/cm^2 sec at the target, an intensity which would result in acceptable dose rates for patients of 10 rad/minute or more. The reason for this is that the customarily used tritiated ice targets in the accelerators melt, because they cannot be satisfactorily cooled at the high

* Exceptions are possibly the treatment of superficial tumors and the interstitial use of the isotope ^{252}Cf.

deuteron beam intensities required. A solution may be found in the future by the use of tritiated metal targets. Cyclotrons for 30-MeV deuterons can produce the minimal beam intensities needed; however, they are considerably more costly for this purpose than 15-MeV neutron generators. Neutron beams from cyclotrons have relatively more undesirable gamma rays and low-energy neutrons than those from monoenergetic sources.

For localized radiotherapy, collimation of the treatment beam is essential. Gamma rays are collimated by the use of heavy metal apertures; since photons of degraded energy scatter from the walls of the collimator and since atoms of the tissue scatter also, sharply delineated beams cannot be maintained at deep treatment depths, and at a tissue depth of 15 cm. the smallest irradiation region has a diameter of approximately 3 cm. The small focal spot of the high-energy x rays produced by electron linear accelerators allows treatment of even smaller regions. Probably one of the best collimated gamma-ray sources for local therapy was constructed recently by Larsson (22).

There are a considerable number of problems encountered with collimation of fast neutrons. They lose energy by a succession of elastic and inelastic collisions with the nuclei of the absorber. Neutrons with lower and, eventually, thermal energies result, and secondary gamma rays are produced. A carbon matrix is good for neutron collimation, with added gamma ray absorbers made of materials that do not produce copious additional gamma rays (e.g., bismuth or tungsten). Finally, the thermal neutrons must be absorbed (usually by boron). Good collimation sometimes necessitates more than one set of collimators, and an increased distance between target and patient; this in turn results in reduced dose rate from the same beam. The practical limits are similar to those for gamma rays.

Protons and Heavier Ions

Protons, accelerated helium ions, and heavier ions have Bragg ionization properties. The energy transfer of these particles gradually increases as they slow down in tissue, and comes to a peak before the particles stop. These properties for single particles and for beams of particles have been recently investigated and reviewed in detail for the 910-MeV-He^4 ions now in use at Berkeley (23,24,25,19,20) and for protons used at Upsala (26,27). Figure 2 shows the Bragg curves for monoenergetic helium and neon ions of about 12 cm. penetration in tissue. The data in Figure 1 were calculated from such curves, assuming the use of ridge filters for heterogeneous energies to fit a desired profile. Figure 2 also shows the contributions of secondary particles which result from nuclear interactions of the primary particles with nuclei of the atoms in tissue.

The skin received less than thirty percent of the peak dose. By choosing an appropriate lower particle energy, or interposing absorbers in a high-energy monoenergetic beam, the Bragg peak can be placed at any lesser depth. The exit dose is very small; for helium beams it is less than two percent of the peak dose, and it is due to neutrons and gamma rays.

We shall show later that by judicious mix of heavy-particle energies by absorbers, the depth-dose curve of heavy particles can be altered to extend the domain of peak dose (1.0 in Fig. 1) to any desired width. We shall also see that the depth-dose distribution from accelerated particles of higher atomic number is quite similar to that of helium ions, except that the LET of heavier ions is greater in proportion to the square of their atomic number (Z^2 at the same velocity). As is shown below, we believe this is a desirable property for tumor therapy, and we estimate that the optimum particle for deep therapy may have an atomic number between 6 and 25.

Heavier particles have narrower Bragg peaks, enabling one to make narrower deep lesions; they scatter less, thereby providing the ability of having a nuclear interaction, and therefore of producing more secondaries, approximately in proportion to $Z^{2/3}$ at the same velocity. However, the exit dose usually remains low, up to Z = 25, the latter being a function of atomic number and depth of penetration (28).

Protons and/or helium ions are available with the required energy for therapy at several laboratories at present (e.g., University of Uppsala; Harvard University; Liverpool; Pittsburg; Langley Laboratories, Virginia; Dubna, USSR; and Lawrence Radiation Laboratory, Berkeley). The beams can be collimated and focused, and they may be piped in vacuum to considerable distances away from the accelerator without appreciable loss. The dose rates can be adjusted at will, from 20,000 rad/min, down. Cyclotrons are somewhat limited in furnishing one or two discrete particle energies only. In the future, synchrotrons or linear accelerators capable of accelerating particles with any atomic number will be constructed which will be suitable for deflecting monoenergetic heavy ions at variable energies and, if desired, with even greater intensities than at present.

Pi Mesons

The depth-dose curve from a monoenergetic Pi meson beam is characterized by a Bragg peak due to ionization by the mesons, augmented by ionization by nuclear secondaries from the capture of the negative Pions by nuclei of tissue. A typical experimental curve from Raju and co-workers (29) is given in Figure 3, showing the contribution from the mesons and the nuclear stars separately. This has a typical shape of a Bragg curve. The width of the Bragg peak for monoenergetic mesons is about twice that of a proton Bragg peak for comparable tissue penetration, because of the fact that Pi particles straggle more. They also scatter more than heavy

particles; scattering coefficients vary approximately as the inverse square root of the mass, so that Pions scatter about three times as much as protons, and twelve times as much as oxygen^{16} nuclei.

Pi meson beams are somewhat contaminated by Mu mesons, electrons, and energetic gamma rays. A great part of the energy released in the capture reaction of mesons goes into fast neutrons. Methods have been proposed to eliminate electron contamination, but this has not yet been carried out successfully.

Since Pi mesons are unstable and decay with a half life of 0.5×10^{-8} sec in the laboratory frame, they must be utilized close to the target. Pi mesons that decay to Mu mesons and electrons decrease the depth dose and modify the LET qualities of the beam. Figure 4 shows the percent of particles that survive a 10-meter flight path without decay. This curve would indicate that for therapy, it is more advantageous to use higher energy mesons. However, at high energy the beam ionization peak becomes lower and broader because of the straggling and scattering of the particles. There is a spatial limitation on collimation of the beam and shielding from the secondaries of the primary proton beam. Since the primary beams are very intense, this requirement poses an expensive shielding problem if Pi mesons are to be used.

METHODS FOR DELIVERING OPTIMAL DOSE DISTRIBUTIONS FOR CANCER THERAPY

It is usually desirable to deliver a dose adequate to inhibit tumor cells in every region where the presence of such cells is suspected. At the same time, it is also important to minimize the integral (e.g., gram-Roentgen) dose to the patient, not only to avoid unpleasant after effects of radiation therapy, but also to enhance the recovery of normal tissues and immunological reactions of normal host cells to tumor cells. Using gamma rays or neutrons, relatively large exposure fields must be chosen, and the internal dose

distributions are controlled by choice of multiple ports or rotation.

Charged, heavy-particle beams scatter much less than the other radiations. Radiosensitive tissues, such as the colon, can be avoided completely. The small exit dose allows protection of bone and of other sensitive tissues, while significant tumor doses are given a few mm away. The protection of skin is a natural consequence of the Bragg peak characteristic. The depth-dose curves can be additionally shaped by choosing appropriate energy distributions for the particles.

In order to illustrate the advantage of the depth-dose distribution of heavy charged-particle beams, we have calculated several dose profiles using a phantom, in each case assuming a situation in which we wished to irradiate an 8-cm. diameter "tumor" volume placed at the center of a 20 x 30 cm. oval. Figure 5a shows a series of isodose curves for irradiation with ^{60}Co-gamma rays, utilizing a 10 x 10 cm. field, 75 cm. SAD, and a 360° rotation. These isodose curves are representative of the distributions that might be obtained by using radiations having exponentially decreasing doses (14 MeV neutrons, ^{60}Co-gamma rays or supervoltage x rays). As representative of the radiations with Bragg peaks, we have chosen a ^{4}He beam (alpha particles); Figures 5b and 5c show isodose curves obtained with a 360° rotation, utilizing ridge filter modified beams (30). In 5b, the resultant beam was shaped to have a broadened 100% dose region from 6 to 19 cm. from the body surface, and 93% dose at the surface; with such a beam during the 360° rotation, the tumor volume is always contained within the 100% dose region, and no range adjustment is needed as a function of rotation angle. If more detailed information is available concerning the stopping power of intervening tissue and the variable depth of the tumor from the body surface, then the range of particles may be more precisely adjusted and the dose delivered outside the tumor region can be further reduced; Figure 5c shows the improved isodose curves obtained with a ^{4}He beam shaped to have an

8-cm. 100% dose region (from 6 to 14 cm. from the body surface), and with the use of a tumor-contour ridge filter the dose delivered outside the tumor area has been minimized. The calculations were performed with special programs (IONPI and DOSEM) on a CDC 6600 computer. Bragg curve calculations were based on appropriate programs prepared by Steward (24) and Litton (25). In these calculations, secondary radiations were neglected for helium; however, we know that these would modify the results by a factor of less than ten percent.

FUNDAMENTAL ASPECTS OF THE "OXYGEN EFFECT" IN CELLULAR RADIOBIOLOGY

The first observation of the oxygen effect is probably that reported by Holthusen (31) who observed a distinct and substantial difference between survival curves of microorganisms exposed to x rays in anaerobic and in aerobic environments. In 1942 Antoine Lacassagne (32) carried out his brilliant experiments on new-born rats, and found that the radiation dose for lethal effect in animals kept immediately after birth in an anaerobic carbon dioxide atmosphere was twice that required by new-born mice kept in air. Early demonstrations by Fricke (33) on the role of free radicals in radiolysis of water, by Barron (34) of the chemical modifications in molecular effects of radiation by reducing and oxydizing substances, and by Patt (35) and Treadwell, Gardner, and Lawrence (36) of chemical radioprotection, have focused attention on the role of oxygen in the "immediate" radiation effect; that is, on the effect of oxygen present in the tissues at the time of irradiation. Consideration of the immediate oxygen concentration effect led L. H. Gray (37) and his school to studies of tissue oxygen concentration, and Churchill-Davidson and others to the use of hyperbaric oxygen in experimental radiation therapy.

Actually, oxygen appears to be involved in radiobiological mechanisms in very complex ways, and therefore in

order to study the oxygen modification of radiation sensitivity, a host of factors must be considered. These include both the immediate and delayed effects, the effects on cells in various physiological states when exposed to radiation, the modifications of low-LET and high-LET radiation injuries, and the modifications in cellular repair mechanisms.

Working with spores of B. Megaterium (organisms which can be exposed to radiation when dry or when in the presence of controlled amounts of moisture), and studying survival under different oxygen situations, Powers (39) demonstrated three kinds of radiation lesions: (I) lesions requiring the presence of oxygen during the radiation exposure period; (II) lesions requiring oxygen during the post-irradiation period; and (III) lesions independent of the presence of oxygen. It was noted that type II lesions can rarely be studied in mammalian cells, although they are probably present. These lesions apparently represent molecular excited stages produced by radiation that can be modified by oxygen or appealed by heat and by reducing substances. When water is admitted to the system, these lesions become fixed.

It was shown that with low-LET radiations (e.g., x rays) types I and II lesions are predominant in causing lethal effects, whereas with high-LET radiations, type III lesions are most important (40). Stated in summary form, for B. Megaterium the oxygen effect with low-LET radiations is marked, the oxygen enhancement ratio (OER*) being 2 to 3, whereas with high-LET radiations (above 100 KeV/micron) the OER is less than 1.10.

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* OER (oxygen enhancement ratio) is often cited as a measure of the effectiveness of oxygen to reduce the dose necessary for the production of a given effect. OER = Dose (anaerobic)/Dose (in presence of oxygen). Strictly speaking, this factor should be used only if one deals with true "dose reduction", usually when survival functions are exponentially decaying functions of dose. In other cases the OER is dependent on survival level.

Many studies are available on the oxygen effect (41) at the cellular level with mixed radiations (37) and, with relatively homogenous beams using the track segment method (42, 43).

The lesions dependent on immediate oxygen effects may relate to the consequences of the action of single ion pairs, and to the free radicals that are formed as consequences of ionization of the water molecule. The radicals OH and, in the presence of oxygen, O_2H; may be responsible for much of the radiobiological action in aqueous systems by interacting with important macromolecules.

The result, at the molecular level, is most often oxydation reduction, interruption of chemical bond, or cross linking. From studies of phage DNA we know that a predominant, oxygen dependent form of damage to the genetic material is scission of one strand of the double strand molecule. Another likely result of the action of a single ion pair can be alteration of one of the purine or pyrimidine bases in the molecule (44). When oxygen is not present, as in anoxic tumor cells, we assume that fewer such molecular lesions are produced by low-LET radiation.

It has been clearly demonstrated, in various types of biological materials, that single chain breaks can be repaired during the post irradiation period by an enzymatic process that involves synthesis of new DNA (45). In some organisms, this process is known to require the presence of oxygen (46). Recently a repair process was indirectly demonstrated in mammalian cells by Painter (47,48) who has shown that following ultraviolet or low-LET radiation "unscheduled" synthesis of new DNA can be demonstrated by the use of labeled thymidine.

It has been repeatedly demonstrated that high-LET radiation can produce lethal lesions in cells in a manner independent of the presence of oxygen or of other chemical radiation modifiers (49,50,42). The action of high-LET particles on phage DNA is often scission of both phosphate chains, causing

severance of the molecule in two parts (51,52). The production of double chain scission in DNA by single high-LET particles may explain their high biological effectiveness and the reason for low OER in heavy-particle lesions. So far no clear cut repair processes have been found for double strand scission, and heavy-particle lesions are regarded as irreversible in their consequences. Several experiments exist, however, that point to the possibility of such repair (46,53).

Radiation effects often express themselves as chromosome breaks and rejoinings. The effectiveness of high-LET radiations to produce such events is higher than that of low-LET, as studied in detail by Neary (54), and the production of aberrations does become independent of oxygen at high-LET. Chromosome rejoinings also occur more frequently following high-LET radiation. This process requires oxygen in the post irradiation period, and in some organisms, it has been shown to depend on new protein synthesis (55).

Mammalian Cells

Mammalian cells have been studied as isolates in culture, and *in vivo* either in murine ascites tumors, in skin, or in specialized systems such as the solid tumors of rat rhabdomyosarcoma. The information available is voluminous and sometimes contradictory. We shall refer to special contributions only of direct interest to the purposes of this review.

Using the special techniques developed by Puck (56), Elkind and Sutton (57) demonstrated that for mammalian cells exposed to acute doses of low-LET radiations, the survival curves can be described as due to multiple hits. When radiation doses are delivered in intervals, then the surviving cells show "recuperation". In addition, Painter (39,40) recently demonstrated "unscheduled" DNA synthesis post-irradiation, and there is a measure of post-irradiation repair.

With high-LET radiation, the survival curves for

mammalian cell isolates (e.g., of human or hamster kidney cells) are of simple exponential form. This is indicative of the ability of a single high-LET particle to cause lethality, in contrast to the case with low-LET x rays. X rays produce secondary delta rays, and usually hits by from 3 to 6 of these are essential to inhibit the proliferative integrity of mammalian cells. Typical survival curves from the work of Barendsen (58,59) are shown in Figure 6. When survival was studied at various LETs, it was found that there is a direct (single hit) in addition to the multiple-hit component at each LET, but that at low LET only a small percentage of cells are affected in this manner. Extensive work on the two components with heavy, accelerated particles (including He, Li, B, C, N, O, Ne, and A) was carried out by Todd (42,43,60,61, Figure 7). His analysis, in terms of "cross sections", yielded the information that the OER factors for direct-hit and multiple-hit events are different from each other. The magnitudes of the two types of event are shown in Figure 8b; with oxygenated cells at low LET there is a dose reduction factor of 2.5 to 3.3, and that at high LET this factor decreases to about 1.1 -- the OER for the "direct" effect is decreasing faster than that for the "indirect" effect. An interesting LET region to note is that between 10 keV/micron and 50 keV/micron; the mean LETs of fast neutrons as well as of Pi mesons are in this domain. With radiations in this range, the OER drops to a level of about 1.4 to 2.0, which is an improvement over the 2.5 to 3.3 reduction factor observed with x rays or gamma rays at lower LET, but not as low as the OER achievable with accelerated heavy particles at very high LET. Table 1 summarizes some of the results reported in the literature.

The use of accelerated particles with the "track setment" exposure methods allows the observation of oxygen enhancement ratios at well defined LET values. In Figure 8 we

compared such data for human cells by Barendsen and coworkers (62,63) and by Todd (42,43,60,61), and for mouse ascites tumor cells by Berry (64,65). Because the OER depends on the dose level, for Todd's data the "direct" effect (corresponding to the initial slope of the survival curves) was separated from the cooperative effects capable of recuperation. The OER for the "direct" effect approaches unity at a lower LET than for the cooperative effects, a factor quite important to consider in radiotherapy.

Most of Barendson's high-LET data were obtained with slow alpha particles, whereas Todd's data were obtained with faster heavy ions. The apparent difference in OERs at the same LET has been interpreted by Todd and Curtis as due to differences in track structure (66); the faster ions have more energetic delta rays and therefore should have a somewhat higher OER at the same LET than the slower ions.

Information from a table such as Table 1, or from Figure 8, is not sufficient in itself to allow one to judge the "merits" of each type of radiation for therapy. One must consider a number of additional factors, and of these the depth-dose relationship is of particular importance. The experiments reported here were performed in a 'thin target" geometry. However, for successful tumor therapy it is essential that a sufficient dose be delivered to the entire tumor volume; and, in addition, it appears to be of advantage to have as high an LET as possible everywhere in the tumor. Conversely, the dose and the LET should be minimized in the surrounding normal and tumor-free tissues.

Pion beams, at present, are available only at relatively low dose-rates (less than 10 rad/hour), and therefore when comparing these to other radiations one must consider the dose-rate effect. This effect can be greater in magnitude than the oxygen effect, and one will obtain different survival patterns depending upon the physiological state of the cells during their exposure to radiation.

Most authors have reported their work in terms of mean LET. However, three different neutron beams, each with a different energy distribution and mean LET, gave approximately the same OER (62). This finding can be explained on the basis of the presence of more heavy nuclear recoils from carbon, oxygen, nitrogen, etc., in tissue in the cases of the higher energy neutron beams, and it indicates that "mean LET" values are not entirely representative of the radiological properties of a given beam; in addition, one needs to know the LET distributions. Finally, with particle beams at high LET, it is becoming more and more apparent that in order to define the beam we need to know, in addition to the LET, parameters such as the velocity and the charge. The oxygen effect acts more on the delta ray penumbra of heavy-ion tracks and less on the track core; consequently, a high-velocity beam of high charge may have a greater OER than another beam with the same LET but having lesser velocity and charge. Since calculations show that more than one-half (and possibly 70% to 80%) of the ionization produced by a high-speed particle beam is in the core at radius less than 50 Å, some believe that the OER of high-velocity beams will still remain low in spite of corrections for the track penumbra (73). This point must be settled experimentally in the future when accelerators for heavy ions of considerable penetrations are available -- for heavy ions with energies to about 500 MeV/nucleon.

RELATIONS OF THE PHYSIOLOGICAL STATE OF CELLS TO RADIATION EFFECTS

With the availability of synchronized cells in culture, it has been possible to assess radiation sensitivity at different stages during cell division and the oxygen effect during these stages -- effects which are of importance to therapeutic radiology. In a mixed population of cells, as is present in tissues <u>in vivo</u>, cells can be present in different

stages; a dose of radiation will affect cells in "resistant" states less than those in more "susceptible" states, and thus relatively more of the "resistant" cells will survive. Furthermore, during the post-irradiation period cell division is delayed, and more cells may then group in "resistant" states for the next installment of dose. Consequently, it is possible that in protracted therapeutic radiology procedures, with each successive installment of dose there will be an increased number of "resistant" tumor cells present. We suspect that this effect may contribute to the relative lack of success experienced using low-LET radiations in protracted therapeutic schedules.

Using x rays, Sinclair and Morton (75) have demonstrated variations in sensitivity to radiation in hamster kidney cells; Terasima and Tolmach (76) worked with HeLa cells, and Whitmore and coworkers (77), with L cells. It appears that generally, in all strains tested, single cells are most sensitive in the G_2 stages and in mitosis. Cells are relatively resistant during late stages of DNA synthesis (5). Results differ for the different strains studied in the G_1 stage preceding DNA synthesis. L cells are particularly resistant in G_1; the extent of radioresistance appears to relate to the duration of the G_1 stage (78). Response to x rays appears to depend also on the availability of free SH groups, oxygen and radioprotectors (79). Variations in radiation resistance during the cell division cycle may also relate to the ability of the cells to repair radiolesions.

Much of the effect of high-LET radiation appears to be independent of the presence of SH groups or of radiation modifiers. We would expect, therefore, less variation in radiation sensitivity during the cell division cycle using high-LET radiations than we find with x rays. Initial work by Skarsgaard and coworkers (80) gave indications that this may be so. Very recently, in our laboratory, Bird and Burki (81, 82) have shown that the survival of hamster kidney cells to

high-LET radiation from accelerated carbon and neon nuclei is essentially independent of the cell-division stage during which the cells are exposed. In Figure 9 we reproduce an evaluation of the available experiments from (73).

It appears to the authors that the demonstrated uniformity of response of cells in various physiological states to high LET might turn out to be an important factor in radiotherapeutic use of heavy accelerated ions.

Repair and Recuperation at Low and High LET

The initial observation of Elkind and Sutton (57), that mammalian cells are able to recuperate and repair between successive installments of radiation doses, has been studied in much detail (83). Those who use protracted therapeutic dose schedules must be aware that between successive radiation treatment recuperation, repair, and even cell proliferation may take place. It is sometimes a tacit condition for successful therapy that normal tissue components, i.e., tissue cells and blood vessels, recuperate more efficiently than tumor cells. The recuperation is, in part, synchronization of cells into more resistant phases of the cycle and, in part, repair. The multiple-hit survival curves, characteristic of several strains of human cells in culture, become single-hit, exponential functions of dose. It has been repeatedly shown (42,43) that at high LET recuperation does not occur, and that no cell division is allowed to occur between dose installments (34,35,50,51). With fast neutrons of intermediate LET, the situation is more complicated; Elkind (84) has recently shown that after irradiation with fast neutrons, cells possess some ability to recuperate.

It is not fully known why, for very high LET radiations, no recuperation has been observed in mammalian cells. It has been suggested that high-LET radiation might preferentially damage the enzymatic repair systems in cells; on the other hand, there is evidence accumulating to show that the

molecular lesions produced by high-LET particles are different from those produced by low-LET particles.

EXPERIMENTAL TUMOR RADIOBIOLOGY STUDIES IN VIVO

In the previous section we have considered the radiobiology of isolated mammalian cells, cultured in vitro. A tacit assumption is usually made that such results also apply to the radiobiology of tumor tissues exposed to radiation in vivo. However, because of the obvious differences between the behavior of cells in vivo and in vitro, such extrapolations must be viewed with some skepticism. In the case of tissues, nutrients and control substances (hormones) are being constantly supplied in a rather abundant manner, while the waste products are being efficiently removed. Cells in culture, however, have a fixed milieu and are often dependent on diffusion for the turnover of nutrients and of waste products. Admittedly, we do not know how to keep cultured cells in differentiated states over long periods of time, and cultured cells sooner or later turn into tumor cells (85). This finding seems to be generally true for cultured cells, with the exception of a very few documented examples (86). In fact cell isolates in culture are often so isolated from their neighbor cells that they must rely entirely on themselves for proliferation; furthermore, there is no competition for survival with other cells. On the other hand, in tissues we now know that cell-to-cell communications exist via cytoplasmic bridges (87). This cell-to-cell cummunication may have regulatory influence on normal cells, and the extent of such communication between tumor cells seems to be impaired (88,89). Cell-to-cell communication may also be related to "contact inhibition" (90), and radiation seems to be able to alter contact inhibition (91). Finally, there seems to be a degree of competitiveness between cells in tissue, part of this being related to antigenic properties of cells. Tumor cells sometimes have specific antigens (92), and in such cases

immunological processes are set in motion resulting in attempts by the body to remove the antigenically active cells.

There is very little quantitative information available at present concerning the properties of tumor tissue enumerated above, and much more development is needed in this field. Nevertheless, there are some definite questions that can be experimentally studied by means of special tumor systems in animals.

Ascites tumors.

The Gardner lymphosarcoma was induced in C_3H mice by methylcholantrene in 1954 and has been carried by serial transplantation in several laboratories since that time (93). This is a solid tumor which can be separated easily into single cells, allowing one to make quantitative determination of the number of cells needed to initiate tumor growth. It is also possible to determine radiation sensitivity of the cells constituting this tumor by using the loss of capacity to produce a tumor in a new host as the criterion for inactivation. For this purpose, the endpoint dilution technique of Hewitt (94,95,96) has been employed by Powers and coworkers. They found a characteristic two-component tumor-survival curve, and interpreted this to be due to the presence of a population of well oxygenated cells (about 99%) and one of more resistant anoxic cells (about 10%) (see Figure 10). The endpoint dilution technique has yielded the information that 50% of hosts will develop a tumor when 40 to 150 presumptive tumor cells are inoculated. It was further shown that if the tumors of the donor animals were exposed to therapeutic doses of radiation, then the surviving tumor cells were equally potent in inducing tumors in new hosts as were unirradiated cells.

However, hosts that had previously received 250 rad whole body radiation, thereby reducing their immunological competence, were susceptible to a reduced number of transplanted tumor cells; on the other hand, hosts that had been

previously "cured" from lymphosarcoma developed new tumors only when 10^5 tumor cells were transplanted. "Cures" achieved by radiation never approached 100% of the tumor bearing population, probably because a significant portion of tumor cells were disseminated via the blood and lymphatic circulations to distant regions of the hosts' bodies.

In this experiment, it was clearly demonstrated that the presence of anoxic cells in the tumors had a great effect on the radiation dose needed to eliminate transplantability. The influence of the presence of anoxic cells on "cure" rates achieved by a given dose of radiation remained somewhat obscure.

Ascites tumors in mice.

Certain lines of murine lymphoma tumors have been kept in ascites form by weekly transplantation; the cells in such lymphomas grow dispersed in ascites fluid and proliferate in a manner similar to that of non-clumping bacteria in liquid nutrients.

The radiobiology of such ascites tumors has been studied in detail. The tumor cells can be exposed to radiation either in vivo or in vitro, using cell suspensions. A great deal of complex information is available. For example, Revesz (99) reported that DNA from cells killed by radiation injury can, under certain conditions, promote the efficacy of transplantation. Evans and coworkers (100) report that the concentration of ascites tumor cells at low oxygen tension affects their survival.

It was also shown that many of the ascites tumors' aneuploid cells are present in varying concentrations. Amos (101) has stabilized some ascites tumor strains, and in our Laboratory one of the near diploid lines (L-2) has been used for radiobiological studies in LAF_1 mice (70,71,102). These studies showed that 10^4 L-2 cells will produce tumors in 50% of mice within 8 weeks following intraperitoneal injection. Heavy ion irradiation of cells, in vitro or in vivo, has

resulted in increasing biological effectiveness for reducing the cell's tumor forming ability in a manner similar to the finding in studies on hamster kidney cells. Helium ions of 118 MeV or 910 MeV kinetic energy at the position of the "Bragg peak" also reduce the oxygen enhancement ratio (OER) to 1.8 ± 0.1, whereas Pi mesons at the Bragg peak have an OER of 1.6. These values are similar to those found on other cells for fast neutrons, but are greater than the OER of 1.2 reported by Berry and Anderson (64) for fission neutrons, or approximately one by Sillesen and coworkers for heavy accelerated ions (102).

It has been shown that in the course of proliferation in the host, ascites tumor cells become so numerous that their oxygen supply becomes deficient. Studies in our laboratory showed that following transplant of a small number of cells (e.g., 100), the cells would proliferate and invariably kill the host in a span of 10 days. By microoxygen electrode measurements in the ascites fluid, it is shown that at 2 days the cells are oxygenated, whereas at 5 days and later, they are severely anoxic. Some experiments were subsequently carried out at 2 days (cells oxygenated) and at 5 days (cells anoxic) with in vivo exposure to radiations (and immediate sampling and transplantation of the exposed tumor cells) in order to assess the oxygen effect in x-ray and in pion beams. The general result obtained was that anoxic tumor cells (those irradiated at 5 days) were more resistant to x rays than oxygenated cells (those irradiated at 2 days), and also that the pion beam was more effective than the x-ray beam in killing tumor cells. These data, however, are quite variable (103).

Rat Rhabdomyosarcoma

At the Rijswijk Laboratories in Holland a multiplicity of techniques have been developed for assessing radiation effects on solid tumors exposed to radiation in vitro or in vivo (104,105,106). Following exposure to radiation in vivo,

the tumor Rhabdomyosarcoma is excised and the cells are separated by a procedure of trypsinization. Then the individual cells are plated, and if able they will form clones on appropriate nutritional medium. The number of clones formed are subsequently counted as an indication of the number of surviving cells. For the Rhabdomyosarcoma cells, the x-ray in vivo survival curves measured show biphasic structure. Anoxic cells are much more resistant than oxygenated cells. As shown in Figure 11 at low doses the oxygenated cells die off first and the "tail" in the survival curve at high doses has been shown to be due to anoxic cells. By extrapolation to zero dose it is possible to estimate the fraction of anoxic cells present. If the animals bearing tumors are exposed to hyperbaric oxygen, the reaction of anoxic cells becomes diminished. The tumors have also been exposed to 15-MeV neutrons which have less oxygen effect (see Table 1). The survival curves obtained by irradiation in vivo are quite similar to those measured when the tumor cells were cloned and exposed to radiation in vitro.

The growth of tumors in vivo depends on so many factors that it is impossible at present to quantitatively assess the influence of each. The effect of the presence of tumors on the host may depend on the size of the tumor, the rate of proliferation of its cells, and on the rate of death of the cells. These factors have been studied in some detail by the Rijswijk group. For example, they have shown that following a large dose of x rays to the tumor, the remaining viable tumor cells can proliferate quite rapidly, eventually causing a delayed regrowth of the tumor. At the same time, the death rate of the progeny of irradiated tumor cells is also increased. Studies of this type are needed for high-LET radiation as well. However, additional factors such as the effect of toxic substances and enzymes elaborated by the tumor and the effects of radiation on blood vessels and capillary bed must also be known. Furthermore, studies are needed on

the effect of radiations on normal cells and on the interaction of normal and tumor cells.

Tumor Therapy and Hyperbaric Oxygen

In an attempt to overcome the disadvantage of conventional x-ray therapy caused by the presence of anoxic tumor cells, two different new therapeutic approaches have been initiated during the past several years. By using hyperbaric oxygen, investigators have tried to oxygenate all cells, thereby hoping to achieve a better tumoricidal effect of the conventional radiation. In mouse mammary tumors, the "cure" rate was indeed increased by such procedures (107), and the delay in growth of rat tumors was also greater when radiation was carried out under hyperbaric conditions (108). Unfortunately, randomized clinical trials have not revealed significant improvements in therapeutic efficacy in man (109,110). An alternative procedure is that of rendering the tumor and all tissues in the vicinity hypoxic by the application of tourniquets. This technique appeared to be helpful in soft tissue sarcomas and radioresistant osteosarcomas (41,111,112), but it did not change the prognosis in these diseases.

The importance of the oxygen effect in radiotherapy has been questioned on the basis of the observation that in fractionated dose therapy of animal tumors, some reoxygenation of anoxic cells occurs after the initial therapeutic dose installments (108,113,114). On the other hand, some tumors reoxygenate only very slowly (115). In no case has it been possible to show that all anoxic cells have disappeared.

In discussing this type of experiment, we should bear in mind that "reoxygenation" must depend on the state of the vascular bed of the tumor. If necrotic foci exist, with their greatly impaired circulation, then reoxygenation in their vicinity may be less complete than elsewhere. It is possible that the presence of relatively few surviving anoxic tumor cells is sufficient to render low-LET radiation therapy locally ineffective.

The above statements imply that additional methods are needed besides hyperbaric oxygen, local hypoxia, and protracted dose delivery schedules. The use of high-LET radiations promises not only to materially diminish the oxygen effect quite independently of the location of the anoxic cells in the tumor or of the state of their circulatory supply, but also to have other important advantages.

Estimations of depth survival distributions.

We have seen that several physical variables help to describe the effects of special radiations for the purpose of radiology, including dose distribution, dose rate, and LET distribution. In order to describe the radiological properties of tissue, it is helpful to have dose-effect relations described in terms of the above independent variables. Such relations are needed for normal as well as for cancer cells in various physiological stages. It is obvious that we do not have enough data to realistically make a model of the overall effects of various types of radiations on tumors. However, in view of the complexity of the situation, and in order to have a better understanding of the relative advantages of various radiations, we have made some simplified models. We wish to compare the effect of treatment on cells and therefore in addition to depth-dose distributions, we have provided depth-survival distributions. The aim of a radiological treatment can be stated in terms of hoping to reduce survival levels of tumor cells to some specified level. The depth-survival calculations are of value because they take into account biological effectiveness and oxygen effect, as well as dose distribution.

The data presented below are the result of calculations based on experimental or assumed knowledge of several factors. These include depth-dose and LET distributions, cross sections for survival of cells, responses to oxygen concentration as well as distributions in the physiological state of cells and changes of radiosensitivity in these states, repair,

recuperation, and cell proliferation between successive dose fractions. Figure 11 gives a schematic representation of the manner in which such calculations are carried out by computer.

In order to illustrate the importance of depth-dose and LET distributions, we have shown some results of such calculations in Figure 12. For these calculations we have assumed that we are treating a 4-cm. thick tumor in the center of a 20-cm. thick body. The radiation is delivered through two opposed ports, treatment being given through both ports on each treatment day. This results in the following: there is no reoxygenation of anoxic cells; there is no growth between dose fractions; there is complete repair of any sublethal damage between fractions; tumor cells and normal cells have the same radiosensitivity. Two types of tumor cell populations have been assumed at the start of the treatment regimen: one of 100% aerobic and no anoxic cells, and the other of 20% anoxic and 80% aerobic cells. As a reference for comparison, the standard treatment was taken to be 6,000 rad at the midline, administered in thirty fractions, using Cobalt-60 gamma rays. This results in a maximum surviving tumor fraction of about 1×10^{-7} if there are no anoxic cells; if initially there are twenty percent anoxic cells, then the surviving fraction is greater than 1×10^{-3}. For helium- and neon-ion irradiations, the dose and the number of fractions are adjusted to reduce the surviving fraction of aerobic tumor cells to less than 1×10^{-7} and to maximize the surviving fraction at the surface.

For heavy ions the standard fractionation scheme, such as that used for x rays and $Cobalt^{60}$ gamma rays, is inappropriate. Whenever the survival curve has a shoulder and the depth-dose distribution is such that the maximum dose occurs within the tumor region, then there will be an optimum daily dose for greatest killing of cells within the tumor while sparing those cells outside of the tumor. With a given survival level within the tumor region, this optimum daily dose

will determine the optimum number of fractions to be used. With a depth-dose distribution which has a maximum dose occurring outside of the treatment region, then this simple model indicates that the daily dose should be small, and consequently the number of fractions would be large.

These calculations show that in the case of a "slab" treated with gamma rays or neutrons, it is not possible to obtain survival of cells in the tumor area less than that obtained near the body surface. If the tumor region is also anoxic, then the situation is made worse, because in this case the number of cells surviving in the tumor region may be increased several times. Pion, helium, and neon beams have very similar isodose curves, but these beams differ more markedly in the mean LETs and the LET distribution patterns. These beams can cause greater lethal effect inside of the slab at the "tumor" region. Furthermore, when anoxia is present relatively fewer cells will survive. In this latter situation the difference between survival of anoxic and normal cells is least when neon beams are used, is a little greater with pions, and an even greater oxygen effect results with helium ions. Optimal treatment of an anoxic tumor with one of these radiations may even require a different dose per fraction than that required for an aerobic tumor. Larger tumor volume will require a larger region of the 100% dose, but by using two opposed ports it should always be possible to get a tumor dose at least woice as large as the surface dose. Therefore, as long as there is sublethal repairable damage at the surface, there should be an optimum dose per fraction. It may be a mistake to attempt to use these radiations with conventional fractionation schemes because of this possible situation.

Overall suitability of radiations for radiotherapy

The success of radiation therapy obviously depends on optimal choice of a number of factors. In each case many biological factors, such as the histopathology, the degree of

invasiveness, the radiation sensitivity, and the location and nearness of radiation sensitive normal tissue region, must be considered. In addition, there are also the physical and radiobiological considerations presented here.

Some authors who are particularly impressed with a single factor,e.g., depth dose or oxygen effect, have advocated a single type of radiation over others, and some have even cited "figures of merit" to support their convictions (138). One must caution against such approach, however, particularly if the presentation does not clearly state how the "figure of merit" was derived.

In order to aid radiotherapists, we have summarized the arguments given in this paper in Table 2. Five radiations were ranked on a scale of 1 to 5, with 1 being "best" and 5 "least" desirable:. The properties ranked were suitability of depth dose, minimal oxygen effect, minimal repair in tumor, minimal response of cells in different physiological states, and minimal entry or exit surface effect.

At the time of this writing only low-energy (10 MeV/nucleon) neon ions and only low-intensity(<10 rad/hour) pions are available for experimental studies. Further experiments in radiation physics and radiobiology are needed for better understanding of several factors, and only eventual therapeutic trials can supply full evaluations. It appears to these authors that acceleration of heavy ions, e.g., of neon, and further assessment of pion beams might be very worthwhile for the future of radiation therapy. In the meantime, we have had many years of experience with helium beams and, as described below, these are being proven to be versatile for radiotherapy.

Clinical Studies

At present there are no sources of pi mesons or heavy ions such as 400-MeV/nucleon neon for use in therapy -- particles which would provide deep penetration and decrease in the oxygen effect. Fast neutrons were tried in cancer therapy in

our laboratory during the period 1937 to 1942 (16,17,117), and are being tried again in one center in England at the present time (15), but the results of the early work and that during the past ten years are not encouraging. We have had some experience with relatively light heavy particles (alpha particles) using the Bragg peak in therapy, but the density of ionization produced is relatively low. What we really need to have available for therapy are particles such as neon or carbon with energies up to 600 MeV/nucleon.

In 1948 animal investigations were carried out using the Bragg peaks of 1980-MeV deuteron and 340-MeV proton beams, demonstrating that transplanted mammary tumors in mice could be successfully eradicated by passing the heavy-particle beam through the animal's body with the Bragg peak placed at the tumor site (2). Thus heavy particles were found suitable for effective and intense irradiation of small volumes deep within the body, and further studies were carried out irradiating the pituitary gland in animals (117). Earlier findings had indicated that the pituitary was resistant to x radiation (118), but the demonstration that it is possible to suppress function in animals by using heavy particles led to their use in treating human disease.

During the past sixteen years we have treated more than 500 patients with heavy particles, first using 340-MeV protons and since 1957, 910-MeV alpha particles. The medical applications of heavy particles, which first centered around suppression of pituitary function in patients with far advanced metastatic breast cancer (119,120), were soon extended to include the treatment of patients with disorders of the pituitary gland, including acromegaly (121, and Cushing's disease (122). Using high-energy heavy particles it is possible to overcome the relative insensitivity of the pituitary gland to externally delivered radiation and to deliver safely, sufficiently large doses to the pituitary area to treat these pituitary disorders successfully. During the treatment period the

patient is ambulatory, the procedure is painless, and there is no need to enter the cranium either surgically or by needle.

Since 1958, 144 patients with acromegaly have been treated using the 910-MeV alpha-particle beam from the 184-inch cyclotron (121). This disorder is usually caused by an eosinophilic tumor of the pituitary gland, with the resultant hypersecretion of growth hormone leading to the development of the many symptoms and signs of acromegaly. These patients do not live long -- over 50% die before age 50, and 80% before age 60 (123). Since, as mentioned above, the pituitary gland is relatively radioresistant, metabolic effects from Roentgen or gamma-ray pituitary irradiation are rarely seen (124,125) because of the limited doses that can be used safely without damage to surrounding vital structures such as cranial nerves, hypothalamus, and the temporal lobes; after such treatment long periods of relief of signs and symptoms are not achieved and life expectancy remains poor. With the availability of cortisone for replacement therapy, surgical hypophysectomy has been used with considerable success (126, 127), as have pituitary implants of gold-198 or yytrium-90 (128,129,130) and, more recently, cryohypophysectomy (131). However, using an externally delivered high-energy heavy-particle beam from a cyclotron, it is possible to deliver safely sufficiently large doses to the pituitary area to control the excessive growth-hormone secretion and thereby to treat acromegaly successfully.

Following heavy-particle therapy, the relief of symptoms and signs is gradually achieved. Headache, which is by far the most frequent and troublesome symptom encountered, has either disappeared or markedly improved in nearly 100% of the patients within one year. Lethargy and weakness also improved. These symptoms, while difficult to assess, are nevertheless of real importance in the patient's illness as they adversely affect his ability to carry on normal activities and further

affect his psychological outlook, and consequently their alleviation is important in judging the effect of therapy. No further acral enlargement as occurred in any of the patients following treatment, and this had decreased in one-third of the patients within four years after completion of therapy. The typical coarse, heavy facial appearance of these patients underwent satisfying changes in thirty-five percent of the group followed for the four-year period. This was evident in a refinement and decrease in mass of the supraorbital ridges, the malar prominences, the jaw, and the nose. Photographs of many of these patients taken before and after therapy show striking changes in appearance. Primarily the changes occur in the soft-tissue mass, but there is also evidence of changes in the bones as demonstrated by comparative head casts, x-ray examination of the hands and feet, and studies on calcium metabolism using radioactive calcium.

The plasma-growth-hormone levels, as determined by radioimmunoassay (133) were elevated in all patients prior to treatment, and subsequently all fell. These levels were within normal limits in twenty-seven percent of the patients within two years, and in ninety percent when re-evaluated in five to nine years after completion of therapy. In addition, abnormalities in carbohydrate metabolism, including insulin resistance, diabetic-type glucose tolerance curves, and the presence of secondary diabetes mellitus disappear following treatment. The remaining normal pituitary gland continues to function, and less than one-fourth of these patients require replacement hormone therapy with hyroid or cortisone.

With the reversal of the metabolic abnormalities it is reasonable to expect extension of comfortable life to normal or near normal. Only nine patients in our series have died, four of these from cardiovascular causes associated with severe cardiomegaly and hypertension prior to heavy-particle therapy. One patient took his own life seven months after treatment, before the maximum effect of therapy could be

achieved. One died of an accidental overdose of barbiturates five years after completion of heavy-particle therapy. One patient, whose growth hormone level remained high, was given a course of proton-beam therapy elsewhere three years after being treated here and died one year later with acute myeloblastic leukemia. One patient died of systemic histoplasmosis, three and one-half years after treatment. The other patient died at another medical center eleven years after completion of heavy-particle therapy from a meningioma (both the patient and his wife had refused treatment for this tumor); the meningioma was in an area of the brain estimated to have received 300 rad, and it seems unlikely that a cause-effect relation between therapy and tumor is present. One additional patient, who did well for a brief period following treatment, subsequently relapsed and underwent surgical hypophysectomy two years after completion of heavy-particle therapy; his growth hormone level is now down to 6 mμg/ml, and he is doing well. The remaining 134 patients are living and well; sixty-seven were treated over three years ago, and thirteen of these have now been followed for more than ten years.

Although it does not seem necessary, the dosage to the sella turcica can be safely increased by using the Bragg peak (five patients who had very large pituitary tumors were treated with the Bragg peak). Significant amounts of prior radiation predisposes to an increased incidence of post-heavy-particle therapy complications. Six of the patients treated before 1961 had already received x-ray therapy, but because they still had active and progressive acromegaly when we first saw them, they were accepted with reluctance for heavy-particle therapy. Three of these six, who had received one to three courses of x ray with total doses ranging from 2,000 to 4,275 rad, subsequently developed mild ocular complications which were not progressive; two developed transient diplopia fourteen months after heavy-particle therapy (they are both doing well today, it now being twelve and one-half years since

treatment), and the third developed a quadrant cut two years after therapy (this patient died seven years later from a cerebrovascular accident, at the age of 68). These mild ocular complications were presumed to have resulted from therapy and their occurrence further reinforces our belief that heavy-particle therapy should be limited to those patients who have not received previous radiation therapy; since 1961 our policy has been not to accept such patients. In addition, we have also eliminated patients who have significant extrasellar extensions of the pituitary tumor. In several instances such suprasellar extensions were found only after carefully conducted tomographic pneumoencephalography, and to ensure ruling out such patients this procedure is now always carried out prior to treatment. With these restrictions in force, the dosage delivered to the brain tissue surrounding the pituitary gland and to the cranial nerves has been limited to less than 3.500 rad. Of the 129 patients treated since 1961, 124 were treated with the plateau portion of the beam using a biplanar rotational technique; we have experienced no neurological complications in this large group. The other five patients had very large pituitary tumors, and therefore were treated with the Bragg peak. Two of them had small suprasellar extensions, and one of these patients developed diplopia and subsequently underwent transfrontal surgical decompression with improvement. Of the other three, one developed small bilateral superior-temporal field cuts following treatment, which subsequently stabilized and fortunately resulted in no major visual impairment; another complained of subjective diplopia following parathyroid surgery, but had no objective extraocular palsies and she is now improving. All five of these patients are working and otherwise well. Our total experience using heavy particles to treat this large number of patients (144) over a thirteen-year period is encouraging and indicates that good control of acromegaly can be achieved by this safe method with a very low incidence of side effects.

The question of possible relation between malignant transformation in pituitary tumors and Roentgen therapy has been raised in the past. Terry, Hyams, and Davidoff (134) reported three cases of pituitary sarcoma occurring from three to twelve years after administration of x-ray therapy for treatment of chromophobe adenoma; Goldberg, Sheline, and Malamud (135) reported three cases of pituitary sarcoma occurring ten and twenty years after pituitary irradiation for treatment of acromegaly; Greenhouse (136) reported one case of pituitary sarcoma occurring nine years after x-ray therapy for acromegaly; and at a Cancer Seminar on Intracranial Tumors held in 1962 (137), Wheelock reported one case of pituitary sarcoma occurring twelve years after initial x-ray therapy for acromegaly. Taveras mentioned two cases of pituitary sarcoma he had seen occurring ten or more years after radiation therapy, and Zimmerman commented on his observation of three pituitary sarcomas which had received previous irradiation. However, it was pointed out that pituitary sarcomas are rare, and the incidence in an untreated group is not known (most patients with pituitary adenomas eventually receive radiation therapy, and there is no large control group for comparison). Also, there is the problem of establishing malignancy in these cases. The literature does not clearly answer the question one way or the other. However, even if a causal relation were to be proved, it is generally felt that this would not negate the value of radiotherapy in the management of pituitary adenomas. Cases of necrosis of brain tissue following treatment of acromegaly with electromagnetic radiations such as x rays and gamma rays have been reported, and recently Peck and McGovern (138) cited three such cases in addition to one case following x-ray therapy for chromophobe adenoma. The brain and cranial nerves can only tolerate doses of radiation up to the range of 3,000 to 5,000 rad, and as pointed out above, in our series we have avoided giving such doses to the surrounding normal tissues.

Just as in the case of acromegaly, heavy particles have made it possible to accurately and safely deliver sufficiently large doses of radiation to the pituitary area to treat patients with Cushing's disease successfully (122). We have used this method to treat twenty-two patients with Cushing's disease during the past eleven and one-half years, and our results so far have been encouraging. We have observed reversal of abnormal metabolic signs, a fall to normal of steroid excretion, and the disappearance of exaggerated response to metyrapone. The first patient, who was treated in April, 1959, remains in remission today. However, follow-up of a larger number of patients for a longer period of time is necessary before final conclusions can be reached.

In addition to their use for the treatment of acromegaly and Cushing's disease, heavy particles have already been investigated for their possible benefit in several neoplastic, neurologic and metabolic diseases. The Bragg peak was first used in January, 1960, (139) to treat a metastatic lesion in the right deltoid muscle of a patient whom we had treated in 1958 for disseminated mammary carcinoma. The local lesion was treated with a dose of 2,500 rad delivered in five treatments over a seven-day interval, it being noted that with the greater RBE of the Bragg peak this dose was equivalent to 4,500 to 5,000 rad of conventional x ray. The major part of the dose went to the tumor itself, the skin dose having been one-third of the tumor dose. Therapy was well tolerated, and three months later the lesion was only a slightly indurated area that was not tender and showed no definite mass. There had been no skin reaction. About one year later, however, there was evidence of progression of other systemic lesions, and thirty-seven months after the inital heavy-particle pituitary therapy the patient died.

We have used 910-MeV alpha particles to irradiate brain tumors in six patients, employing the Bragg peak in five cases and the plateau of the Bragg peak had brief periods of improvment (3 to 12 months), and the other one did well for a

period of five years. However, in each of these patients there was subsequently evidence of tumor recurrence outside of the radiation field, and the patients died at intervals ranging from six months to six years after treatment. In the four cases where post-mortem results are available, the tumor extension outside the radiation field was shown. Thus, while cessation of tumor growth in the treated area may be achieved, there is often recurrence later, outside of the radiation field, and this points out a major difficulty to overcome in treating these cases -- the exact delineation of the tumor area must be known. Even though one can take advantage of the heavy particles' favorable radiobiological characteristics and thereby deliver greater tumor doses while sparing the skin and intervening tissues, unless one can place the radiation throughout the entire tumor area improved results cannot be expected.

In the case of the sixth patient with a brain tumor (pinealoma), because of the central location and small size of the tumor it was decided to employ a technique similar to that for pituitary irradiation using the plateau of the alpha-particle beam with rotation. This patient was essentially asymptomatic for ten months following therapy but then again noted diplopia. Ventriculography revealed a third ventricular mass which was interpreted as tumor recurrence, but which in retrospect actually represented a hematoma. He died five days after a right occipital craniotomy, and at autopsy the essential cranial findings were post-surgical hemorrhagic necroses of the right occipital lobe, right and left thalamus, and pulvinar; there were post-irradiation changes in the target area, but notably none outside the target area. There was no evidence of residual cells.

We have also used the Bragg peak of the 910-MeV alpha particle beam to perform thalamotomies in two patients with Parkinson's disease (132), but there is not sufficient data to discuss the results. More recently we have used the Bragg

peak to treat pulmonary metastases, and following is a case history of this patient.

Case History: A 44-year old woman with a six-year history of cylindroma of the palate was referred in September, 1969, for treatment of pulmonary metastases. Resection of the hard and soft palate without radical neck dissection (no cervical nodes were palpable) had been done in March, 1963, the pathological section showing adenoid cystic carcinoma in all margins except one. Post-operative radiation therapy with 2-MeV x rays was administered, the total dose being 5,000 rad in twenty-five days. Multiple follow-up examinations revealed no evidence of local recurrence nor distant metastases until February, 1969, when both were detected. The primary site was treated with implantation of two radon seeds (1,500 rad to a 2-cm. diameter), and a cluster of five nodules in the left lung base were treated with cobalt-60 gamma radiation (3,000 rad in 11 days) to determine radiosensitivity.

Three months later (may, 1969) there was marked diminution in the size of the treated metastases, and growth-rate measurements of the untreated pulmonary lesions showed the doubling time to be in excess of 100 days. There was no readily identifiable tumor in the right maxilla, and the tissue washing of that area was negative for tumor cells. It was felt that if tumor were present, it was extremely show growing, and since the radiosensitivity of the lung lesions had been established, it was decided to defer further treatment until symptoms warranted interference.

In August, 1969, there was continued slow growth of the untreated pulmonary metastases, but no pulmonary symptoms. The patient had a sensation of "tightness" in the right maxillary region, but there was no recognizable tumor in the primary site. Because of the apparently well controlled primary lesion, the rather slow growth of her pulmonary metastases, the proven radiosensitivity of the treated lesions, the absence of metastatic lesions other than those in the

lung, and the good general condition of the patient, she was referred to us for consideration of heavy-particle irradiation of her right lung nodules. In order to carry out treatment, a special chair was constructed (see Fig. 14). In March, 1970, a biopsy of the hard palate showed local recurrences, but it was decided to proceed with heavy-particle treatment of the pulmonary metastaces and then to treat the primary recurrence.

Heavy-particle (Bragg peak) therapy: On April 3, 1970, and in cooperation with the Professor of Radiotherapy in charge of her case, four lesions in the right lung were treated with 910-MeV alpha particles. Three of the nodules were lined up horizontally (by inclining the patient backwards about 20° from the upright sitting position) and irradiated with 910-MeV alpha plateau particles through an anterior 38-mm. circular port. A total dose of 1,000 rad was delivered at a dose rate of approximately 1,000 rad per minute. There were three momentary interruptions to allow the patient to catch her breath, she being asked to hold her respiration during mid-inspiration just before each of the four irradiation periods. Localization films were taken before and after treatment. The fourth lesion was treated with 910-MeV alpha Bragg-peak particles (see Fig. 15), using a beam of similar size and in a 20° anterior oblique direction. Ridge filters were used to widen the peak to approximately 4 cm, and the beam was terminated at a depth of about 6 cm from the skin surface, and seventy percent of the peak dose of 1,000 rad was delivered at that depth. Carbon-11 positron scanning pictures were taken within ten minutes of the Bragg-peak treatment, and they qualitatively confirmed the dosimetry (see Fig. 16). Thus, in one instance, 1,000 rad of radiation with an approximate RBE of one was delivered (plateau), and in the second the same dose of Bragg-peak irradiation was delivered with the latter sparing considerably the tissue beyond the tumor and, to a lesser extent, the skin surface, producing a denser

ionization in the tumor and therefore having a somewhat higher RBE and somewhat decreased oxygen effect (67).

Following completion of heavy-particle therapy to the pulmonary metastases, the local recurrence of the primary site was treated elsewhere. On April 14, 1970, radon seeds were implanted on the right side (antrum, orbit, and nasal passage) with an estimated tumor dose of 4,000 rad; then, between May 12 and May 21, 2,000 rad were delivered to the area using 4-MeV x ray through two ports.

On May 14, 1970 (40 days after completion of heavy-particle therapy) repeat chest x rays were taken. These are shown in Figure 16 and reveal a marked diminution (75%) of all four lesions in the right lung which had been treated with heavy particles. However, the left lower lobe deposits were regrowing.

On July 13, 1970 (3-1/2 months after heavy-particle treatment) the patient returned for a follow-up visit. She was doing well. The recurrence of her primary lesions was regressing well following treatment, with moderate reaction of surrounding normal tissue; the pulmonary metastases had been very responsive to radiotherapy, but neither appeared curable by radiation. It was decided to retreat the four lesions in the right lung (had received 1,000 rad in April, 1970 and an additional 1,000 rad were to be given), and to treat two new lesions in the left lung with a dose of 2,000 rad using the Bragg peak for one of them and the plateau for the other.

Second heavy-particle (Bragg peak) therapy: On July 15, six pulmonary nodules were irradiated with 910-MeV alpha particles. A 38-mm circular aperture was used throughout the procedure. The patient was requested to take shallow respiration during the irradiation periods. Localization pictures were taken before and after each treatment and these confirmed that fairly consistent alignment was maintained. Lesions 1, 2, 3, 4 had been previously treated; lesions 5 and 6 were

treated for the first time. Therapy was administered as follows:

Lesion 1 was retreated with the Bragg peak, a second dose of 1,000 rad being delivered through a 45° oblique anterior field which was adjusted to have a 6-cm penetration. To ensure full coverage of the tumor, there might have been some overshoot into lung tissue.

Lesions 2, 3, 4 were lined up horizontally, as before, by inclining the patient backwards about 30° from the upright sitting position; these lesions were retreated with the plateau, the second dose of 1,000 rad being delivered through an anterior field.

Lesion 5 was irradiated with the Bragg peak, using two 45° oblique right lateral portals, each delivering 1,000 rad to make a total tumor dose of 2,000 rad. There was probably some overshoot with these fields which were estimated to terminate at approximately 7 cm of soft tissue equivalent beneath the skin surface.

Lesion 6 was irradiated with the plateau, using an anterior and a left lateral portal, each delivering 1,000 rad so that the tumor received a total of 2,000 rad.

A dose rate of about 1,000 rad per minute was used in each instance, except in the treatment of lesions 2, 3, and 4, where it was higher by a factor of almost six.

In August, 1970 (1 month after the second treatment) x rays revealed almost complete disappearance of the irradiated metastases (there was tanning of the skin at the position of the entry and exit beam portals). The primary tumor was extending, and was being treated again.

In October, 1970 (3 months after the second treatment), the primary site (right antral and orbital region) was under reasonable control, and all of the treated pulmonary lesions had shown good regression. It was decided to treat the pulmonary lesions in the left lung with heavy particles.

Third heavy-particle therapy: on November 24th we treated four more nodules, three of them in the left lung (these had received Cobalt-60 gamma radiation in February, 1969, 3000 rad in 11 days), and the remaining lesion in the right cardiophrenic angle (this had received no prior therapy). Altogether three separate AP ports and two slightly over-lapping lateral ports were used to deliver 750 rad each (plateau alpha particles). The ports were all circular and measured either 45 mm or 63 mm in diameter. A total dose of 1,500 rad was delivered to three of the lesions; the fourth lesion received only 750 rad because one lateral field hit the cord.

We are waiting now for follow-up information on this patient.

Because of the potential advantages of heavy particles in therapy, other important applications of this form of energy must be further investigated. We believe that the treatment of certain types of malignant tumors might be improved if it were possible to administer an adequate dose of densely ionizing radiation. It seems important that there be eventual construction of an accelerator capable of accelerating heavier particles and thereby making available very high energy heavy particles, such as 400-MeV neon particles or even calcium ions, for use in therapy. As pointed out in this chapter, by being able to deliver dense ionization with an LET of around 50 to 100 MeV per micron to deeply-lying tumors the oxygen effect would be nearly completely eliminated. It is known that some neoplastic cells are anoxic or hypoxic, and such particles would be particularly advantageous in treating these neoplastic cells, with the other characteristics of densely ionizing radiation effects on tissues. Also the finite range of the particular beams would be of special value in the treatment of patients with circumscribed tumors and tumors that lie closely adjacent to sensitive structures. Some lesions especially suitable for clinical trial for these

reasons, or because of the poor prognosis, are the craniopharyngioma, pinealoma, brain-stem tumor, and glioblastoma multiforme; esophageal carcinoma; advanced carcinoma of the cervix; osteogenic sarcoma; Ewing's tumor; soft tissue sarcomas and synoviomas, especially of childhood; chordomas and malignant tumors of the vertebral bodies; parotid and middle ear tumors; chest wall lesions (e.g., en cuirrasse breast cancer recurrences); and carcinomas of the prostate (142).

Even today, however, there are accelerators in many centers throughout the world which are capable of producing protons and alpha particles with sufficient energy to be used therapeutically. Groups in Uppsala (26,143), in Cambridge, Massachusetts (143), and in Russia (9) are using high-energy protons in therapy; and it seems important that other groups begin to use their cyclotrons to do this kind of work. But for the future, it seems to us exceedingly important that very heavy penetrating particles, as high on the periodic table as neon and calcium, be available for therapeutic trial. In Berkeley, we hope that a synchrotron ring can soon be added to the presently operating super HILAC which would act as the ejector of these particles at low energy for acceleration to 400-MeV per nucleon.

OVERALL SUITABILITY OF RADIATIONS FOR RADIOTHERAPY

The success of radiation therapy obviously depends on optimal choice of a number of factors. In each case many biological factors, such as the histopathology, degree of invasiveness, radiation sensitivity, location and nearness of radiation sensitive normal tissue region must be considered. In addition to these are the physical and radiobiological considerations presented here.

Some authors, particularly impressed with a single factor, e.g., depth dose, or oxygen effect, have advocated a single type of radiation over others, and have even cited "figures of merit", to support their convictions (138). One must caution against such approach, particularly if it is not clear from the presentation how the "figure of merit" was derived.

In order to aid radiotherapists we have summarized the arguments given in this paper in TABLE II. Five radiations were ranked on a scale of 1 to 5, 1 being "best" and 5 least desirable. The properties ranked were suitability of depth dose, minimal entry or exit surface effect, minimal oxygen effect, minimal repair in tumor, minimal response of cells in different physiological states.

At the time of this writing only low energy (10 MeV/nucleon) neon ions and only low intensity (<5 rad/hour) pions are available for experimental studies. Further experiments in radiation physics and radiobiology are needed for better understanding of several factors and only eventual therapeutic trials can supply full evaluations. It appears to these authors that acceleration of heavy ions, e.g., of neon and further assessment of pion beams might be very worthwhile for the future of radiation therapy. In the meanwhile we have had many years of experience with helium beams and as described below, these are being proven to be versatile for radiotherapy.

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TABLE I

Some Oxygen Enhancement Ratios (OER'S) Found Experimentally For Mammalian Cells

Cell Strain	Radiation Used	OER	Remarks
Human kidney cells (T_1) irradiated in vitro cultured in vitro	250-kVp x rays	2.5 ± 0.2	J. J. Broerse and coworkers (62)
	fission neutrons; 3 MeV neutrons; 14-MeV neutrons (all on tissue equivalent support)	1.6 ± 0.2	OER for heavy recoil component was found lower than that for secondary proton component
	neutron irradiation on carbon support	1.1	see Figures 6 and 8a
	accelerated carbon, oxygen, neon, argon particles	1.1	P. W. Todd (42,43,60,61) see Figures 7 and 8b
	accelerated 910-MeV helium ions at Bragg peak	1.8	M. Raju and coworkers (67)
	pi mesons at ionization peak	1.8	M. Raju and coworkers (68)
Ehrlich ascites tumors irradiated in vitro cultured in vivo	200 kVp x rays	3.1	Hornsey and Silini (69)
	fast neutrons	1.8	
Mouse ascites leukemia irradiated in vivo cultured in vivo	fission neutrons	1.2	Berry and Andrews (64)
irradiated in vitro cultured in vivo	cyclotron accelerated helium (86 keV/μm)	1.1	Berry (65); see Figure 8a
	deuterons (14 keV/μm)	2.0	
Mouse ascites lymphoma irradiated in vitro cultured in vivo	cyclotron accelerated 910-MeV helium ions at Bragg peak	1.5 - 1.7	Feola and coworkers (70)
	Boron-11; neon-20	about 1.0	Sillesen and coworkers (102)
	Pi mesons	1.8	Feola and coworkers (71)

*- Pi mesons are exceedingly difficult to test at present since these are available only at very low dose rates of 5 rad/hour, or less. Vicia faba roots tested with pi mesons yield an OER of about 1.5 (71) as they do with fast neutrons (74).

TABLE II

Ranking of Therapeutic Suitability
of Five Different Radiations

Radiation	Ratio of Depth Dose To Surface Dose	Minimal Oxygen Effect	Repair In Tumor	Physiologic Variation In Tumor	Minimal Lesion To Skin At Entry And Exit
A. Tumor or lesioned region: 1 cm diameter					
cobalt gamma ray	4-5	5	5	5	4
15-MeV neutron	4-5	2	2	2	5
pion	3	3	3	3	1
helium ion	2	4	4	4	2
neon ion	1	1	1	1	3
B. Tumor or lesioned region: 8 cm diameter					
cobalt gamma ray	4-5	5	5	5	4
15-MeV neutron	4-5	2	2	2	5
pion	1-3	3	3	3	1
helium ion	1-3	4	4	4	2
neon ion	1-3	1	1	1	3
C. Tumor or lesioned region: 20 cm diameter					
cobalt gamma ray	4-5	5	5	5	4
15-MeV neutron	4-5	2	2	2	5
pion	1	3	3	3	1
helium ion	2-3	4	4	4	2
neon ion	2-3	1	1	1	3

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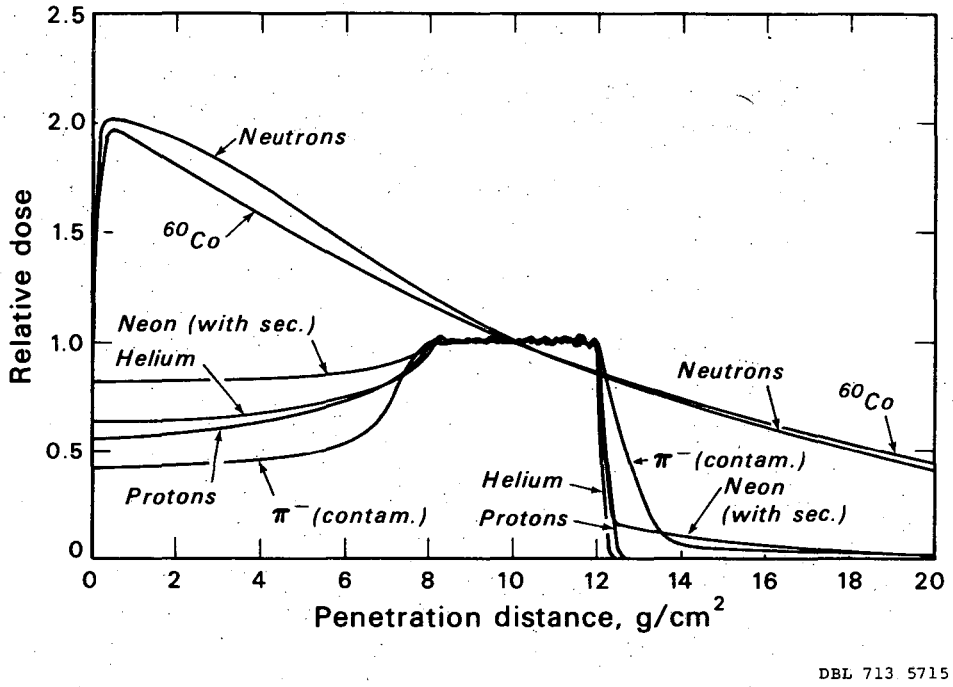
Figure 1. Depth dose curves calculated or measured for various radiations in a hypothetical case.

The aim is to deliver unit dose to a region extending from 8 to 12 cm in depth. All the curves have been normalized to 1.0 at 10 g/cm^2, the assumed midline depth. A single beam, 10 cm in diameter, enters "tissue" at point "0"; the relative dose along its path through the "tissue" is indicated as a function of depth. The depth-dose distributions for the charged particle beams have been calculated with maximum dose region 4 g/cm^2 wide (from 8 to 12 g/cm^2 in penetration distance); by the use of appropriate energy distribution the depth-dose curves for charged particle beams can be made to have this characteristic "flat-top" shape. The negative pion beam includes the influence of 5% electron and 5% muon contamination. The neon beam depth dose curve is for the indicent primary beams and for the estimated secondary charged particles produced in nuclear interactions. With the exception of the build-up region, the cobalt-60 and neutron curves are based on data from references 13 and 14. Helium and neon depth dose curves were calculated from data based on information of the type shown in Figure 2; the pi meson curve was calculated from data of the type shown in Figure 3.

In order to deliver unit dose at a depth of 10 cm, in the cases of both neutrons and gamma rays the entry doses must be about two units; the exit doses for both these radiations are also uniformly high. In contrast, for heavy particles and pions, the entrance doses are lower than the "tumor" doses, and the exit doses are negligibly low (in this example, pions have the lowest entry dose).



DBL 713 5715

Fig. 1

Figure 2. Calculated depth doses due to parallel beams of strictly monoenergetic accelerated helium ions and neon ions in water. The energy of neon ions is about 340 MeV/nucleon, and that of helium ions a- about 131 MeV/nucleon. Note the sharp rise in dose in the Bragg peak region. The neon Bragg peak rises in a significantly narrower region than that of helium ions. Localized particle induced depth lesions can be best delivered by accelerated nuclei: pions, neutrons, and gamma rays scatter significantly more.

The depth dose distributions are modified due to ionization by secondaries produced by collisions with atomic nuclei of tissue. Calculations show that the contribution due to secondaries is small for neon, but becomes very important as the atomic number of accelerated particles increases.

These curves are based on calculations by Litton (18) and Curtis (21). Those for helium are amply verified by experiment. It will be necessary to experimentally test the neon data when appropriate accelerated particles become available.

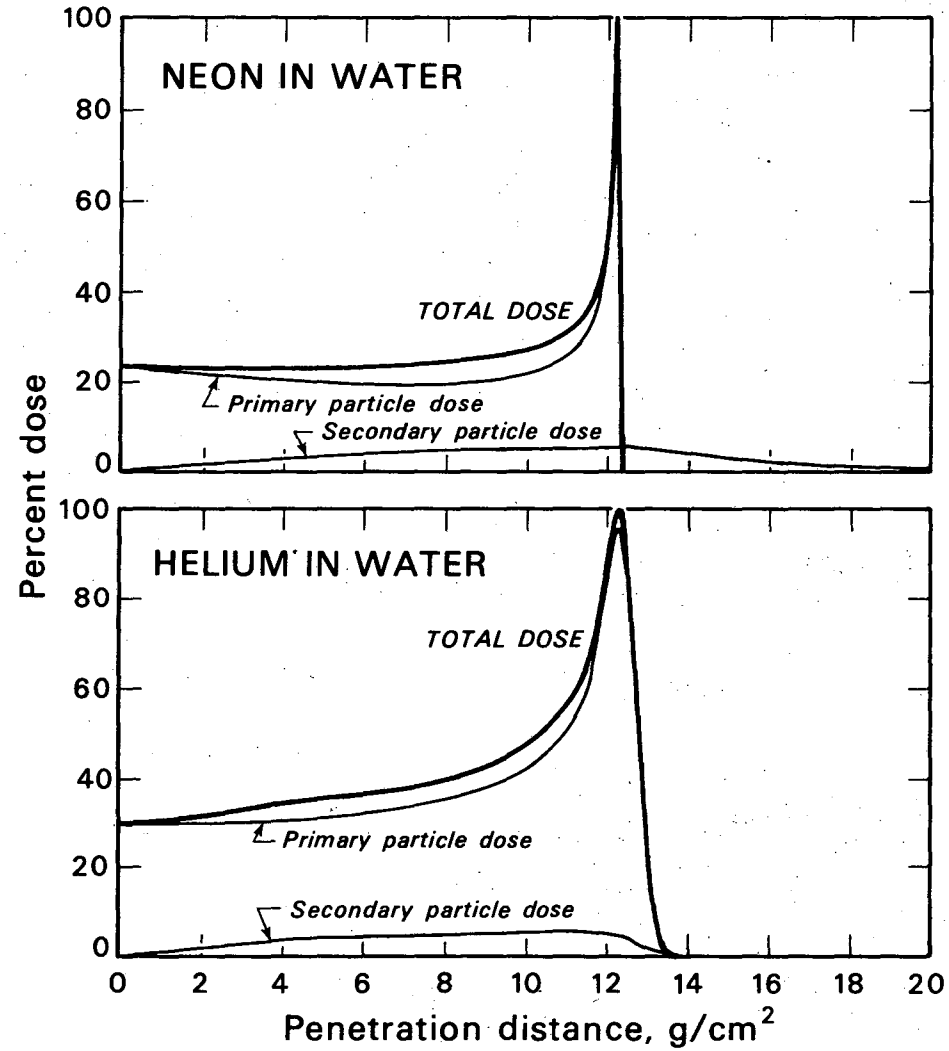


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Fig. 2

Figure 3. Depth-dose distributions of 65-MeV positive and negative pion beams (pure pions) in water. The increase in dose for the negative pion beam at the peak is due to the star events except for the small contribution due to μ^+ and e^+ resulting from positive pion decay (57).

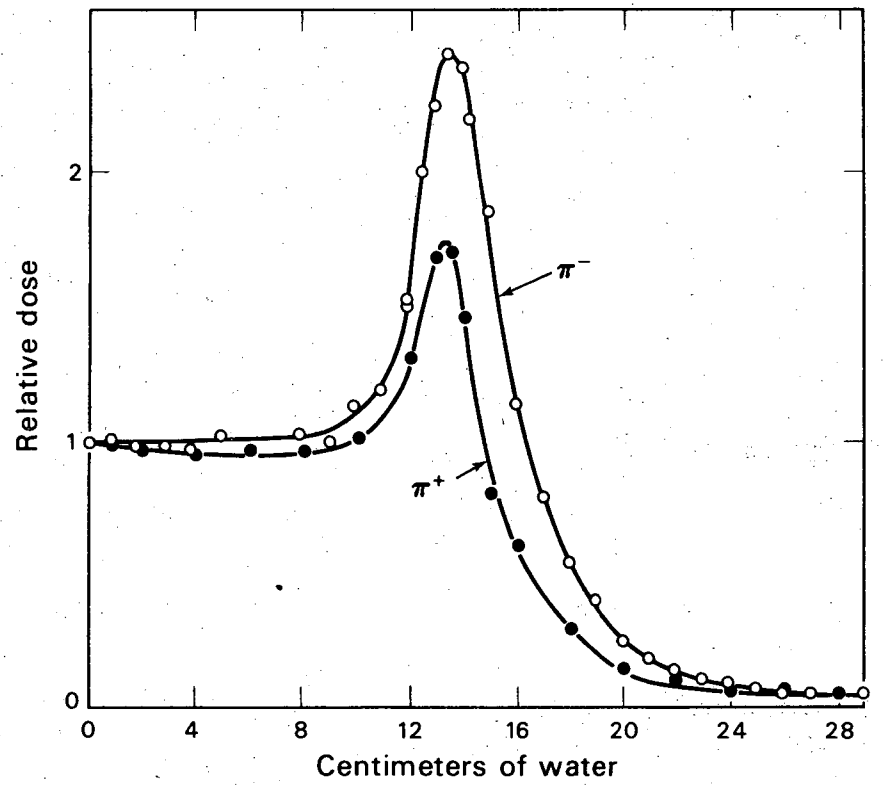

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Fig. 3

Figure 4. Percent of particles that survive a 10-meter flight path without decay. (Courtesy of D. E. Lobb, University of Victoria, British Columbia, Canada)

Figure 4

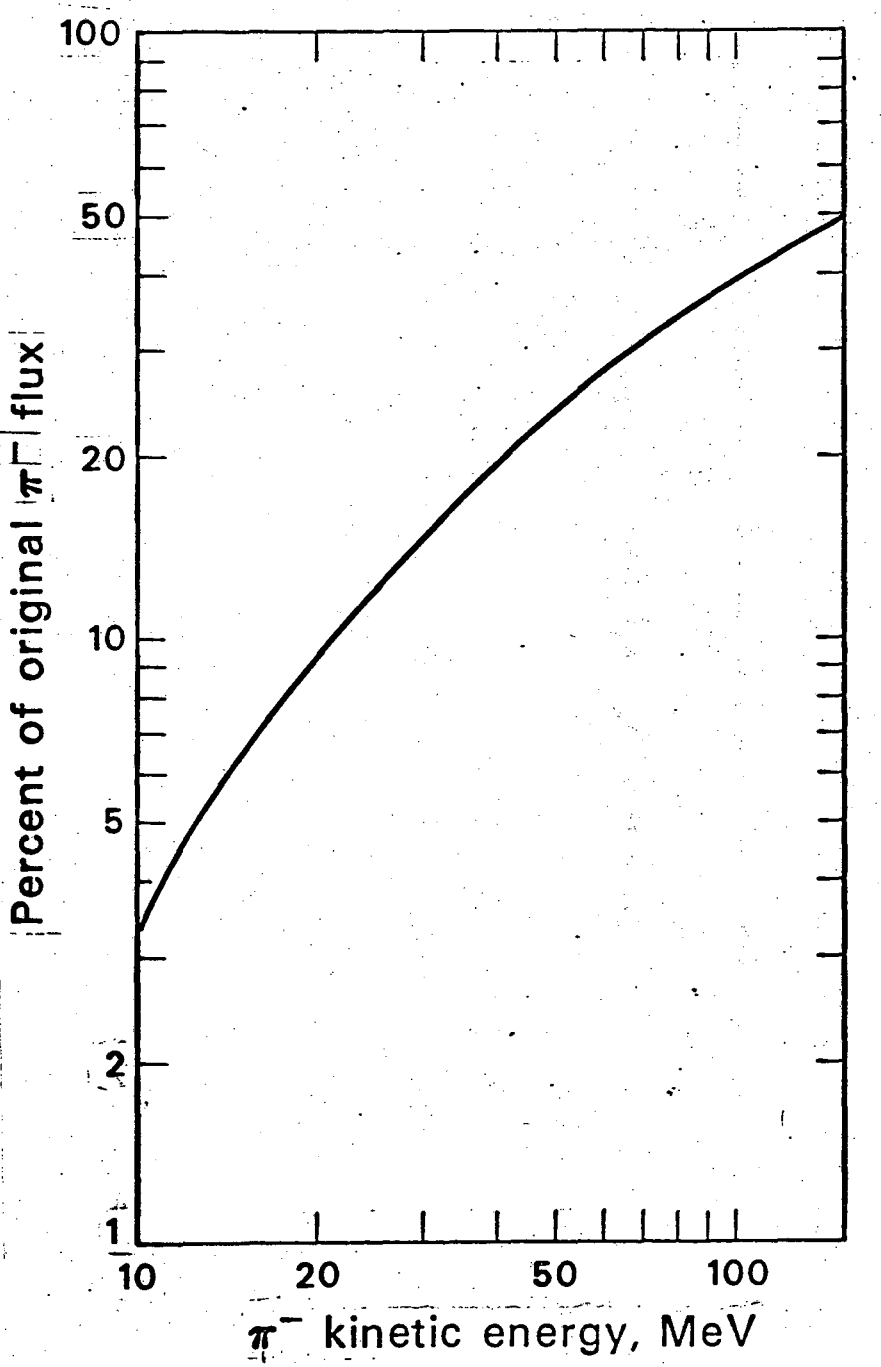

Figure 5. Isodose curves calculated for three possible treatments of a "tumor" 8 cm in diameter at the center of a phantom (20 x 30 cm oval). 5a shows the isodose curves for cobalt-60 gamma rays, using a 10 x 10 cm field, 75 cm SAD, 360° rotation (this was redrawn from K. Tsien and coworkers (139)); this isodose distribution is typical of those achieved with cobalt gamma rays or 14-MeV neutrons. 5b was calculated for helium-4 ions, using an 8 x 8 cm field, 100% region extending from 6 to 19 cm, and 360° rotation. 5c was calculated for helium-4 ions just as in 5b, except that the 100% dose region was narrowed to a width of 8 cm; the depth of penetration was adjusted so that the "tumor" was always within the 100% dose region by using a compensating filter to minimize the dose beyond the tumor. Isodose distributions in 5b and 5c are typical of those that can be achieved with protons, heavy ions, or pi mesons. The rapid fall of the dose at the edge of the "tumor" region allows a much reduced dose and smaller integral dose to the surrounding normal tissues than is feasible with gamma rays or neutrons.

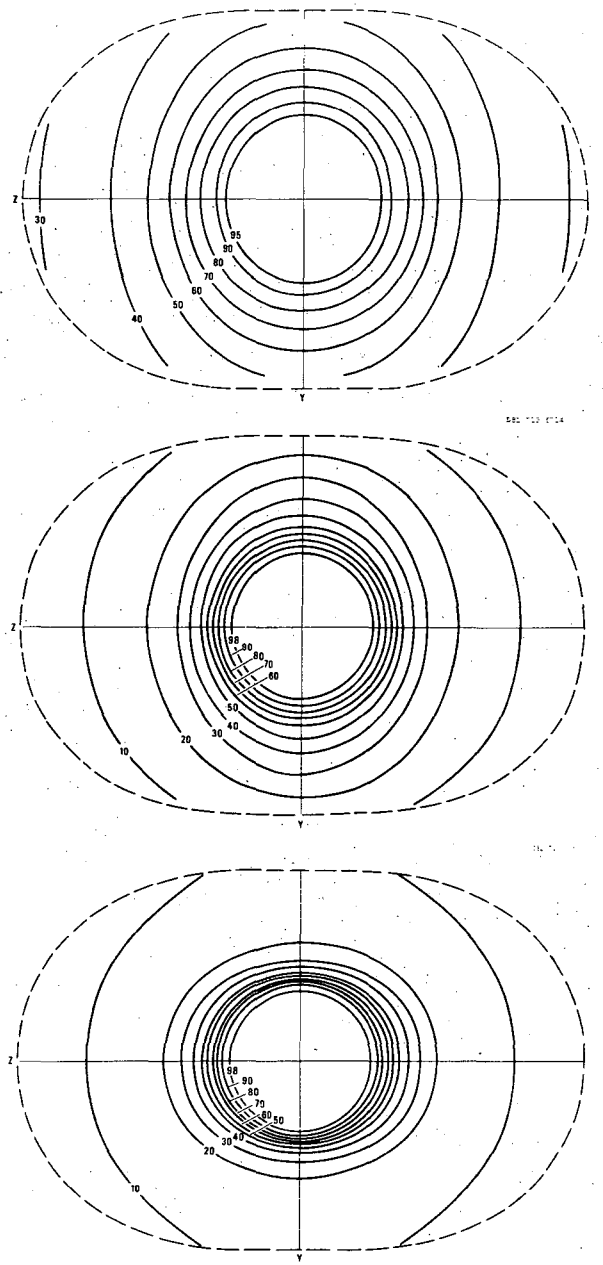

Fig. 5

Figure 6. Effects of irradiation on the capacity for clone formation.

1.	5.2 MeV alpha particles	85.8 keV/μ tissue
2.	8.3 MeV alpha particles	60.8 keV/μ tissue
3.	26.8 MeV alpha particles	24.6 keV/μ tissue
4.	3.5 MeV deuterons	17.4 keV/μ tissue
5.	6.3 MeV deuterons	11.0 keV/μ tissue
6.	14.9 MeV deuterons	5.6 keV/μ tissue
7.	200.0 keV x rays	2.5 keV/μ tissue

As the LET of the particles increases, the cells become more and more sensitive to radiation. Survival curves at high LET are exponential functions of doses; at low LET multiple hits are required for inhibition of clone formation. (By courtesy of Barendsen, Walter, Fowler, and Bewley (59).)

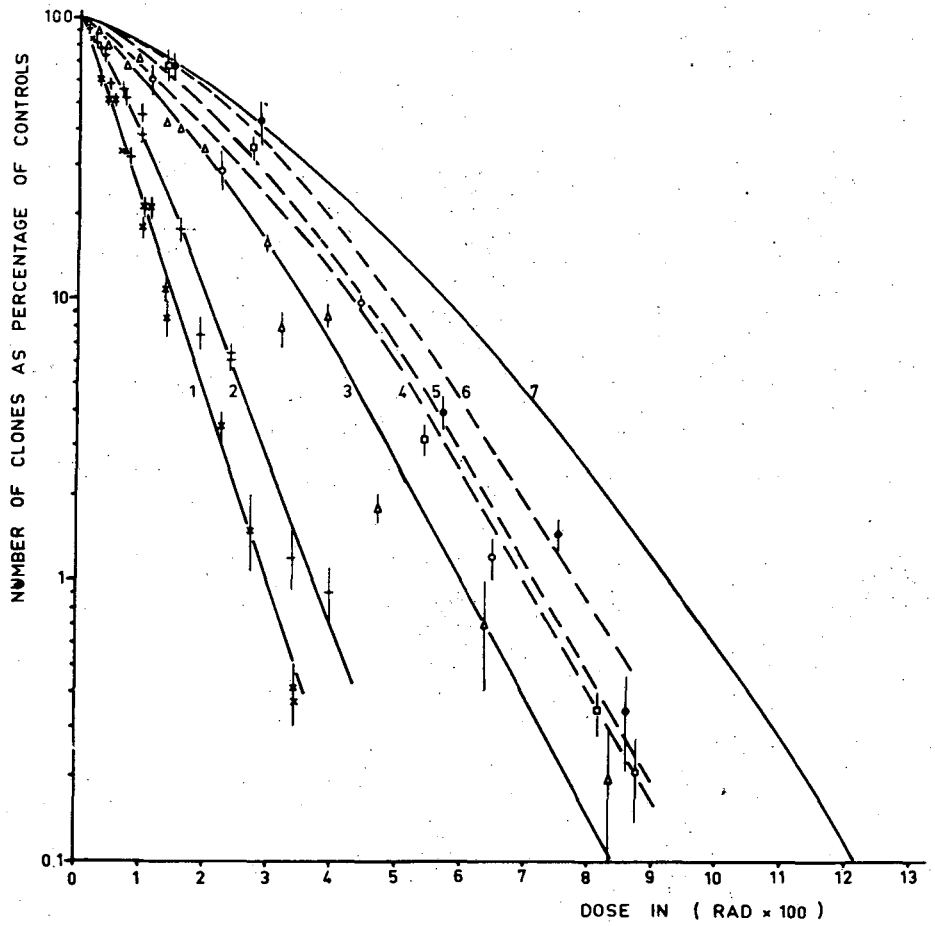

Fig. 6

Figure 7. Survival curves for cultured human cells exposed to nearly monoenergetic accelerated particles at the Berkeley HILAC under aerobic and anoxic conditions at 6.6 MeV per nucleon (5.7 MeV/nucleon for argon nuclei). Open circles, aerobic; open squares, anaerobic; solid circles, standard survival curve to x rays. (By courtesy of P. Todd, (42, 43); Figure 4 in (43).)

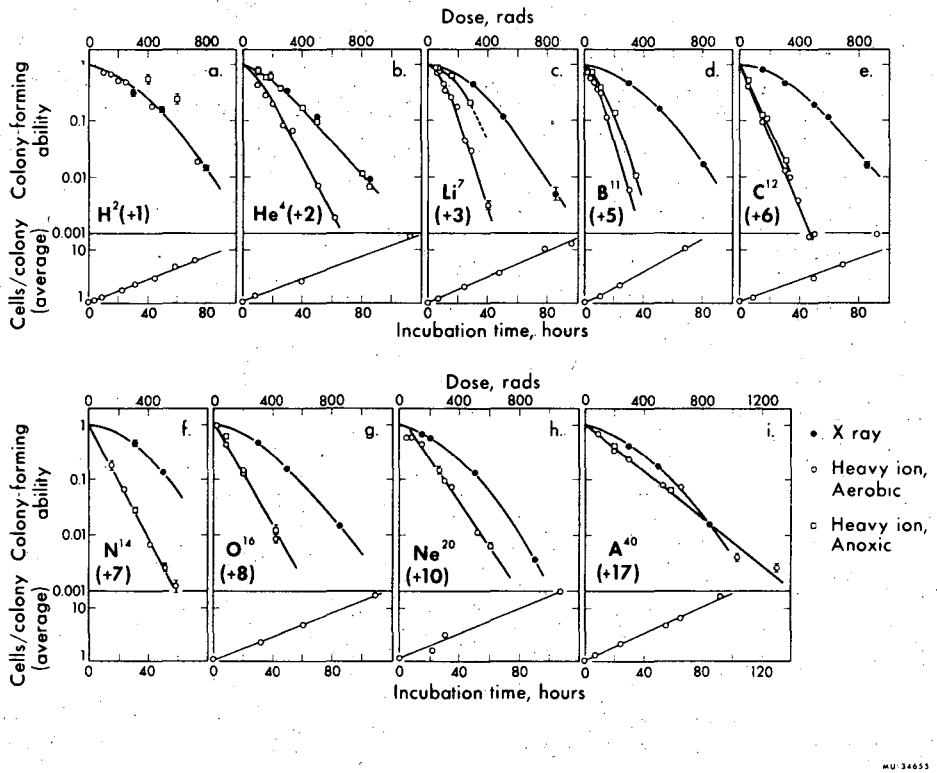

Fig. 7

Figure 8. OER values from track-segment experiments.

8a (top). Open circles, OER values obtained by Barendsen and coworkers for human kidney cells by exposure to x rays, deuterons, and helium ions at the Hammersmith cyclotron. Closed circles, OER values obtained by Berry and Andrews (64,65) for mouse ascites leukemia cells, irradiated in vitro and cultured in vivo

8b (bottom). Cross section ratios ($\sigma_{O_2}/\sigma_{N_2}$) calculated from the work of P. Todd (34,35). Open circles refer to "direct" effects, obtained from the slope of survival curves at low dose; closed circles, refer to reversible components responsible for "multi-hit" survival curves at low LET.

There is general agreement in the trend and values of OER and cross section ratios, though the reasons for minor differences remain to be clarified. (By courtesy of G. Barendsen, R. Berry, and P. Todd).

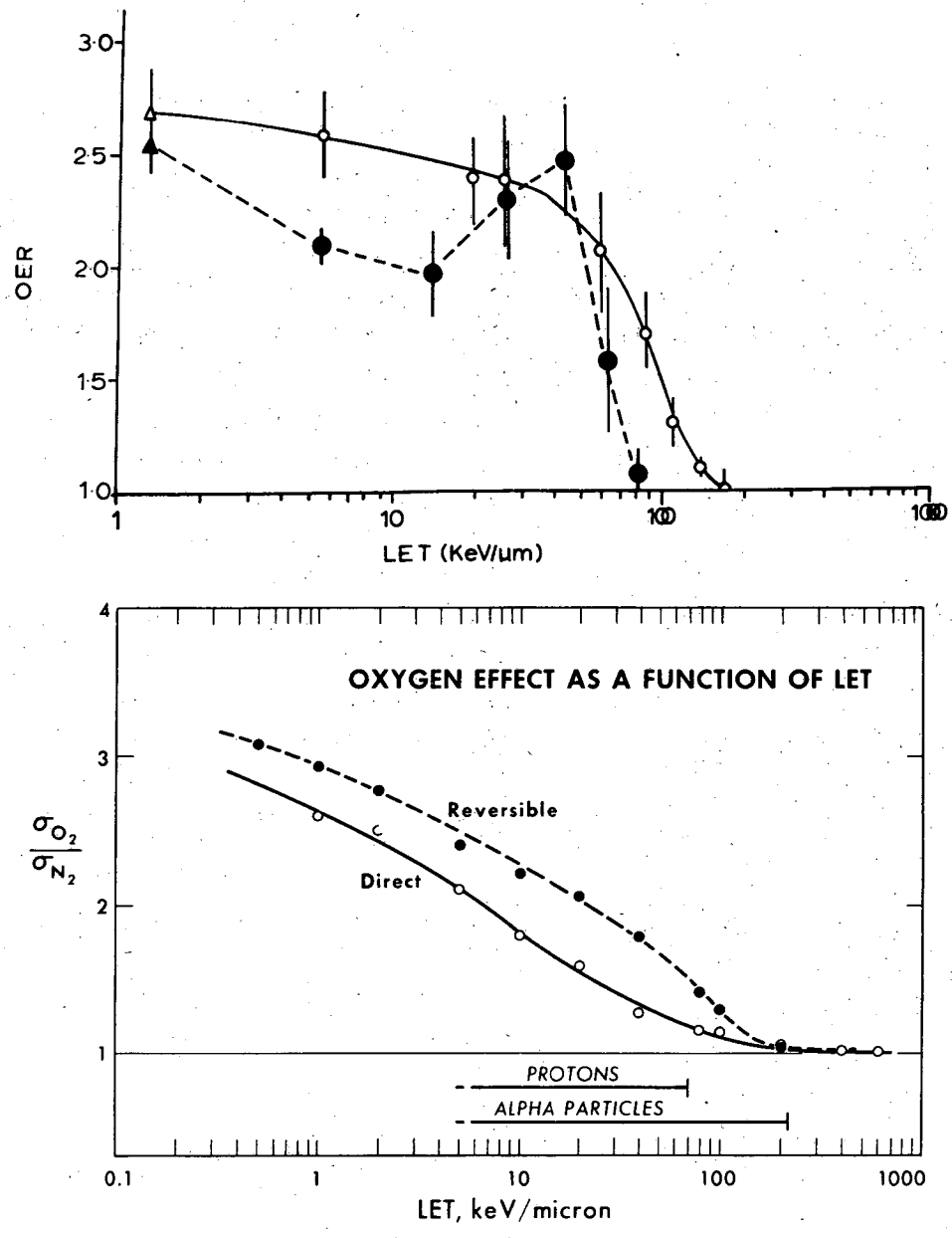

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Fig. 8

Figure 9. The variations in survival to a single dose of radiation as function of LET are summarized. Data are derived from several investigations each of which carried out radiation experiments on synchronized cell populations. The authors are indebted to R. Bird and J. Burki for use of this Figure (83).

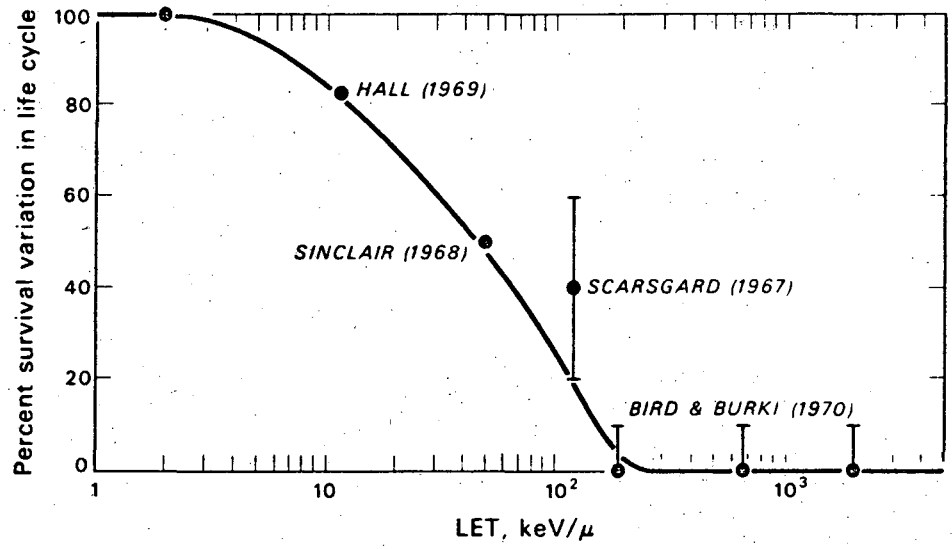

Fig. 9.

Figure 10. Survival curve of 6C3HED mouse lymphosarcoma cells irradiated in vivo (220 kV x rays) determined by endpoint dilution titration in mice. Each point represents the number of cells required to produce tumors in 50% of 30 mice, relative to the unirradiated control. The tumor cell population is shown to be heterogeneous; the main component, amounting to about 99% of the cells, exhibits a mean lethal dose of about 110 rad, whereas the remaining 1% of the cells are about 2-1/2 times less sensitive (mean lethal dose 260 rad). (Courtesy of W. E. Powers, L. A. Palmer, L. J. Tommach (97).)

Figure 10

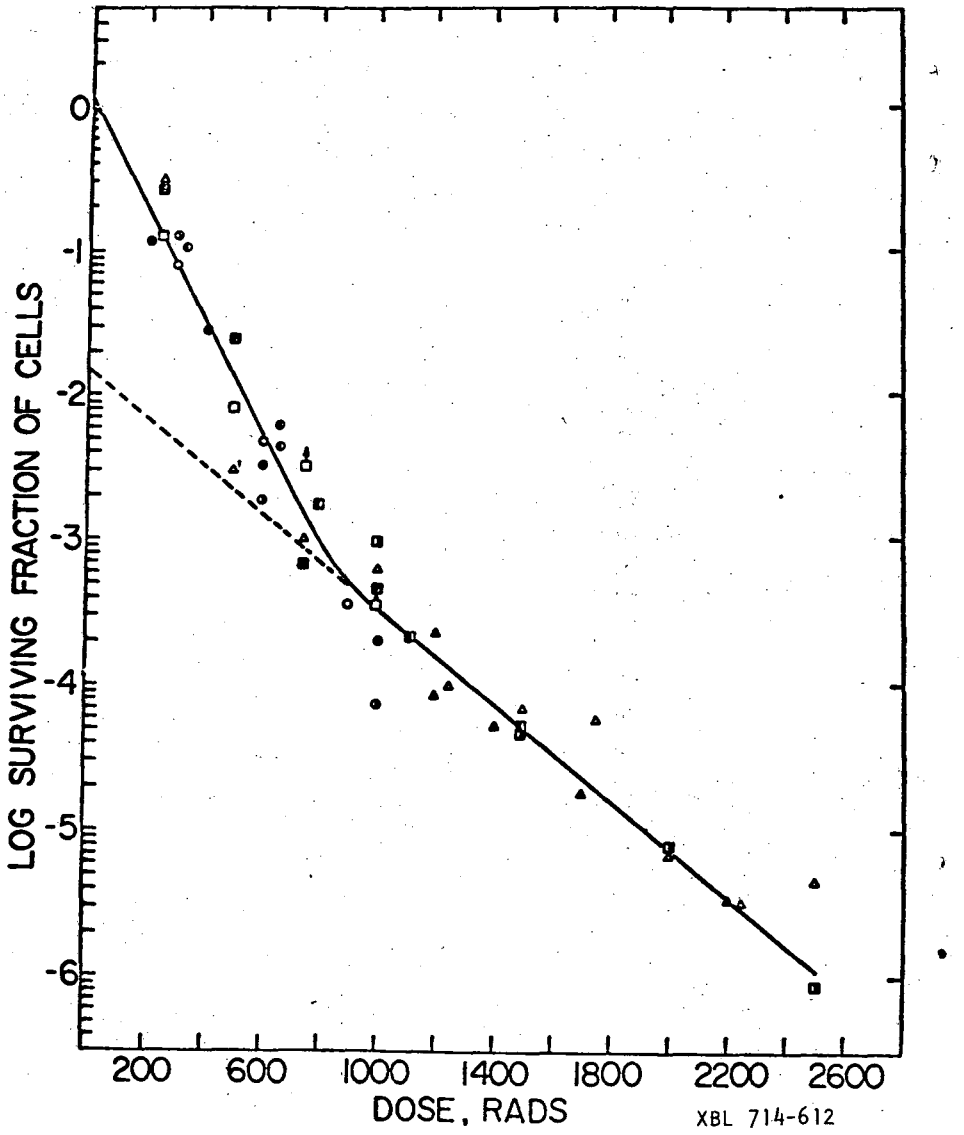

Figure 11. Survival curves obtained by 300-kV x irradiation of R-1 rhabdomyosarcomas growing in the flanks of rats, followed by excision of the tumor and plating of cells in vitro. Curves 2 and 3 are for tumors irradiated in living anesthetized and dead rats, respectively. Curve 1, included for comparison, represents the survival curve for cultured R-1 cells in equilibrium with air. The cells in anesthetized and in dead animals are anoxic; cultured cells have more oxygen available, and require less dose. (Courtesy of G. W. Barendsen and J. J. Broerse (106).)

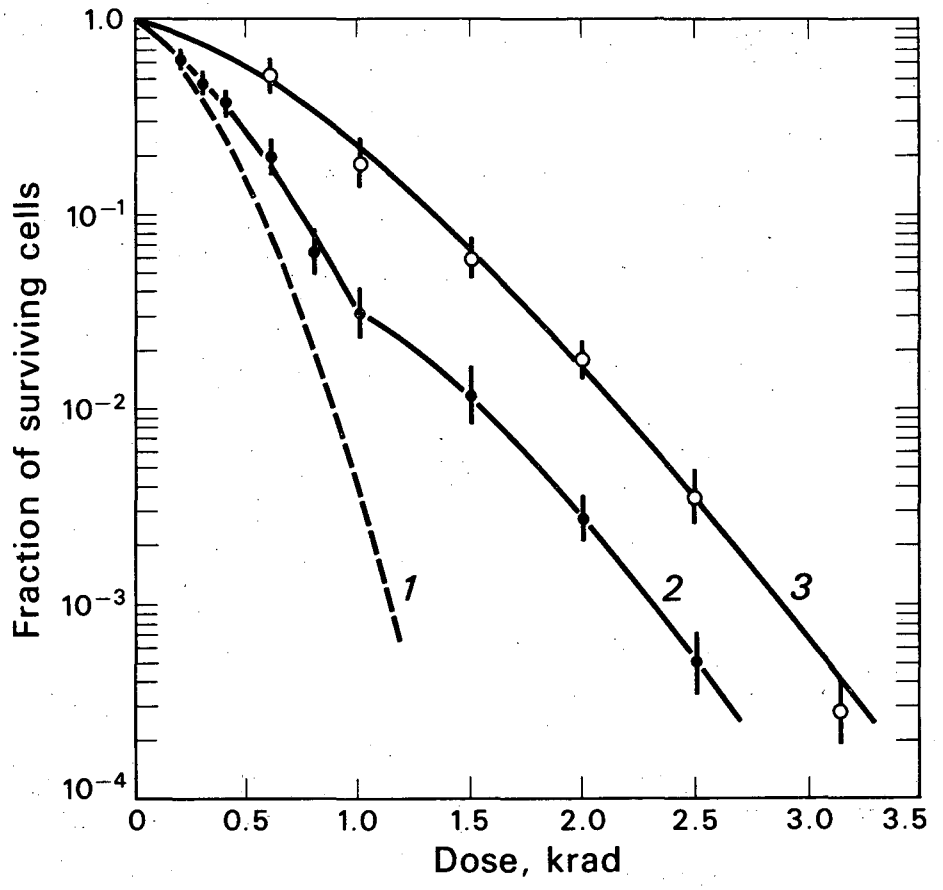

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Fig. 11

Figure 12. Model for calculating depth survival values.

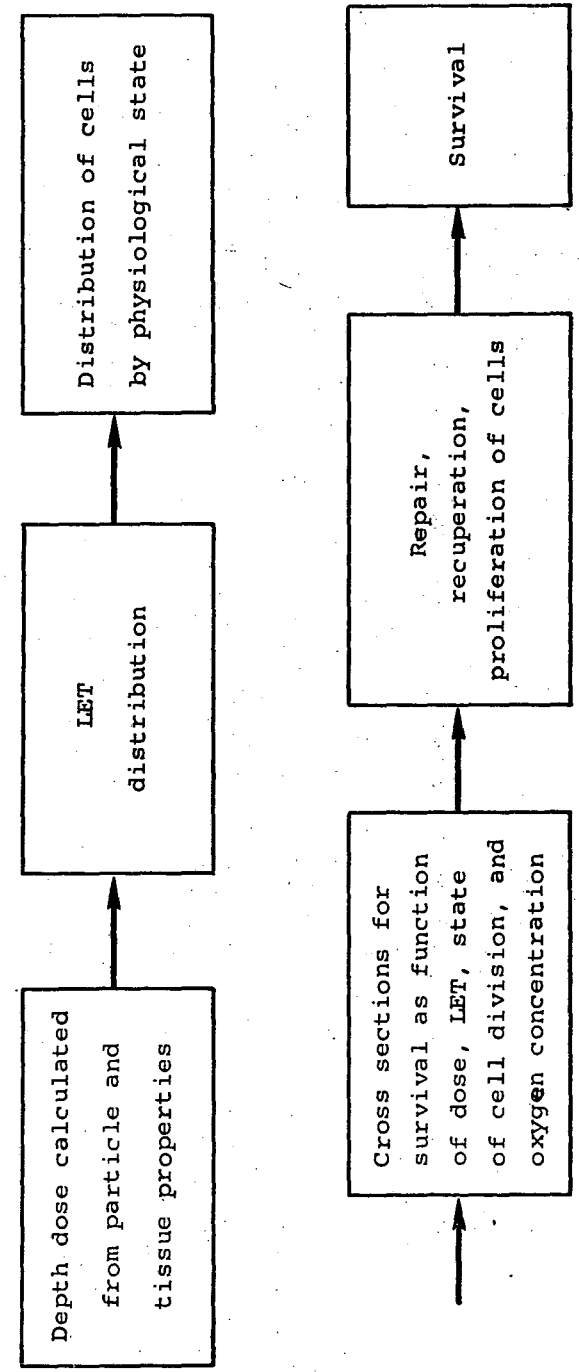

Fig. 12

Figure 13. Surviving fraction of cells with reproductive capacity as a function of depth from the anterior surface. The depth-survival values are calculated in a hypothetical tissue (refer to Figure 1 for depth-dose curves). The thickness of the body is assumed to be 20cm. Therapy is administered by cross-firing with single beams from right and left, and by use of appropriate particle energies.

Solid lines: survival level for fully oxygenated normal and/or tumor tissue (no anaerobic cells present). Dashed lines: survival level in a 4-cm "tumor" that, at start of treatment, contained 20% anaerobic cells and 80% oxygenated cells. It is assumed that a successful treatment schedule requires survival levels of 10^{-7} of less.

12a (top): Cobalt gamma rays delivered in 30 fractions. Survival fraction for fully oxygenated normal tissue regions is less (10^{-10}) than for tumor (10^{-7}). With 20% anaerobic cells, 10^4 times more tumor cells survive.

12b (middle): Accelerated helium-4 ions delivered in 5 fractions. Cells in normal tissues, outside of the tumor region, have good survival (nearly 10%). In the tumor, survival is the required 10^{-7}. When 20% anaerobic cells are present in the tumor, survival jumps to 10^{-3}.

12c (bottom): Accelerated neon ions delivered in 5 fractions. For fully oxygenated tissues, the survival fractions in tumor are 10^{-7} and in normal tissues 2×10^{-2}. The presence of 20% anaerobic cells in the tumor hardly makes any difference; only 10^{-6} survive.

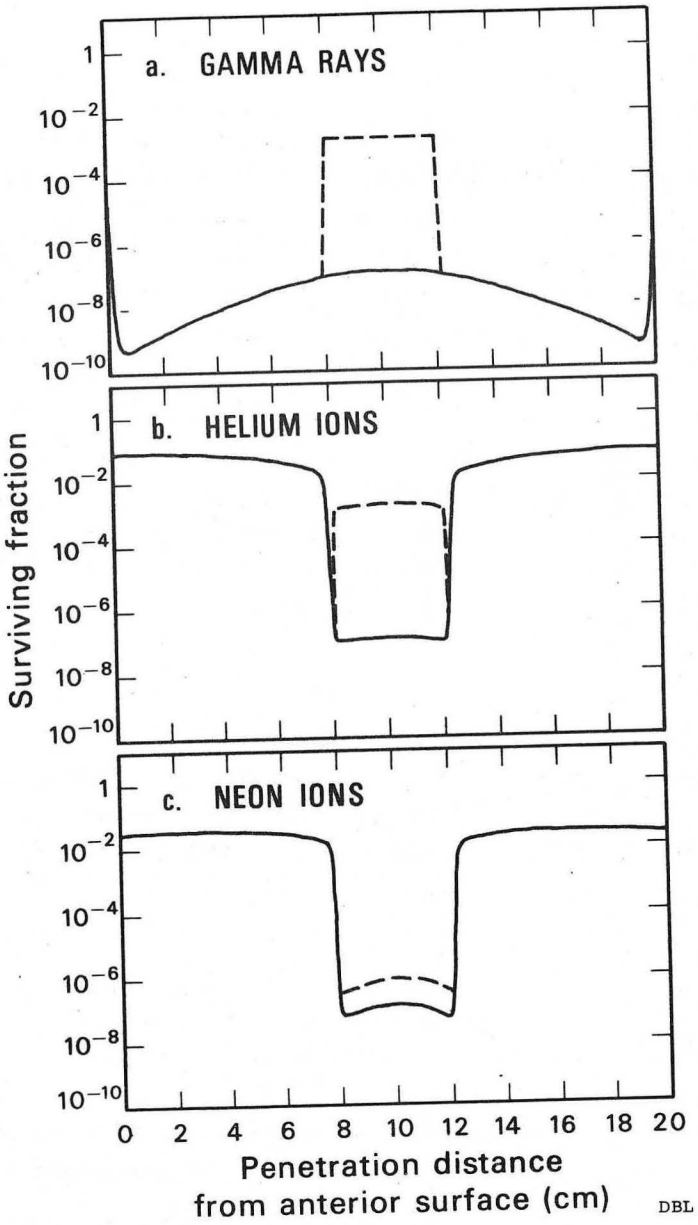

Fig. 13

Figure 14. Patient with pulmonary metastases seated in an especially designed positioning chair in preparation for treatment with 910-MeV alpha particle beam. Lined up from left to right in front of the patient are: beam source (coming from 184-inch synchrocyclotron); two ionization chambers; aperture block (collimator); patient in chair which can be rotated or inclined to desired position and is equipped with immobilization straps, overhead hand-bar, and remote control relay system. The ridge filter which is used for the Bragg-peak treatment of this patient has not yet been put into place -- it is seen on the floor just in front of the patient's feet.

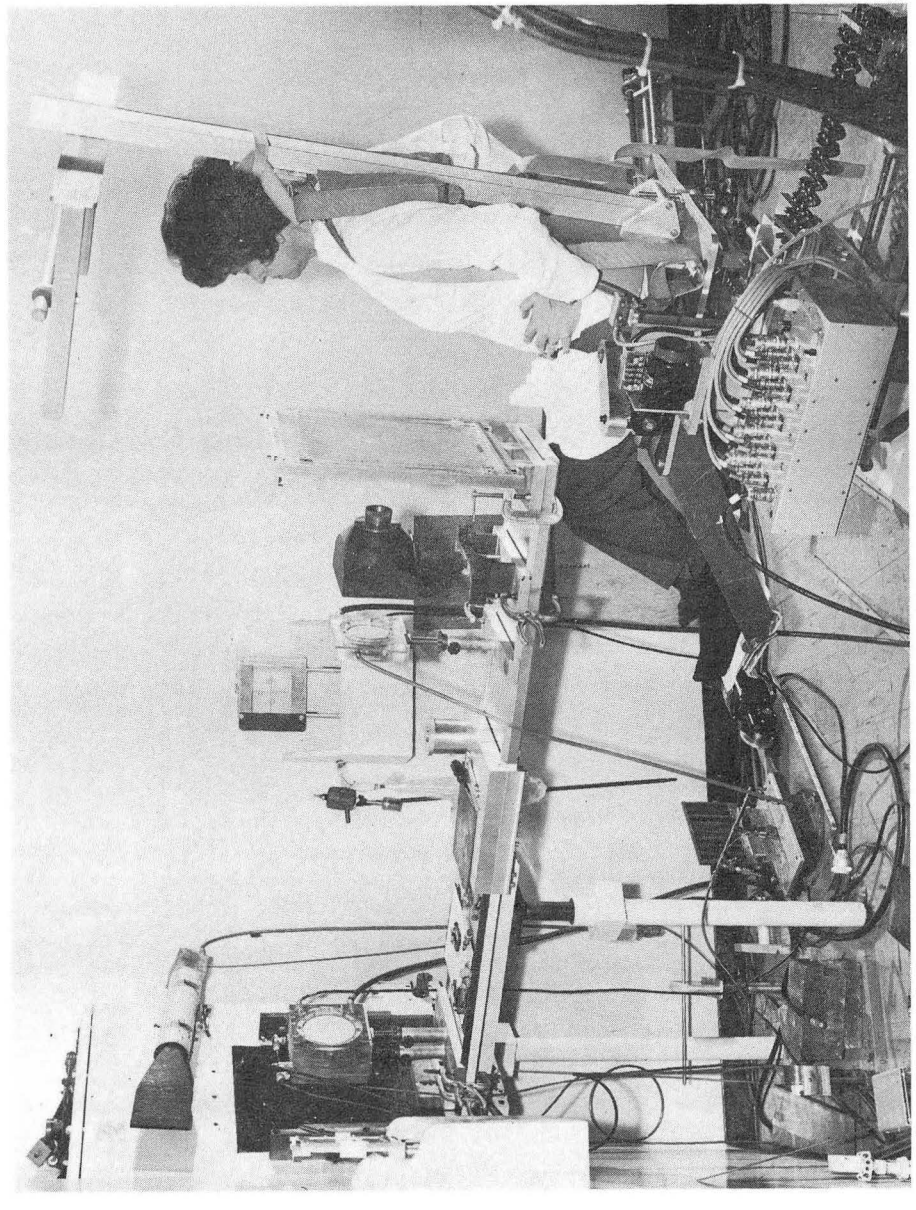

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Fig. 14

Figure 15. X-ray localization pictures taken during alignment for Bragg-peak irradiation of the anterior nodule in the right lung. On the left is a right lateral view, and on the right a 20° anterior oblique view, showing the cross hairs centered on the nodule. A 38-mm circular aperture was used to cover the lesion and a 5-mm margin around it. The Bragg peak was adjusted to terminate at a depth 6 centimeters beneath the skin surface by using absorbers and a moving ridge filter. (Note: see also the helium-ion curve in Figure 1 which illustrates how the Bragg peak is broadened with the use of ridge filters.)

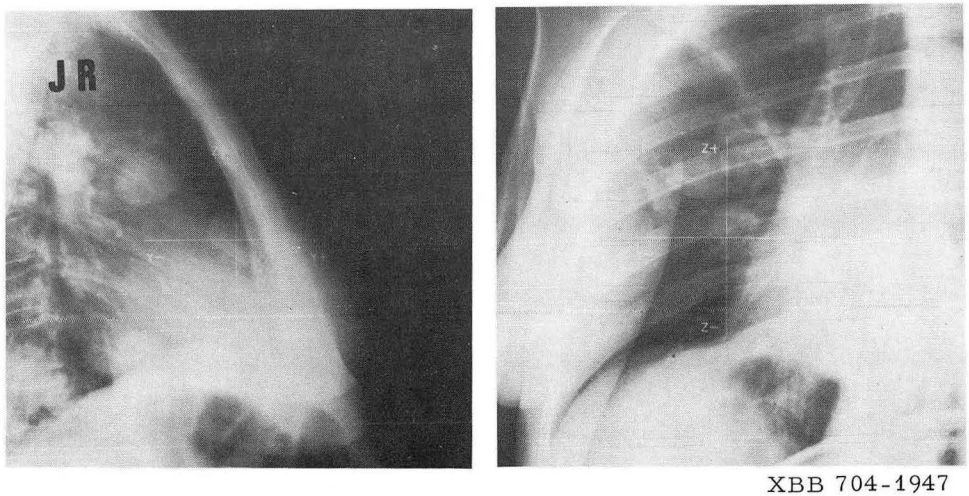

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Fig. 15

Figure 16. Carbon-11 positron scanning pictures confirming Bragg-peak dosimetry. The patient was taken as quickly as possible from the treatment cave to the positron scintillation camera room. An anterior view and a right lateral view of the chest were taken; tomographic scans were taken at the surface (far right circles in above sets of circles), and at depths of 1 inch (center circles) and 2 inches (far left circles). These show a clearly demonstrable area of induced activity in the anterior chest wall with a depth of 1-1/4 to 2 inches. The activated area was oval shaped with cephalo-caudal diameter of approximately two inches.

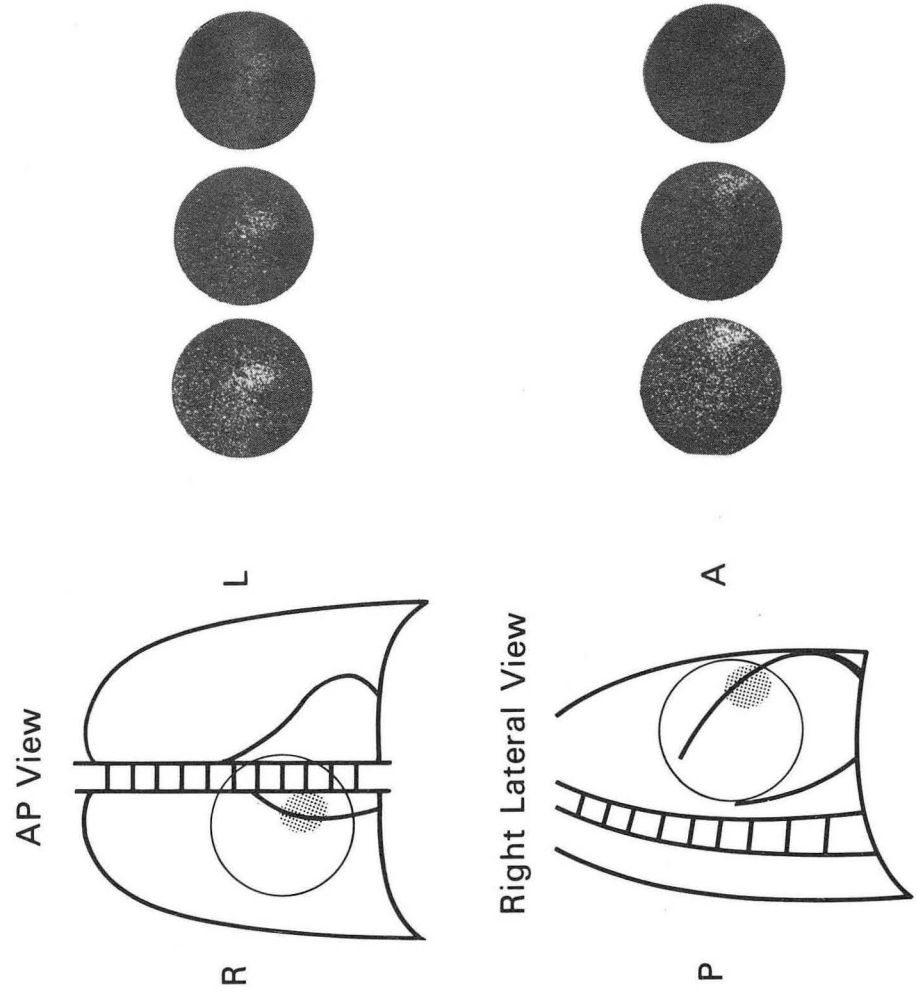

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Fig. 16

Figure 17. Chest x rays taken before treatment (April 4, 1970) and 40 days after treatment (May 14, 1970) showing decrease in size of the lesion treated with Bragg-peak heavy particles. See Figure 13 for position of Bragg-peak-treated lesion.

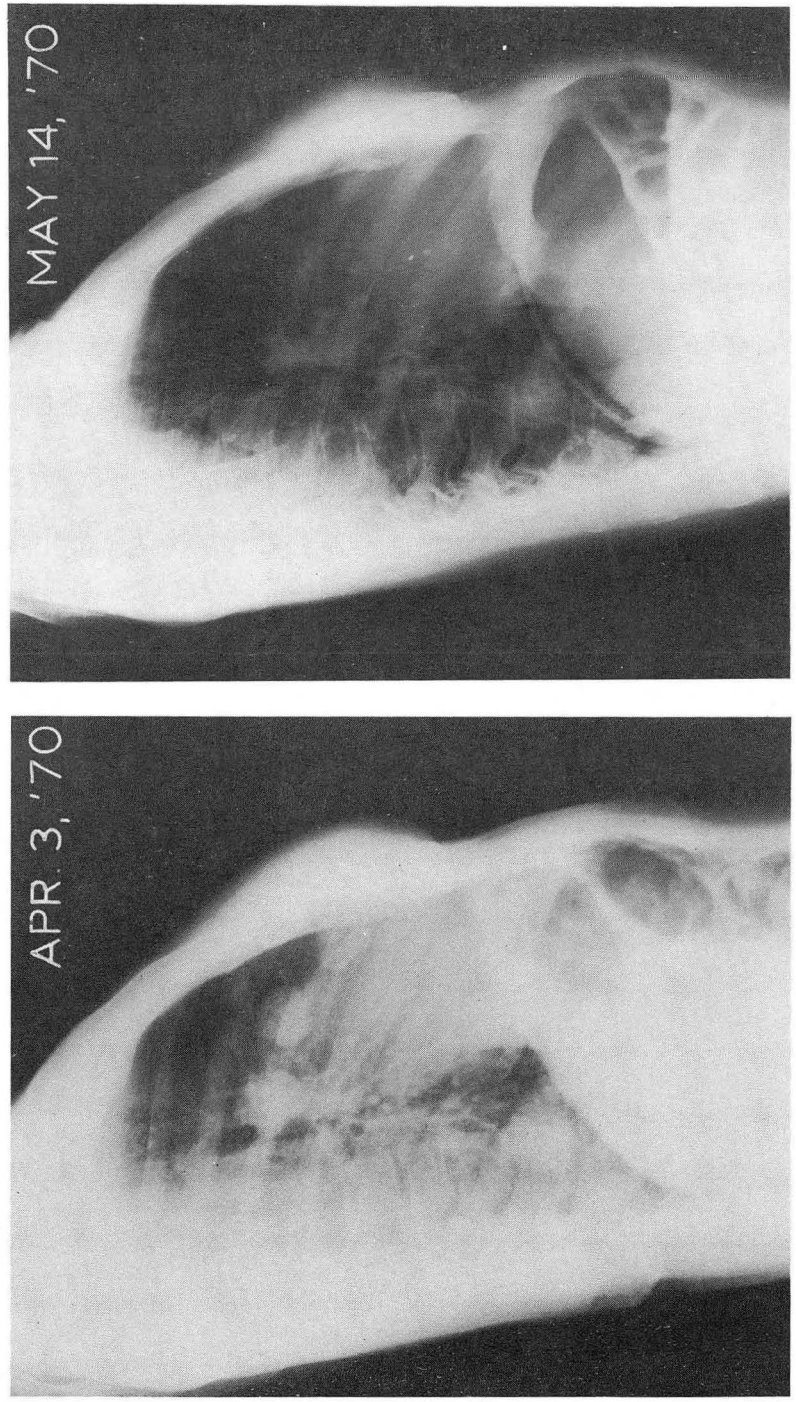

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Fig. 17

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