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MEDICAL USES OF ACCELERATORS

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ABSTRACT

A variety of particle accelerators have either potential or already demonstrated uses in connection with medically-related research, diagnosis, and treatment. For cancer radiotherapy, nuclear particles including protons, neutrons, heavy ions, and negative pi mesons have advantages compared to conventional radiations in terms of dose localization and/or biological effectiveness. Clinical evaluations of these particles are underway at a number of institutions. Accelerator-produced radionuclides are in widespread use for research and routine diagnostic purposes. Elemental analysis techniques with charged particles and neutrons are being applied to bone, blood, and other tissues. Finally, low-dose medical imaging can be accomplished with accelerated protons and heavy ions. The status and future of these programs are discussed.

INTRODUCTION

Particle accelerators, originally developed for physics research, are playing an increasingly important role worldwide in both routine medical applications and the testing of new medical techniques. Photon and electron beams produced by electron accelerators in the few hundred keV to 40 MeV range are in use at many medical centers for cancer radiotherapy. Accelerator-produced heavy particles including protons, neutrons, heavy ions, and negative pions are currently being evaluated for radiotherapy as a result of the improved dose localization and/or improved biological effect provided by these particles compared to conventional radiations.

Accelerators are also being used to generate both proton and neutron deficient radioisotopes for a variety of medical diagnostic procedures. Many of these are well-established; others are still in the research or evaluation stage. Isotopes with relatively short half-lives are needed to study dynamic processes within the body and must be produced either in the vicinity of their intended use or in large quantities to allow long-range distribution of useful amounts to medical centers. High-current accelerators are being developed to meet isotope production requirements.

Medically useful analyses of the elemental composition of various tissues can also be performed with particle beams using techniques such as particle-induced x-ray emission, neutron activation analysis, and muonic x-ray analysis. Images with unique characteristics can be obtained of various parts of the body using energetic protons and heavy ions. Disposable medical apparatus is often sterilized by radiation arising from beams produced by particle accelerators. Synchrotron radiation from electron storage rings can be used to produce lithographs of cell components and provide molecular details of radiation-induced changes in biological systems. Finally, it should be noted that accelerator development for physics research has resulted in technological spin-offs important to medicine such as radio-frequency hyperthermia techniques and the side-coupled cavity accelerating structure now in use in modern megavoltage electron accelerators for cancer radiotherapy.

In this article the focus will be upon some frontier developments in the medical uses of accelerators. Nuclear particle radiotherapy, practical

generation of some radioisotopes, imaging with particles, and several analysis techniques fall into this category.

PARTICLE RADIOTHERAPY

Background

There are approximately 800,000 new cases of cancer each year in the U.S. and about one-half of these receive radiation therapy, either as the sole modality or in conjunction with surgery or chemotherapy. Although tumor sites and incidence certainly vary on a geographic basis throughout the world, the magnitude of the cancer problem is clear.

The principal objective of radiotherapy is to destroy as many as possible of the diseased, malignant cells while keeping the dose to normal tissues as low as possible. An optimum radiation dose is needed which prevents recurrence of the disease but does not prevent repair of healthy tissue. The current practice of fractionated doses with conventional radiations is aimed at allowing normal cells to recover between fractions from sublethal damage while tumor cells, having lost some repair capacity, accumulate a lethal dose. Multiport treatments are used to spare normal tissues as much as possible.

Radiation therapy is particularly effective in those patients with localized tumors and treatments have greatly improved in the last 25 years. This improvement has been the result of 1) increased use of radiation sources (electron linacs, ^{60}Co) to produce beams of electrons, gamma rays, and x rays with more suitable physical dose distributions, 2) better understanding of cancer biology and the radiation tolerance of normal tissues, and 3) advances in treatment-planning capabilities. Nevertheless, it is estimated that approximately 100,000 deaths occur annually in the U.S. as a result of failure to eradicate localized tumors, i.e., about 25% of those treated with radiation (1). Any modality that will enable the radiotherapist to increase the effective radiation dose to the tumor while maintaining or reducing the effective dose to critical normal tissue will enhance control of large lesions.

The radiotherapy success rate may be increased by 1) improving dose localization, thereby sparing normal tissue which is often the limiting factor in conventional treatments, and 2) improving the biological effect

of the delivered dose. Either of these may result in an increased differential between damage to tumor tissue and damage to normal tissues. Nuclear particles including protons, neutrons, heavy ions, and mesons provide one or both of these effects and are currently being clinically evaluated at various institutions throughout the world. The following terms are used to discuss relative merits of the radiations.

DOSE Dose is the mean energy absorbed per unit mass by the irradiated material, and dose is usually measured with an ion chamber. The unit of dose is the rad (100 ergs/gm) or gray (1 joule/kg).

RBE Relative Biological Effectiveness (RBE) is a measure of the relative effectiveness of different radiations for producing a given effect, and is defined as the ratio of the dose required of a standard radiation (e.g., ^{60}Co source) to the dose required of the radiation under consideration for producing a given biological effect, e.g., 10^3 cell survival.

OER Oxygen Enhancement Ratio (OER) is the ratio (for the same radiation) of the dose required to give an effect under anoxic conditions to the dose required to give the same effect under oxygenated conditions.

LET Linear Energy Transfer (LET) is very similar to stopping power, dE/dx , and is usually expressed in keV/ μm .

Electrons, x-rays, gamma rays, and neutrons have essentially exponential depth-dose distributions implying maximum dose near the surface of the skin, moderate dose at the tumor location and significant exit dose. Improved dose localization may be achieved using charged particles heavier than electrons such as protons, heavy ions, and negative pi mesons. Some characteristic dose distributions are shown in Fig. 1. The depth-dose curve of heavy charged particles has two portions, an initial relatively low-dose plateau region, and a high-dose terminal peak (Bragg peak) in the stopping region. This occurs because dE/dx varies approximately as $\frac{1}{v^2}$, resulting in a proportionately greater amount of energy absorbed per unit volume of tissue near the end of range of the particles. By time-varying the momentum of charged particle beams, the depth-dose distribution can be modulated to encompass a particular tumor. Increased localization of the dose to the tumor volume implies that higher doses can be delivered, thus increasing the probability of destroying all tumor cells. The sharpness of

the edges of the three-dimensional dose distribution depends upon multiple scattering effects, range straggling, the momentum spread of the beams, and the dose resulting from any long-range secondary particles.

A number of studies have established that biological damage depends upon more than the absorbed dose; the energy deposited in sites with dimensions the order of micrometers or perhaps even nanometers is crucial in determining biological effect. Cells are damaged by the absorption of ionizing radiation through a complex sequence of physical, chemical, and biological processes; one such process is the induction of breaks in a DNA molecule through ionization. A heavily ionizing (high LET) particle, although perhaps short range, stands a better chance of producing multiple breaks than a lightly ionizing (low LET) particle. Thus, in addition to the amount of energy deposited per gram, the biological effect depends strongly on the microscopic manner in which the energy is deposited.

Several radiobiological effects common to high-LET radiation may act to increase tumor cell killing: (a) Many tumors contain hypoxic cells apparently as the result of an oxygen-deficient state arising from the tumor outgrowing its blood supply. These cells are up to three times more radiation-resistant to x rays than oxygenated cells (see definition of PBE). High LET-radiation has been shown to be more effective in killing these hypoxic cells than low-LET radiation. (b) Variations of cellular radi sensitivity within cell-cycle phases have been shown to be less marked with high-LET radiation; and (c) tumor cells with a high capacity for repair of sublethal damage may be inactivated (2).

In terms of biological effectiveness, radiation may thus be broadly classified as low LET (x rays, gamma rays, electrons, protons, and negative pions in their plateau region); or high LET (neutrons, heavy ions, and pions in their stopping region). The relevant physics will be discussed in later sections. Both PBE and OER are functions of LET as shown in Fig. 2. The PBE increases with increasing LET up to some maximum (100-150 keV/ μ m) after which saturation (overkill) effects occur. The OER is near three for low LET radiations and decreases to near one for very high LET values. The measurement of LET distributions is called microdosimetry and is done with special proportional counters with low pressure gas simulating tissue dimensions of the order of 1 μ m. Conventional radiations are low LET, i.e., less than 10 keV/ μ m, whereas some of the particle beams are high LET

radiations possessing a significant dose component with LET greater than 50 or 100 keV/ μ m.

Extensive radiobiology studies have been carried out with all of the particles. Various cell systems, multicellular tumor spheroids and both small and large animals (normal tissues and induced tumors) have been utilized with a variety of different end points to characterize the biological effects of the beams. Both single dose and fractionated experiments have been performed. For cells, both aerated and hypoxic conditions have been employed. These investigations have led to PBE and CER values as summarized in Fig. 3. The variability results from differences in beam parameters, biological systems, end points, dose rates, etc.

A large amount of literature exists regarding the physics, technology, radiobiological results, and clinical studies of the nuclear particle therapy studies. Comprehensive reviews with extensive references through 1979 are provided in (3,5).

Nuclear physics must make several important contributions to the production and evaluation of the particle beams. For secondary beams of neutrons and pions, attempts are made to optimize equipment in terms of radiobiological properties, dose distribution, and dose rate. Beam contamination (gamma rays for neutron beams, electrons and muons for pion beams) should be minimized. Thus, nuclear cross-section data and models are used to determine primary beam type and energy, production target material and length, shielding configurations, channel angle, and other parameters. For any of the particles to be used in a widespread fashion, there must be detailed economic, operating, and reliability considerations balanced against output beam quality.

Nuclear physics is also required to calculate dose distributions. Differences of about 5% in dose are clinically observable due to the slim margin between tumor control and normal tissue complications. The available nuclear data are not always sufficient for such precision. Calculations are needed to design hardware such as collimators and range shifters; the hardware configuration may change from patient to patient requiring the complete experimental documentation of three-dimensional dose measurements impractical. Finally, the generation and optimization of treatment plans providing the 3-D dose distributions in a specific patient,

taking into account body inhomogeneities, rely on nuclear data which are not known with sufficient accuracy in some cases.

Another role of nuclear physics involves the interpretation and calculation of microdosimetric distributions which are an important factor in determining biological effective dose. For neutrons, pions, and heavy ion beams, this effectiveness varies in depth and sometimes the transverse dimensions. The required data are the detailed energy spectra of all particles impinging on the biological system. Eventually, biological effect models and particle data may be sufficient to allow us to tailor mixtures of low and high LET radiations (protons and neutrons, for example) to preserve some dose localization and also obtain the desired biological effectiveness.

To fully realize the advantages of dose localization in charged particle radiotherapy, it is crucially important to tailor the dose distribution as precisely as possible to the tumor volume. This entails knowing with considerable accuracy both the usually irregular contours of the tumor and the nature of the inhomogeneities (bone, air spaces, etc.) between the skin surface and the tumor. The advent of computerized tomography (CT) has revolutionized diagnostic radiology and is now used routinely to identify tumor volume and inhomogeneities in the heavy charged particle programs. In this technique, detectors measure x-ray transmissions through small slices in the body providing photon linear attenuation coefficients which can be converted to particle stopping powers. Computer algorithms are used to produce three-dimensional density distributions of that portion of the body to be irradiated.

Protons

Proton beams ranging in energy from 150 to 250 MeV (range in tissue from 16 to 35 cm) are of interest in radiation therapy. As a result of their definite, yet adjustable, range and minimal multiple scattering, proton beams can be used to precisely and selectively irradiate tumor volumes with very small doses to surrounding normal tissue. Using small collimated beams, areas with radii as small as 4 mm may be addressed. Statistical fluctuations in energy loss (range straggling) cause a path length spread of about 1%.

For protons of energies near 200 MeV, 96-98% of the dose is due to energy loss by ionization, a physical process very well understood; the remainder comes from nuclear interactions, yielding recoil nuclei, fragments, and neutrons. Since the RBE of protons appears to be slightly greater than one, this small dose fraction may be significant. The nuclear interaction cross sections for tissue materials are not very well known in the 200 MeV region and hence a detailed calculation of the microdosimetric spectra cannot be made. Another source of uncertainty is the W value (energy/ion pair) for fast protons; this same problem exists with heavy ions and pions making absolute dose determinations uncertain by perhaps 5%.

All proton facilities currently in use for radiotherapeutic applications were originally constructed for physics research. The characteristics of these facilities are listed in Table I.

Table I

Proton Medical Accelerators

<u>Location</u>	<u>Accelerator Type</u>	<u>Typical Energy (MeV)</u>
Uppsala, Sweden	Synchro-cyclotron	187
Dubna, USSR	Synchro-cyclotron	90-200
Moscow, USSR	Synchrotron	70-200
Harvard, USA	Cyclotron	160

In the Soviet Union, a medically-dedicated proton accelerator is planned at a new oncological center in Moscow.

Primary particle beams are too small for large-field radiotherapy. Spreading in the transverse dimension is accomplished either by scattering or magnetic scanning, and spreading in depth is achieved by range modulation. In order to conserve beam particles and provide dose uniformity, the Harvard group uses a double-scattering technique in which a first scatterer is followed by an absorber removing the central portion of the beam; the resulting void is filled in by a second scattering foil. Uniform fields up to 27 cm in diameter utilizing 30% of the original

intensity have been obtained (6). At Uppsala large uniform fields are obtained by horizontal and vertical magnetic sweeping allowing utilization of nearly 100% of the original beam intensity (3). Energy degraders are used to adjust the Bragg peak to the desired penetration depth. Superposition of a number of such peaks using a variable thickness rotating wheel or a ridge filter then produces the desired depth-dose distribution.

Proton radiobiology has been carried out at a number of institutions and the data have been summarized in (3). The RBE would be expected to rise above one at the very distal portion of the peak, perhaps the final few mm, since the LET increases there, but this may not be clinically relevant. Overall there is some variation in RBE values but much of the data indicate a value in the range 1.0 to 1.2 compared to ^{60}Co values. The RBE for therapeutically range-modulated peak beams is about the same as at the entrance. OER data for protons are not significantly different from x rays (3).

The sharp dose distributions that can be provided with protons are well-suited for treatment of pituitary tumors. Using Bragg peak protons the Harvard group has treated well over 1000 patients with acromegaly and Cushing's disease with a very high success rate using total doses in the 4,000 to 15,000 rad range. Costs are very much less than frontal craniotomy.

Large-field proton therapy at Uppsala has been applied to genital carcinoma, glioblastomas, nasopharyngeal carcinoma, and head and neck carcinomas with diverse clinical results. For those regions with nearby critical organs (e.g., eyes, spinal cord, rectum) protons may offer a distinct advantage over conventional radiations. The Soviet large-field proton radiotherapy effort is the largest in the world (over 500 patients) and there is close collaboration with the Uppsala group. A variety of advanced cases have been treated including lungs, esophagus, melanomas, and cervix. Statistically, it is probably premature to definitively describe the efficacy of protons but there does appear to be a relative absence of the normal tissue complications commonly observed in conventional radiotherapy (3). In the U.S. at Harvard, techniques for large-field therapy were initiated in 1973 with emphasis on localized prostatic cancer (7). Tumors of the thyroid, bladder, nasopharynx, and parotid gland are due to be treated in the program.

Neutrons

Photons interact with the orbital electrons of the constituent atoms of tissue and transfer energy through photoelectric, Compton, and pair-production processes while neutrons interact primarily with tissue nuclei. These collisions result in elastic and inelastic scattering and nuclear disintegration except at very low energies where capture processes may become important. About 70% of the tissue dose deposited by 14 MeV neutrons is due to recoil protons with LET values less than about 30 keV/ μ m (8). Elastic collisions with carbon and oxygen produce heavily ionizing recoils of short range and high LET (up to 800 keV/ μ m) thus leading to large values of RBE.

Inelastic collisions between neutrons and the heavier atoms result in nuclear disintegration with the emission of alpha-particles, deuterons, and gamma rays. These can provide a substantial fraction of the dose with LET values ranging up to 200 keV/ μ m. The presence of gamma rays in both the primary neutron beams and the deposited dose complicates dosimetry.

There are about 20 fast neutron radiotherapy facilities in the world using sources such as d-T generators (14 MeV neutrons), cyclotrons, and linear accelerators. Therapeutically useful d-T generators require outputs of about 10^{13} sec⁻¹ which are just being approached, the major problem being the design of the tritium target for longevity. Cyclotron-generated deuteron and proton beams incident upon lithium or beryllium targets produce neutrons through stripping reactions and (p,n) reactions respectively. The Li or Be target is usually fairly thick, implying a large amount of primary energy loss; neutrons emerge with a spectrum of energies. Production by deuterons yields an average neutron energy of about 0.4 of the primary energy; the neutron yield at 0° and the average neutron energy are higher for deuterons compared to protons of the same energy. The neutron energy spectrum can be "hardened" by using thinner targets (at the expense of yield and dose rate) or by filtering techniques (e.g., polyethylene) which reduce some of the low energy component. All neutron beams contain gamma-ray contamination arising from self-absorption in the target and collimator effects. More skin-sparing and better penetration can be obtained with higher neutron energies, but the RBE is higher for lower neutron energies since low energy recoils are more densely ionizing. In designing a therapy neutron beam one must thus consider

primary energy, target type, target thickness, dose rate, filtering, and collimator effects. Although a large number of measurements have been made of spectra, yields, and dose distributions, there is some disagreement between different experimental groups; there are numerous parameters so it would be valuable to be able to reliably calculate these quantities, particularly if fine-tuning energy spectra eventually proves to be useful for achieving certain effects with respect to specific tumors. One deficiency in the spectrum measurement is the low energy region below about 1 MeV. These neutrons have a very large RBE, and hence a relatively small dose in that energy region could have a significant biological effect.

Examples of deuteron-produced and proton-produced neutron energy spectra are shown in Fig. 4. The deuteron-produced neutron spectra display the characteristic shape associated with stripping reactions. The proton-produced spectra indicate a large, low-energy component of evaporation neutrons.

Neutron dosimetry is extensively discussed in Ref. (10). Plastic tissue-equivalent ionization chambers are used with care taken to match the hydrogen concentration to that in tissue. Activation techniques are also applicable. In the depth-dose distribution there is a buildup region, leading to some skin-sparing, which is due to the forward scatter of recoil protons. As the neutron energy increases, the distribution also becomes flatter as a result of increasing dose attenuation length. The dose distribution depends on the details of the neutron energy spectrum, target thickness, and material, and collimator, and in general, could be somewhat different for each patient.

Microdosimetric spectra are commonly obtained using spherical proportional counters containing tissue-equivalent gas at pressure equivalent to a few microns of tissue. Two calculated microdosimetric spectra are shown in Fig. 5 (11). The ordinate is the dose per unit logarithmic interval of y , so that the area between two values of y is proportional to the fraction of dose in that y interval. Qualitatively, there are four distinct regions of interest. First, there is a secondary-electron distribution extending from about 10^{-2} keV/ μ m to about 10 keV/ μ m. Overlapping the higher energy portion of this section is the proton distribution extending from about 1 keV/ μ m to about 150 keV/ μ m. The distribution peaking at 250 keV/ μ m and extending to about 350 keV/ μ m is due

to alpha particles; the events at higher LET are from heavy ions. The higher energy protons produce a neutron spectrum resulting in a definite shift to lower values for the mean LET of the recoil protons. Such spectra strongly influence the RBE: for 14 MeV neutrons the RBE is about 3, while for 35 MeV neutrons, the RBE is 1.8 to 2.

Numerous radiobiological experiments with neutrons have been carried out using cultured cells, normal tissues, and tumor tissues. The results are reviewed in (3). The RBE and OER are typically observed to be about 3 and 1.7 respectively. Worldwide about 7000 patients have now been treated with neutrons. Although the results have been less encouraging than original expectations, intercomparisons of the experience at different institutions are difficult as a result of considerable variation in energy spectra, gamma-ray contamination, fractionation schedules, dose per fraction, and the use of mixed-beam therapy. It must be emphasized that for neutrons to be more effective than x rays, which possess a similar depth-dose distribution, the RBE for tumors should be higher than that for limiting normal tissues. This should be true for hypoxic tumors. The RBE for late effects versus acute effects in normal tissues must also be considered as the former is often a limiting factor in radiotherapeutic dose delivery. There is some evidence that the late effects RBE is higher than that for acute effects.

The trend in clinical results with neutrons seems to be positive for salivary gland and bladder tumors and negative with respect to brain tumor. Head and neck tumors respond better to neutron-photon treatments than either modality alone. However, in terms of multiphot neutron delivery and optimal fractionation, neutron radiotherapy certainly has not yet been optimized.

Heavy Ions

Helium, carbon, neon, and argon ions are currently being evaluated for radiotherapeutic applications. Helium ions with 800 MeV are required for 20-cm penetration in tissue. The LET of a helium ion rises to about 150 keV/cm near the end of its range and both range straggling and multiple scattering effects are very small. Carbon and heavier ions lose energy through ionization and nuclear interactions (including projectile

fragmentation, target fragmentation, and central collisions. In projectile fragmentation

- grazing collisions are responsible for the reactions
- total reaction cross sections are generally independent of energy in the region above about 300 MeV/nucleon
- velocity of the fragments is close to that of the projectile, i.e., emission is very forward.

Target fragments, in contrast to projectile fragments, are emitted roughly isotropically and at lower energies and are characterized by high multiplicities. Central collision processes result in nucleons and light fragments from both the projectile and target. In such a process the target and the projectile "melt" in an evaporative compound system which emits fragments independent of the formation process. A number of neutrons and gamma rays may accompany any of these processes.

Radiobiologically, the most important process is projectile fragmentation since the fragments have the same velocity, less charge, and longer range than the projectile, thus contributing to the dose in the "range peak" and beyond (exit dose) and changing the LET distribution as a function of depth. Since nuclear mean free paths are of the order of tumor depths, a significant fraction of the incident beam will undergo breakup. Some of the fragments deposited near the end of the range of the primary beam will be radioactive; the annihilation radiation from positron emitters can be used to visualize the stopping region. Products from target fragmentation and central collisions tend to broaden the lateral dose distribution around the beam.

The 184-inch synchrotron at the Lawrence Berkeley Laboratory in California (LBL) has been used since about 1970 for helium ion radiotherapy. The synchrotron at Saclay, France, also is planned for use in that application. The only facility presently operating capable of producing ions heavier than helium of sufficient energy for use in radiotherapy is the BNLAC at the Lawrence Berkeley Laboratory. Here a heavy-ion linear accelerator (Superhilac), producing fully stripped ions with energies up to 8.5 MeV/nucleon, is used as an injector for the Bevatron (6.2 GeV proton synchrotron) which can yield heavy ions of energies up to 2.7 GeV/nucleon. Therapeutically useful carbon beams should have energies of about 400 MeV/nucleon (25 cm range) while argon beams

should have up to 700 MeV/nucleon. The BEVALAC facility and experimental results are described in Ref. (11). Heavy ion facilities capable of biomedical applications have been proposed in France, Soviet Union, Germany, Japan, and Canada.

Unmodulated beams of heavy ions have very narrow Bragg peaks, the order of millimeters. As described in the proton section, uniform therapeutic beams are obtained with scattering-occluding systems for providing the required transverse beam size and range-shifting with a variable-thickness water column or ridge filters to obtain the desired depth distribution. The dose distributions for typical range-shifted Ne and C beams are shown in Fig. 6. Some degree of localization is apparent, but the plateau to peak dose ratio increases as the mass of the ion increases due to a larger contribution from in-flight nuclear interactions. The slope of the peak is intended to compensate for the changing biological effectiveness with depth. Dose distributions in the transverse dimensions are relatively sharp owing to the reduced multiple scattering. The LET distributions in the heavy ion peaks exhibit prominent peaks (e.g., about 50 keV/ μ m for Ne) corresponding to their energy loss through ionization near the end of the range (12).

As in the case of the other particles, extensive radiobiological investigations have been carried out with heavy ions. These are discussed in Refs. (3) and (11). Heavy ions such as neon are comparable radiobiologically to fast neutrons. Representative GPR and RBE data are shown in Figs. 3.

As of July 1979, 194 patients (non-melanoma) had been treated with heavy ions using doses per fraction near 200 cG_{Ne} (the equivalent of 33% of x-ray irradiations), four to five fractions per week with total doses ranging from 6,000 to 7,000 cG_{Ne}. By mid-1981 80 patients (C, 24; Ne, 54; A, 2) had received heavier ions as at least part of their treatment with somewhat higher doses per fraction and total doses per fraction in the range 4,800 to 5,500 cG_{Ne}. Tumor sites included head and neck, brain, eye, thorax, abdomen, and pelvis. Some randomized clinical trials are underway and optimization of irradiation parameters will continue.

Negative Pions

Soon after the characteristics of the negative pi meson (negative pion or π^-) were identified, it was noted that these particles might have considerable potential for cancer therapy (13). The interactions of π^- in matter involve the production of protons, neutrons, and heavy ions so much of the physics discussed in previous sections is applicable.

Negative pions are hadrons having a mass of about 140 MeV, one-seventh that of the proton. The π^- has a lifetime of 2.6×10^{-8} s and decays virtually always into a muon and a neutrino. Pions interact with particles through both the electromagnetic and strong nuclear forces and are, indeed, the fundamental particles associated with the strong nuclear interaction.

As is the case with other heavy charged particles, pions lose energy by ionization in traversing matter producing a Bragg peak near the end of their range with concomitant localization of dose. There are also in-flight nuclear interactions which include elastic and inelastic scattering, charge exchange, and pion absorption. At the end of their range, π^- undergo an interaction which enhances the Bragg peak dose. When the π^- reaches electron-volt energies, it is captured into an outer orbit of an atom and cascades down through the atomic energy levels through Auger transitions and the emission of characteristic x rays. As a result of its strong interaction character, the π^- is absorbed by the nucleus when their wave functions possess a large overlap; the whole process takes less than 10^{-14} s, a time short compared to the π^- lifetime. The rest mass of the π^- (140 MeV) is absorbed by the nucleus and, for light nuclei such as O and C, about 50 MeV is consumed in overcoming nucleus-binding energies with the remainder appearing in the emission of gamma rays, several neutrons (total energy of about 70 MeV on the average), and charged particles (total of about 30 MeV) such as protons, deuterons, alpha particles, and heavier ions. In a nuclear emulsion, this process leads to a "star" of tracks.

The emitted particles, except for the high-energy neutrons, have short ranges and increase the dose in the peak region. A significant fraction of the heavier charged particles are densely ionizing, yielding a high LET component which produces an increase in RBE and a decrease in OER in the peak region. For large treatment volumes, the emitted neutrons also contribute strongly to the high LET dose. The advantages of pions for therapy thus include considerable dose localization capability and the

production of a high-LET component in the peak region. Positron emitters (e.g., ^{11}C , ^{15}O) and gamma rays are also produced in the capture process and with appropriate detection techniques these can be used to reconstruct the distribution of stopping pions to verify the position and shape of the treatment volume.

The production of secondary beams of negative pions is accomplished by impinging beams of protons or electrons greater than 500 MeV upon suitable targets. Low dose-rate radiobiology studies have been carried out at a number of institutions including CERN (Switzerland), NIMROD (England), Dubna (USSR), and LBL(US). High dose-rate radiobiology and therapeutically useful beams require about $10^9 \pi^-/\text{sec}$, which implies high primary beam currents and/or high acceptance channels. For a given current and energy, protons produce about 30 times more pions than electrons.

Pion radiotherapy programs are currently underway at the three "meson factories" listed in Table II. A meson factory is under construction in the USSR, and there are several proposals in Japan.

Table II

Meson Factories

<u>Location</u>	<u>Accelerator-Energy</u>	<u>Medical Current</u>	<u>Medical Target</u>	<u>Channel Type</u>
CEC (Berkeley)	cyclotron=590 MeV H^+	20 μA	variable	super-conducting toroid system
TRIUMF (Canada)	cyclotron=520 MeV H^+	150 μA	Be	conventional magnet
LAMPF (US)	linear=800 MeV H^+	650 μA	C	conventional magnet

The pion energies needed for therapy range from about 63 MeV (14 cm water range) to perhaps 96 MeV (26 cm water range). Practical dose rates, i.e., more than 10 rads min^{-1} into a volume of one liter, require either 1) several hundred microamperes of primary beam proton current impinging upon a thick target and a collection system with acceptance solid-angle of greater than 30 msr, or 2) proton currents from 20 μA to 100 μA and high acceptance collection systems with solid angles of the order of 500

msr. Channel length is an important consideration since the decay length for 75 MeV π^+ is about 9 meters.

All pion beams are contaminated with electrons (from conversion of gamma rays produced in the target by decaying π^0) and with muons from pion decay in the target region and in the magnetic channel used to deliver the beam to the patient. This contamination, which is low LET radiation with usually longer range than the pions, constitutes an undesirable exit dose and can be minimized by choosing low-Z targets and production angles that are not too forward; both of these procedures involve a compromise with pion production rate. At LAMPF typical e^-/π^- and μ^-/π^- ratios at a π^- energy of 75 MeV are 0.09 and 0.16 respectively. Target design at high current intensities is difficult. The LAMPF biomedical production target is 6 cm of pyrocarbon ($\rho = 2.2 \text{ gm/cm}^3$) and must dissipate 25 kW of power under vacuum and withstand intense radiation fields. The present water-cooled target is shown in Fig. 7 (14).

At both LAMPF and TRIUMF conventional magnetic channels with quadrupoles and bending magnets are used at the pion biomedical facilities. The LAMPF channel is shown in Fig. 8. A wedge is used to condense the large spread in momentum accepted by the channel to about $\Delta p/p = 3.6\%$ so that sharp edges may be provided in the depth dose distributions (15). A catalog of beam tunes exists with transverse dimensions ranging from about 5 cm x 5 cm to 20 cm x 20 cm and $\pm 7\%$ uniformity. Fan and spot beams have also been developed for use in dynamic treatments in which the patient is moved in one or both transverse dimensions under the beam; properly coordinating the depth and depth-spread of the beam with patient position provides improved dose localization (16). At LAMPF a hydraulically actuated range shifter varies a column of oil to provide the desired pion stopping distribution in depth. The magnetic channel, range shifter, treatment couch, and dose monitoring apparatus are all under computer control.

As in the other charged particle programs x-ray CT scanners are used to identify the position and shape of the tumor, critical organs, inhomogeneities, and integrated density of the material between the skin surface and tumor volume. On the basis of these data, appropriate pion energies, bolus configuration, collimator dimensions, and depth-dose distribution are defined. Parallel opposed overlapping or abutting ports

are often used. At SIN the pion collection system consists of sixty superconducting toroidal magnets providing sixty beams which are delivered in a radial fashion to the patient (Fig. 9). The acceptance of the system is about 1 sr. allowing 20 μ A of protons to produce reasonable pion dose rates. The treatment parameters available include variation of the momentum and momentum band of the pion beams; switching on and off of each single beam; translation of the patient within the treatment chamber in all three directions; and addition of absorbing material (bolus) in the path of the pion beam. The patient is surrounded by a cylindrical water bolus and the momentum is chosen so that all pions stop on the axis of the collector producing an intense small spot of dose. By scanning the patient in three dimensions, it is possible to tailor the dose distribution to a given tumor volume (17).

Dosimetry techniques in the pion biomedical program include the use of ion chambers, thermoluminescent detectors, solid-state detectors, Faraday chambers, carbon and polyethylene phantom comparisons for determining neutron dose, and activation techniques. In-vivo dosimetry is performed when possible during treatments to verify the accuracy of the treatment planning.

Dose distributions for several LAMPF pion biomedical beams are shown in Fig. 10. The narrow beam reflects the resolution of the channel. The range-shifted beams have decreased peak to plateau ratios since many narrow beams are being superposed. One of the broad beams contains a flat extended dose while the other has a decrease in physical dose which tends to compensate for the increasing PBE as a function of depth. This occurs because the dose in the downstream region is due mainly to stopping pions while the upstream region has a substantial contribution from passing energetic pions.

Programs specifically designed for patient treatment planning have been developed which take into account such factors as the phase space of the beam, beam composition and decay products, collimation, range-shifter effects, boluses, and patient inhomogeneities. Calculated quantities include the absorbed dose, stopping distributions, and the dose from neutrons and heavy charged particles and there is generally good agreement with experiment.

The extensive pion radiobiological data are reviewed in (3) and (19). In the peak region, the RBE is of the order of 1.5 and the OER is about 2.4 (compared to 2.9 for x rays).

The patient treatments at SIN and TRIUMF are in the pilot stage; mainly skin nodules are being irradiated to compare the relative effectiveness of pions and x rays. At LAMPF, about 200 patients have been treated, many with large advanced tumors. Clinical trials have been aimed at defining tumor response, normal tissue reactions, and optimal time-dose-fraction relationships for pion irradiation, as well as identification of those disease sites and categories most likely to benefit from pion irradiation.

The distribution of 96 tumors treated with curative intent and followed for a minimum of one year includes 67 tumors treated with pions alone, 19 tumors treated with pions plus conventional radiation therapy and/or implant, and 10 patients treated with pions plus surgery (20). Except for five patients receiving cone-down pion irradiation to the brain, all patients received a minimum of 2700 π^- rad. Only 24 were treated to dose levels currently thought to approximate tolerance doses of relevant normal tissues, that is, approximately 4500 π^- rad in 35 fractions over 7 weeks. Local control (no evidence of tumor) in the 96 pion patients treated with curative intent was as follows: head and neck, 47 percent; brain, 13 percent; prostate, 87 percent; pancreas, 0 percent; and other miscellaneous sites, 58 percent.

The Future

The future widespread use of the four new particle modalities will depend upon the relative importance of dose localization and biological effectiveness and whether one of the two advantages is sufficient or they should be applied in combination. RBE and OER data for the particles are compared in Fig. 3. A second consideration is facility cost and cost per patient treatment. Estimated costs for medically dedicated radiotherapy installations range from about \$6-8 million for neutrons and protons to \$12-18 million for pions and heavy ions (5).

New accelerator developments may also be realized. Proton cyclotrons with a superconducting magnet could be very compact (perhaps 1 m radius) and could be used in a hospital environment for proton therapy. The output

of D-T generators can be expected to increase as target design improves, and isocentric neutron delivery from cyclotrons is now possible. At least three U.S. institutions will install hospital-based cyclotrons to conduct neutron therapy clinical trials. These cyclotrons will accelerate protons to approximately 40 MeV and use thick beryllium targets.

Heavy ion therapy facilities are being proposed in Japan, Germany, USSR, France, and Canada. The Canadian facility will utilize a synchrotron, possibly with a linear injector, to supply various heavy ion beams ranging from helium to argon to several treatment rooms. Isocentric beam delivery will be provided either with an isocentric gantry or by the use of multiple fixed beam directions.

For negative pion therapy a dedicated accelerator denoted PIGMI (pion generator for medical irradiation) has been designed, which incorporates many new features including high acceleration gradients, radio-frequency quadrupole (RFQ) focusing which permits low energy injection, and a novel type of control system (21). A schematic of the accelerator, estimated to cost about \$15 million, is shown in Fig. 11. It is designed to operate at a conservative 100 nA of proton current which implies pion collection channels of moderately high acceptance. Such channels could be similar to the superconducting, 60-channel system being evaluated at SIN, a shaped solenoidal field system (22), or a double-coaxial coil system (23).

The question of cost/benefit for such relatively expensive facilities is both complicated and subjective but the cost appears justifiable if significant increases in cure rates can be achieved in some of those tumors with a presently very poor prognosis, e.g., pancreatic cancer. In the U.S., it is estimated that the "savings" resulting from a patient cure versus patient death is \$20,000 - \$25,000 (24). If 20% of the 100,000 deaths occurring annually due to failure to achieve local control could be saved by one or more of these new modalities, this might imply a "benefit" of 400 million dollars—enough to construct and operate a number of PIGMI or heavy-ion type facilities at reasonable patient cost.

RADIOISOTOPE PRODUCTION

Accelerator-produced radioisotopes are in wide use for medical diagnostic purposes and for implant procedures in radiotherapy. The accelerated particles include protons, deuterons, ^3He , and ^4He which impinge upon suitable targets. A variety of nuclear reactions are used in producing the desired radioisotope such as (p, xn) , (d, xn) , $(^3\text{He}, p)$, $(^4\text{He}, p)$, and $(^4\text{He}, \alpha)$ where in most instances x is in the range 1 to 4. Particle type, particle energy, and target are chosen to provide useful radioisotope yields; following target bombardment, radiochemical isolation and purification techniques are employed to derive the medical product. The radioisotopes are usually used as labels for biologically active compounds which seek particular organs or types of tumor. The overall usefulness of a given radioisotope, for a particular application, depends upon its ease of production and half-life as well as the energy of the emitted photons.

Nuclear medicine radioisotopes are usually either emitters of gamma rays in the few hundred keV range or emitters of positrons which, due to the annihilation process, yield two 511 keV photons in coincidence and 180° apart. Detection systems for the gamma emitters are of two general types: the Anger camera and the multicrystal scintillation camera (25). The Anger camera utilizes a multichannel collimator (e.g., parallel-hole) and a large NaI crystal coupled to 19 or more photomultiplier tubes. The spatial distribution of the radioisotope in the body is determined through the selection process of allowing only those gammas which pass through the collimator to reach the position-sensitive detector. The optimum gamma energy range for both spatial resolution and camera sensitivity is 120-200 keV which explains in part the popularity of reactor-produced $^{99\text{m}}\text{Tc}$ (140 keV photo peak) as a radionuclide. In the multicrystal scintillation camera, a large matrix of crystals, individually coupled to photomultiplier tubes, is used to provide position information. Arrays of semiconductors are also being evaluated. Finally, multiwire proportional chambers detecting conversion electrons from the gammas are being used in some research laboratories. Such systems have good spatial resolution but relatively poor sensitivity. For all detection systems the physician interprets the image in terms of the amount and distribution of the isotope in the organ under examination.

Most of the commonly used gamma emitters are isotopes of elements which do not play a significant role in human physiology, the principal exception being ^{123}I . However, radiolabels such as ^{11}C , ^{13}N , ^{15}O , ^{18}F can be incorporated into physiologically active compounds without significantly altering their behavior. These isotopes are positron emitters yielding photons with an energy too high for conventional gamma cameras. Using the coincidence and angular correlation properties of the annihilation photons, detection systems have been constructed in the form of arrays of detectors (scintillators or multiwire proportional counters) around the patient which provide information about the line of emission of the gammas. By viewing the body from many angles positron emission tomography is possible, i.e., the determination of the three-dimensional distribution of the radioisotope in the patient using reconstruction algorithms similar to those employed in x-ray computerized tomography (26).

The short half-lives of ^{18}F (110 min), ^{15}O (2 min), ^{11}C (20 min), and ^{13}N (10 min) imply that production should occur on the same site as the utilization. Cyclotrons costing in the range of 0.5 - 2 million dollars are commercially available for these isotopes. As an example, ^{18}F can be produced through the reaction $^{18}\text{O}(p,n)^{18}\text{F}$ with a threshold energy of about 1.6 MeV. ^{18}F labeled 2-fluoro-2-deoxy-D-glucose is well-suited for studying glucose metabolism in the brain (27). However, for studying a change in metabolism as a function of other parameters, a shorter-lived isotope is needed, e.g., ^{11}C labeled deoxyglucose. Widespread use of positron emission tomography requires biomedical generators which deliver positron-emitting nuclides. Higher energy machines can be used to produce long-lived "mother" radionuclides for transport which, at their destination, yield useful quantities of short-lived "daughter" positron emitters (28).

Some examples of commercially available gamma-emitting radioisotopes and their production reactions using low-energy cyclotrons are shown in Table III.

TABLE III

Accelerator-Produced Gamma Emitters

<u>Radionuclide</u> <u>Half-life</u>	<u>Typical</u> <u>Reaction</u>	<u>Application</u>
^{67}Ga (78h)	$^{68}\text{Zn}(p,2n)$	Presence and extent of Hodgkins's disease, lymphomas, and bronchogenic carcinoma.
^{123}I (13h)	$^{122}\text{Te}(d,2n)$	Thyroid imaging with about fifty times less dose than ^{131}I .
^{111}In (2.8d)	$^{102}\text{Cd}(p,2n)$	Localization of head and neck tumors, bone marrow studies
^{43}K (22h)	$^{40}\text{K}(\gamma,p)$	Myocardial infarct studies
^{201}Tl (73h)	$^{203}\text{Tl}(p,3n)$	Potassium analog for imaging myocardium.

Examples of biomedical positron emitter generator systems are shown in Table IV. For efficient radionuclide production, most of these require fairly intense medium energy (> 100 MeV) particle beams such as those available at "meson factories."(28)

Table IV

Biomedical Positron Generators

<u>Parent</u>	<u>Daughter</u>	<u>Application</u>
^{44}Tl (17v)	^{44}Sc (3.9h)	Localization of bone tumors
^{68}Ge (282d)	^{68}Ga (68m)	Multipurpose short-lived emitter
^{72}Se (8.4d)	^{72}As (26h)	Neurological studies
^{82}Sr (25d)	^{82}Rb (1.2m)	Myocardium and dynamic renal blood flow studies

In the U.S. there are over forty cyclotrons operated primarily for medical research and nearly twenty cyclotrons operated commercially for radioisotope production (29). Production requirements have escalated proton beam energies to the region of 40 MeV and beam currents to the order of several hundred microamperes. The New England Nuclear Company is constructing a proton linear accelerator with a proton energy of 45 MeV and an average beam current of 5 nA; this machine will be used primarily for

the production of ^{201}Tl . Finally, all of the three operating "meson factories" in the world (Villigen, Switzerland; Vancouver, B.C., Canada; Los Alamos, NM, USA) are routinely producing through spallation processes many curies per year of radioisotopes which are either impossible or inefficient to produce at lower beam energies and intensities. The radioisotope production facility at Los Alamos is schematically depicted in Fig. 12.

ELEMENT ANALYSIS

Particle-Induced X-Ray Emission

Particle-induced x-ray emission (PIXE) is rapidly developing into an important analytical tool for some medical applications. Samples are usually exposed to beams of protons or α -particles with energies of a few MeV and the emitted characteristic x rays are detected with an energy dispersive detector such as Si(Li). Quantitative information can be obtained for all elements which have characteristic x rays of sufficient energy to reach the sensitive volume of the detector. Highest sensitivities are usually observed for the $Z = 22$ (Ti) to $Z = 38$ (Sr) region but Na, K, La, Mo, Cd, Hg, and Pb can also frequently be measured (30). Due to absorption of the x rays in the sample, thin layers ($0.1 - 5 \mu\text{g}/\text{cm}^2$) are usually analyzed and concentration measurement limits are about 1 ppm due to competing effects such as bremsstrahlung from secondary electrons (31). Multi-element analyses can be carried out in about one minute implying relatively low cost per sample. Also PIXE may be combined with nuclear measurements such as proton backscattering or proton-induced gamma rays to extend the mass range of analysis capability to low Z elements such as C. Finally, very small beams are being developed so that the PIXE method can be employed to map samples with a resolution of the order of 1 μm , perhaps with detection limits more than one order of magnitude better than electron microprobes.

The PIXE technique, sometimes in conjunction with proton backscattering measurements, has been used for many types of biomedical analyses. Many of these are discussed in Ref. (32). Examples include measurements of bromide metabolism in uremia, halothane content during anesthesia, and trace elements in tooth enamel. Also the elemental

concentrations of normal and malignant tissues, whole blood and serum, and hair have also been performed.

Neutron Activation Analysis

In neutron activation analysis (NAA) radioactive species produced in samples by neutron-induced reactions are quantitatively detected. Accelerated particles can produce suitable fluxes of neutrons with appropriate energies through (p,n), (d,n) and (t,n) reactions, for example ${}^7\text{Li}(p,n){}^7\text{He}$ and ${}^3\text{H}(d,n){}^4\text{He}$. NAA may be performed in a purely instrumental mode in which induced gamma-ray emitters are detected using Ge(Li) detectors or in a radiochemical separation mode. More than 70 elements can be identified with NAA and it is in routine use in many applications with detection levels ranging from 10^{-6} to as low as 10^{-14} . Analysis of the data is generally more time consuming than for PIXE, but due to the very high sensitivity and large sample-size capability of NAA, it may be considered a complementary technique. Examples of biomedical applications include studies of human serum and serum albumin, investigation of the relationship between trace element levels and cancer, and the determination of mineral levels in bone.

Muonic X-Ray Analysis

When negative muons are implanted in a sample, they slow to an energy of a few eV and are then captured by a nucleus forming a muonic atom. The muon cascades down to more tightly bound orbits in the atom with the emission of characteristic x-rays which are about 200 times more energetic than the corresponding x-rays from electronic transitions. These x-rays can penetrate bulk samples with low absorption and may be detected with good efficiency by Ge(Li) detectors. All elements with Z greater than two can be detected with a concentration limit of 10^{-1} to 10^{-7} . In particular, the technique can be applied to biological samples whose primary constituents are low- Z elements. Also the interior of very large samples can be interrogated with some spatial selectivity. The obvious drawback of this method in terms of widespread use is the need for a high-current proton accelerator with energy greater than about 300 MeV to generate the required muon beams. A number of biological samples have been analyzed at LAMPF (33). The technique has potential *in-vivo* applicability

for identifying such conditions as cirrhosis, hemochromatosis, changes in bone calcium levels, and possibly tumors.

MEDICAL IMAGING WITH PARTICLES

Energy Loss Radiography and Tomography

The energy-loss method of charged particle radiography is based upon the effect on the residual range of the particles caused by the material being radiographed. High contrast images on film can be obtained as a consequence of the Bragg peak that occurs near the end of the particle range. It has been demonstrated that proton radiographs provide improved imaging of low contrast lesions in human specimens compared to conventional x-ray techniques (34). Even higher contrast images may be obtained using heavy ions and plastic track detectors (35).

Computed tomography (CT) may also be performed with charged particles. A nearly monoenergetic beam of 200 MeV protons is passed through a sample and the residual energy of individual exiting protons precisely measured with either a large-pure Ge solid-state detector or a scintillator range telescope thereby providing a measure of the integrated density along the beam path (36). By passing the beam through the sample in a number of different directions, the density distribution within the sample may be reconstructed using computer algorithms in a manner analogous to that employed with commercial x-ray CT scanners. On the basis of both theory and experiment, it has been shown that scans with protons require at least a factor of five less dose than x-rays for a given density resolution. Also, proton CT images relative linear stopping power while x-ray CT images the linear attenuation coefficient; it might be expected that the two modalities could produce somewhat different images although this has not been demonstrated in an in-vivo situation. A number of human organs were scanned with both protons (about 6×10^7 protons per slice) and x-rays. The results for an adult heart specimen with myocardial infarction of the left ventricle are shown in Fig. 13 (37). The dose was about a factor of five less for the proton scan. The spatial resolution of proton scans is fundamentally inferior to that of x-ray scans as a result of multiple Coulomb scattering although an approximate correction can be made by recording the exit position of the proton after passing through the sample

with a multiwire proportional counter. The density resolution as measured in a test phantom was about 0.3% for a 1 cm object.

The limitation on spatial resolution arising from multiple scattering may be reduced through the use of heavy ions although some reduction in dose advantage relative to protons also occurs. At the Lawrence Berkeley Laboratory beams of He, C, and Ne ions have been used to produce radiographic images in plastic detectors (11). Radial spatial resolution of about 2 mm and density resolution of about 0.1% for a 1-cm object embedded in a 12-cm-dia phantom have been obtained. A number of tissue specimens have been examined particularly in connection with breast disease. A dose of 0.02 rad is adequate for neon or carbon-ion mammograms which seem to provide better contrast for soft-tissue abnormalities and tumors than x-ray radiographs. Heavy-ion tomography has been applied to brain specimens and a full-scale apparatus has been constructed for in-vivo use on humans.

Nuclear Scattering Radiography

In the nuclear scattering radiography technique (38), three-dimensional reconstructions of the density distribution in extended objects are obtained by measuring the scattering of protons in the 1-GeV energy range. The spectral distribution of the protons is characterized by a small contribution of coherent elastic scattering from the whole nucleus and a large peak from the quasi-elastic scattering on bound nucleons. Very small solid angle proportional detectors are used to localize with high accuracy the position of every incoming and outgoing charged particle and compute, therefore, the coordinates of the interaction points. This information can be used to derive the density in volume elements of the object (39,40). In addition to the element density, the amount of hydrogen present can be determined since there are distinct kinematic differences between the scattering of protons on bound protons and on free hydrogen. A human head specimen was examined with 1.0 GeV proton scattering radiography and an x-ray CT scanner (38). The proton results showed reasonably good localization of anatomical structures at a much lower dose than the x-ray image and the hydrogen radiography provided an interesting display of the hydrogen distribution. For a state-of-the-art system, the experimental

-29-

estimate that a dose of about 2.5 rads is required to achieve 1% density precision in a volume element of 5 mm^3 .

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FIGURE CAPTIONS

1. Physical dose distributions of various radiotherapy beams. The charged particle peaks have been range-modulated to cover a tumor extending from 8 cm to 12 cm and all curves are normalized to 1.0 at 10 cm depth (4).
2. Representative values of relative biological effectiveness and oxygen enhancement ratio as a function of linear energy transfer with survival of cultured cells as the endpoint.
3. Representative values of (a) relative biological effectiveness and (b) oxygen enhancement ratio for the various particles (3).
4. Examples of neutron energy spectra produced by 35 MeV protons and deuterons on thick Be and Li targets. The ordinate is proportional to the number of neutrons/proton-Sr-MeV (9).
5. Neutron microdosimetric spectra for protons of 35 MeV and 45 MeV on Be. The ordinate is the dose per unit logarithmic interval of LET; the area between two values of v is proportional to the fraction of dose in that v interval (9).
6. Dose distributions for Ne and C ions with the peak region spread in depth to 10 cm (12).
7. The LAMPE biomedical pion production target. The thin target films are used for counting experiments for which the thick target produces too much flux (14).
8. The LAMPE biomedical channel.
9. The SL⁺ Pionron; the 60 beams of negative pi-mesons are guided and focused by the two superconducting torus magnets (17).
10. Typical depth-dose distributions produced by the LAMPE biomedical channel. The sloped distribution compensates for the increase in PBE with depth. [Redrawn from (18).]
11. Fusion components for PIGM. The accelerator is 134 m in length and is suitable for installation underground in a tunnel of modest cross section.
12. The isotope production facility at LAMPE. Nine water-cooled targets can be remotely inserted and retracted from the proton beam. After irradiation, the targets are transported to a laboratory for isolation of the desired radioisotope.

-34-

13. CT reconstructions of a fixed adult heart specimen: a) protons,
b) GE 8800 x-ray scanner (17).

Fig. 1

Fig. 2

Fig. 3(a)

Fig. 3(b)

Fig. 4

Fig. 5

Fig. 6

FIVE-TUBE WATER COOLED
A-5 TARGET

Fig. 8

Fig. 9

Fig. 10

PRINCIPAL COMPONENTS OF PIGMI

Fig. 11

Fig. 12

Fig. 13(a)

Fig. 13(b)