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RADIOLOGICAL USE OF HIGH ENERGY DEUTERONS AND ALPHA PARTICLES

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FOR almost twenty years there has been a trend in experimental radiation therapy to develop new methods and instruments that would enable radiologists to irradiate deep lying regions of tissue with the same facility as they irradiate skin. Parallel with that trend, continued efforts were being made to produce radiations which have negligible scattering properties and which serve to irradiate well defined volumes of tissue mass.

When Stone *et al.*[1] built their million volt roentgen-ray generator, the chief aim seemed to be to increase the penetrating power of the roentgen rays, since the low voltage roentgen rays were absorbed exponentially and too rapidly in tissue. The high penetrating power of the roentgen rays obtained solved the problem of transmission, but there was still not enough ionization produced in the deeper tissue relative to the more superficial tissues to produce selective effects. In spite of the increased penetrating ability, the skin dose imposed severe limitations on depth therapy.

Further progress was made a few years later in 1937 when Dessauer *et al.*,[2] du Mesnil de Rochemont[3] and others[4] introduced rotation therapy, in radiological practice. This method consists of rotating the patient around a fixed point in his body, while the roentgen-ray apparatus remains stationary. The tissue immediately around the center of rotation receives the maximum dose, and the dose falls off as the distance from the center of rotation increases. Recently Trump has combined the use of high energy roentgen rays with the rotational method.[12]

With the construction of high energy particle accelerators further progress was made possible. Starting in 1935 biological and medical use of fast neutrons (0–20 mev.) was begun by the Lawrence brothers[5] and these were therapeutically utilized by Stone and his associates.[6] It seemed possible at the time that the high specific ionization of fast neutron recoils might have a differential effect on tumor tissue as compared with normal tissue.

In 1948 the first accounts of the techniques of utilizing high energy roentgen rays from Kerst's betatron appeared.[7] High energy roentgen rays have the advantage of reaching maximum specific ioniza-

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FOLDER RBE and Specific Ionization

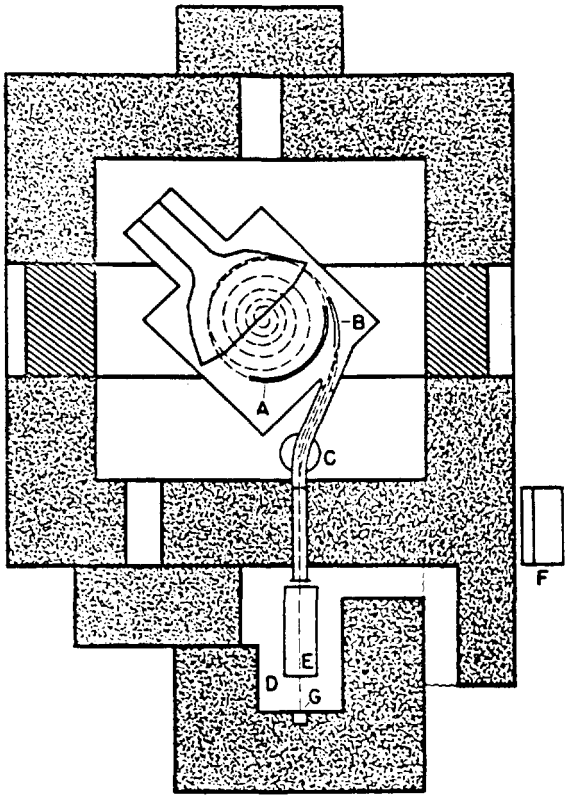

FIG. 1. Schematic layout of the Berkeley 184 inch cyclotron with the deflector system and shielding. The particles start from the ion source in the center of the square vacuum chamber and proceed in a spiral path to larger and larger radii at higher and higher velocities. The ions are produced in pulses of two to ten microsecond duration at the center of the cyclotron vacuum chamber and proceed outward in bunches keeping in step with the frequency modulated oscillations of the Dee. When the required radius of 81 inches is reached, the electrostatic deflector A is turned on momentarily deflecting the particles away from it. The particles then go through a region of higher magnetic field near the center of the magnet and rebound to a deflector B which is essentially a space with reduced magnetic field intensity. The path of the ions then straightens so that they are able to leave the cyclotron chamber and enter an evacuated focusing tube. They pass through some apertures, arriving at an external magnetic focusing device C. A group of protons, deuterons or alpha particles of homogeneous energy is selected and is directed through the focusing tube. The particles proceed out into air through a thin aluminum window in the exposure room D. A special irradiation bench was built for exposing small animals, E. Doses are measured and the beam is controlled from externally located control board, F. While the cyclotron is turned on no one is admitted in chamber D. Outside the concrete shielding, which completely surrounds the cyclotron, the dose is sufficiently low to permit the operators to work all day.

tion at a depth of a few centimeters from the surface of the body; the ionization then decreases exponentially. The roentgen-ray beam is now being used in medical therapy[8] and for biological investigations.[9]

Meanwhile, the 20 mev. electron beam was brought outside of the betatron. The depth tissue dose characteristics[10] of the high energy electrons seem to be better for some purposes than those of high energy roentgen rays because the exit dose is much smaller and the dose rates easily attainable are higher than with roentgen rays. In Germany a group of workers[11] is already using 6 mev. electrons for therapeutic purposes.

By combining rotation or multiple port techniques with the use of high energy roentgen rays or electrons from betatrons, one is able to produce depth doses which are considerably higher than the skin dose.

When radioactive isotopes with high selective uptake are used for internal irradiation of tissues, as in the case of thyroid cancer, it has been determined that the dose delivered to tumor cells should be at least twenty times the dose delivered to surrounding tissues.[13] The external radiations discussed can very seldom achieve this. Furthermore, it is well known to radiologists that in certain cases of radiation treatment, it would be desirable to have the ionization fall off abruptly in a direction lateral to the beam, as well as in the direction of the beam (low exit dose). The latter is desirable, for example, in cancer of the neck region where conventional external radiation treatment often leads to a severe reaction of nearby sensitive tissues (the pharynx, etc.).

In 1946 Wilson[14] suggested the use of high energy proton beams for radiological purposes, proposing that the sharp increase

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in ionization near the end point of high energy proton tracks be utilized for the purposes of depth dose therapy.

Two years later, when the Berkeley 184 inch cyclotron was completed by E. O. Lawrence and his associates[15] and after the internal particle beam was successfully deflected and brought out into the air,[16] biological investigations were started by the authors with the high energy nuclei available. The present paper will be chiefly concerned with deuterons (heavy hydrogen ions) and alpha particles (helium ions). We wish to review some of the physical properties of these radiations, their range, dosage determination, biological use, and potential medical applications.

DESCRIPTION OF APPARATUS AND MEASURING TECHNIQUE

The Berkeley 184 inch frequency modulated cyclotron[15] supplies 190 mev. deuterons, 380 mev. alpha particles, and 340 mev. protons. These particles appear in pulses of ten to fifteen microsecond duration ninety times per second. The particles undergo some 10,000 revolutions in the cyclotron along a spiral path until the radius of the path increases to 81 inches. Then a pulsed electrostatic deflector (A, Fig. 1) changes the direction of the particles, bending them toward the center of the magnet. At the next revolution the particles rebound to find themselves in a field free region in the so-called magnetic deflector (B, Fig. 1) which allows them to escape from the pole pieces of the electromagnet. The slightly divergent beam proceeds in an evacuated tube to an external magnetic focusing field (C, Fig. 1) which bends them toward the exposure room (D, Fig. 1). Here, the particles go through a thin aluminum window and emerge as a well collimated, approximately monoenergetic beam. Since only about 1 per cent of the internal beam is deflected, considerable fast neutron and gamma-ray background is also present. A heavy concrete shield surrounds the cyclotron, decreasing the neutron and gamma-ray background to a low level in the exposure room. The exposure room is shielded on all sides with additional concrete. All biological exposures were done on a specially constructed treatment table (E, Fig. 1 and 2) operated from a remote control station (F, Fig. 1 and 3).

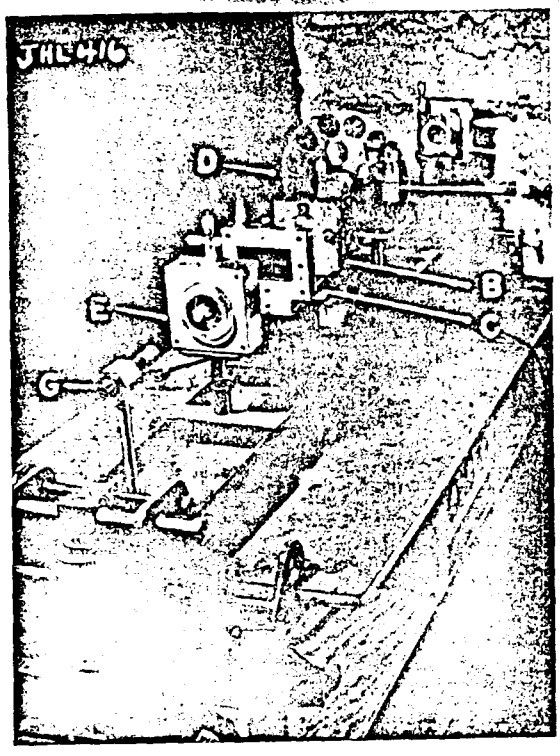

Fig. 2. Photograph of the irradiation bench. The irradiation bench consists of a set of two tracks approximately 8 feet long mounted on a suitable table. Its chief purpose is to support instruments for the measurement of physical properties of the beam and small animals during exposure. Usually it supports some ionization chambers which indicate whether or not the beam passes along the axis of the radiation bench, located 8 inches above the center of the track. It is possible to raise or lower and tilt the irradiation bench by remote control until the beam is exactly aligned with the bench. Also shown is the limiting aperture A, quadrant chamber B, monitoring chamber C, a set of absorbers in a so-called "absorber wheel" remotely controlled D, an analyzing chamber of similar type to the Failla extrapolation chambers E, and a lucite box suitable for holding mice F. At the end of the bench is a telescope pointing down along the beam axis G. This telescope is used for exact alignment of portions of animals to be irradiated.

The electrical controls on the cyclotron

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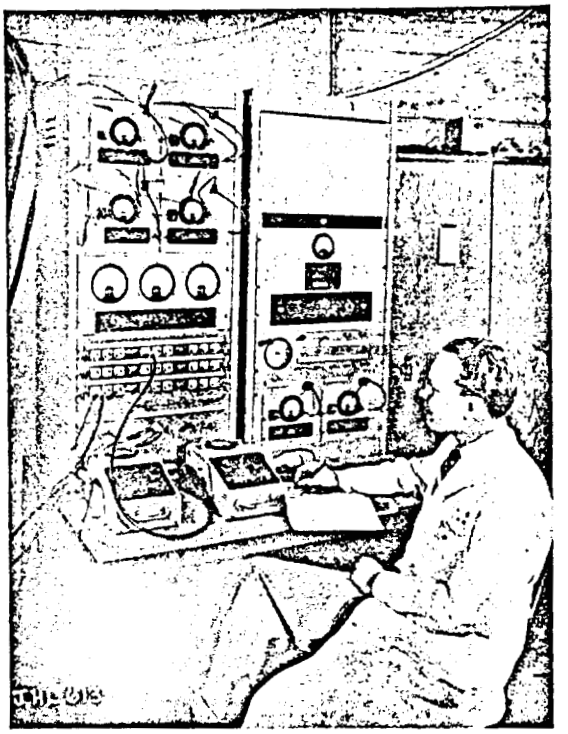

FIG. 3. Remote control station. Located outside of the shielded area, the operator is able to control the position of the irradiation bench electrically and check continually that it is lined up with the external beam. It is also used for dose rate and accumulated dose determinations.

allow focusing the beam in a definite position and direction as well as stable fixation of the focused beam for several hours in the same position and direction.

The cross section of the beam available for biological study may be varied with suitable apertures from 2 inches in diameter down to any smaller size. The average operating deuteron beam current density is 1.6×10^8 particles cm.$^{-2}$ sec.$^{-1}$ corresponding to a soft tissue dose rate of 1,200 rep* per min. The highest dose rate used was 4,000 rep/min. with an instantaneous dose rate during individual pulses of 2.8 million rep min^{-1}. The helium ion beam intensity is lower by a factor of about ten, the 340 mev. proton intensity higher by a factor of two.

PHYSICAL MEASUREMENTS

We wish to report here results of the following measurements:

I. Ionization and dose distribution as a function of absorber thickness.
II. Beam current as a function of absorber thickness.
III. Stopping power measurements.

The measurements are usually conducted in the following fashion: After the resonance conditions in the cyclotron have been established, the beam is allowed to pass through an aperture sufficiently small to cut out a fairly uniform section (Fig. 4); then the treatment table is aligned so that the beam passes exactly along the axis of the monitoring instruments. Alignment is accomplished by adjusting the position of the table by remote control. The position

* 1 rep = 93 ergs/g.

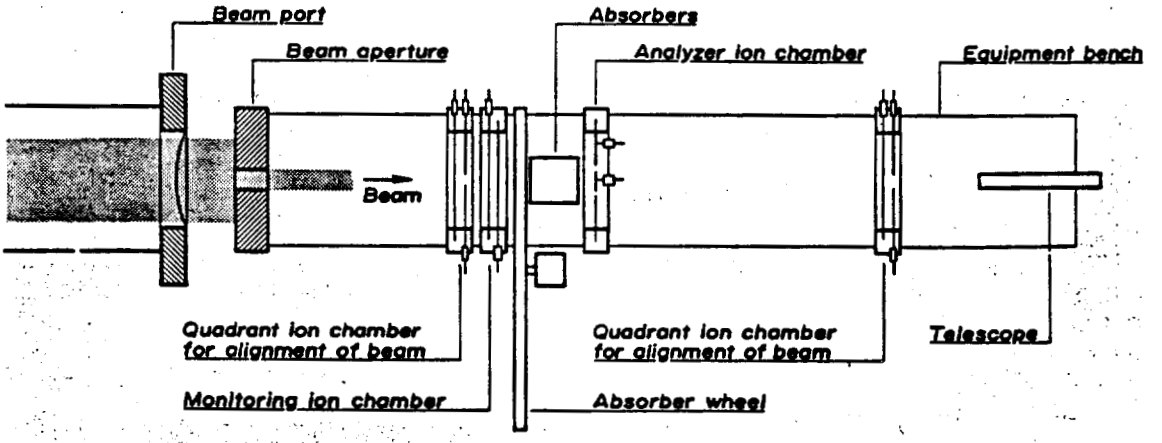

FIG. 4. Schematic arrangement of instruments for study of ionization.

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of the table is indicated at the control station by two "quadrant" ionization chambers which have been described in reference 17 (Fig. 4). When the table is aligned, ionization chambers are placed on it for dosimetry. Usually the beam passes first through a monitoring ionization chamber (Fig. 4). The collecting electrodes in this chamber are larger than the cross section of the beam. Behind the monitor may be placed absorbers of various thickness and atomic number, conveniently mounted on a remotely controlled "absorber wheel" (Fig. 4). Behind the absorber is the "analyzer ion chamber" (Fig. 4) for total ionization measurements. The analyzer is similar to the monitor; for dose measurements the analyzer usually has a well defined small ion collection volume. If the beam intensity, that is the number of particles in the beam, is to be measured, the analyzer is a Faraday cage of special design.

PHYSICAL PROPERTIES OF 190 MEV. DEUTERONS

Ionization. When it was certain that the ionization chambers collect all ions formed by the beam in their sensitive volume by taking a plateau curve, the ionization of deuterons in air was measured when the beam passed through various absorber thicknesses. The variation of ionization versus thickness of lucite absorbers is plotted in Figure 5. For purposes of comparison, the ionization of 200 kv. roentgen rays and of 16 mev. electrons is also plotted on the same graph. The advantages of the deuteron beam for producing high ionization at a considerable depth are clearly indicated. The ratio of peak ionization to ionization at the point of entry in lucite, which is roughly equivalent to soft tissue, is about 4.1 for 190 mev. deuterons. This ratio, however, varies between 3.4 and 4.5 from day to day, due to variations in the homogeneity of the beam energy and it is higher if the cyclotron beam energy is held constant to a high precision. The experimental curve agrees

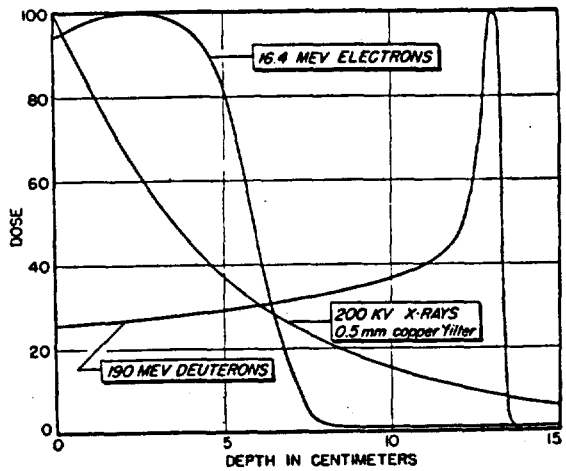

Fig. 5. Comparative ionization in air of three different radiations as a function of absorber thickness. The 200 kv. roentgen-ray curve is taken from Glasser, Quimby, Taylor and Weatherwax,[27] *Physical Foundations of Radiology*, page 225. The ionization as a function of depth of 16.4 mev. electrons has been measured originally by L. S. Skaggs *et al.*[9] The ionization curve for 190 mev. deuterons was measured in the present work. Note that as far as the ratio of depth dose to surface dose is concerned, the deuteron beam is superior to the other two radiations, indicated by ratio of approximately 4:1. The peak ionization for the 190 mev. deuterons lies at absorber thickness approximately 13.5 grams/cm^2. in lucite which is similar in composition to soft tissue.

very well with the predictions made by Wilson[14] for high energy protons.

Dose Distribution. It is reasonably easy to obtain measurements of the scattering properties of high energy particle beams. These measurements were made with a variation of the Failla extrapolation chamber. The isodose curves obtained by this method for an aperture size of 2.54 cm. diameter are shown in Figure 6. These curves are corrected for the stopping power of soft tissue. The actual isodose surfaces are obtained by rotating the curve in Figure 6 around the beam axis.

The increase of ionization with decreasing penetrating power is due to the increased rate of energy loss of the individual particles as their velocity decreases. The lack of excessive scattering may be photographically demonstrated. For this

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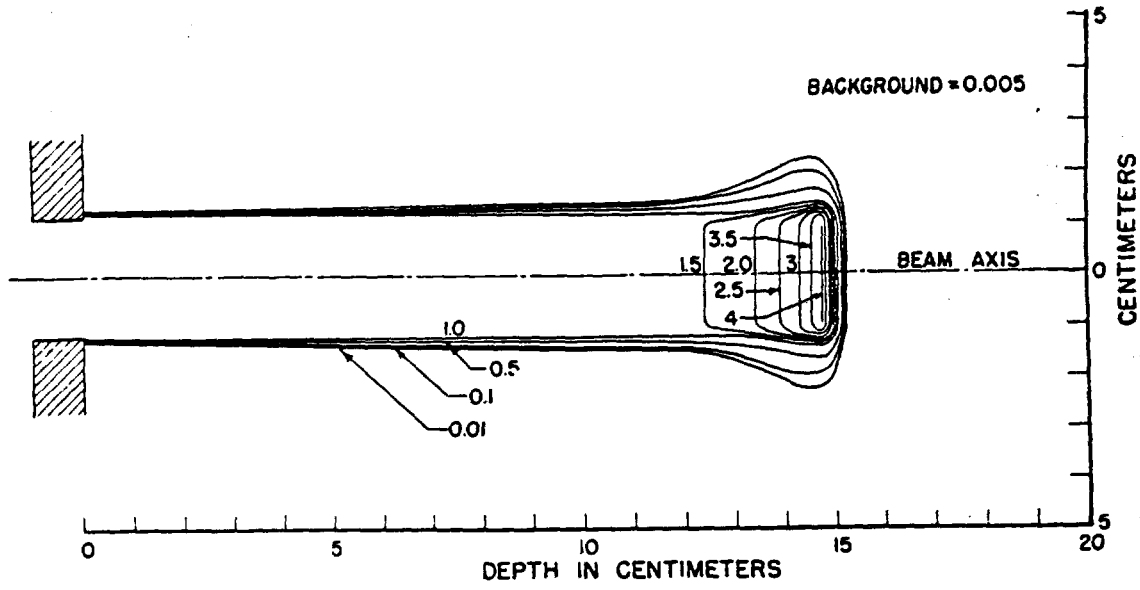

FIG. 6. Isodose curves plotted from actual measurements on a lucite phantom. The beam is limited by a circular aperture 2.5 cm. in diameter. Notice the sharp high peak of ionization, the very rapid drop of the dosage when the beam is near the end of its range, coupled with the low exit dose which is only 0.5 per cent of the dose at the skin. Scattering is almost completely absent from the point of view of dosage. The beam in some respects is similar to a straight pencil of radiation, with a peak of ionization at the end of the pencil. The spatial isodose surfaces are obtained by rotation of this diagram around the beam axis.

purpose, the deuteron beam was passed through an aperture ½ inch in diameter, then through a thick piece of aluminum with a photographic film behind it (Fig. 7). The increase in the effective diameter of the ionizing beam is very small. The experimental conditions are not favorable for determining the exact multiple elastic scattering coefficients.

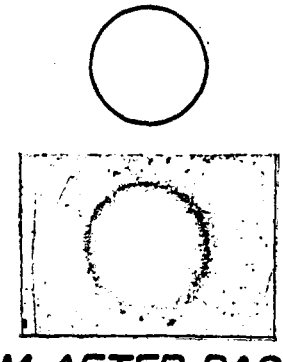

FIG. 7. Radioautograph of the deuteron beam that passed through an aperture ½ inch in diameter (shown on top of the figure) and subsequently through 17.5 g.cm.$^{-2}$ aluminum absorber. The outline of the beam is quite clearly defined. Note the absence of excessive scattering.

The above described characteristics give briefly the ionizing properties which should make high energy nucleon beams valuable in experimental radiology. Briefly, they may be summarized as: low skin dose, high peak dose at considerable depth, low scattering, and very abrupt fall off of ionization, both in the forward and lateral directions. An additional advantage is the great flexibility with which high energy nucleons may be used to achieve a wide range of dose distributions. It seemed clear to us that large doses of localized ionizing radiation could be placed at considerable depths in tissue with a much smaller surface skin dose.

VARIATION OF THE DEPTH AT WHICH THE MAXIMUM DOSE OCCURS

Using a cyclotron designed for monoenergetic ions, the depth of penetration in tissue may be decreased by using an ab-

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sorber of appropriate thickness between the cyclotron and the body to be exposed. The entire ionization curve will shift in this case. The thickness of the absorber is chosen according to the required range of the beam in the tissue.

Another method that offers some advantage in reduction of straggling would be the use of particles with proper energy for each penetration desired. While this method is not available now it could be achieved in a machine expressly designed for medical purposes.

MAXIMUM AVAILABLE DEPTH DOSE

The ratio of depth dose vs. surface dose may be considerably increased by three different techniques: These are multiple port irradiation, rotational irradiation, and beam focusing. The ratio of depth dose to surface dose may be increased more than 100-fold in these ways. As an example, consider 360° rotation of deuterons in a 1 inch diameter beam around an axis coinciding with the peak of the ionization curve. This curve is often called the Bragg ionization curve in honor of Sir William Bragg who studied it for natural alpha emitters. Figure 8 gives the dose distribution in the plane of rotation for this case. Note the sharp increase in dose near the center of rotation. By varying the beam aperture from the circular form and combining different aperture shapes with rotation, it is possible to achieve dose distributions at any desired tissue depth to fit the shape of almost any desired volume to be irradiated.

It is possible to obtain a radiograph of the deuteron beam by placing a roentgen film in water with the film surface parallel to the direction of the beam. One obtains only a qualitative picture in this fashion. The blackening on the film is not exactly proportional to the ionization since the photographic film is relatively less sensitive to high specific ionization. Nevertheless such a picture was made and one is reproduced in Figure 9, showing the effect of the Bragg ionization curve combined with 120° rotation.

It is also possible, though this has not been done so far, to focus the deuteron particles so that they converge conically in a small area. This method also increases the ratio of depth dose to surface dose.

WIDENING OF THE HIGH DOSE PLATEAU

If the volume to be irradiated is thicker than the width of the Bragg ionization

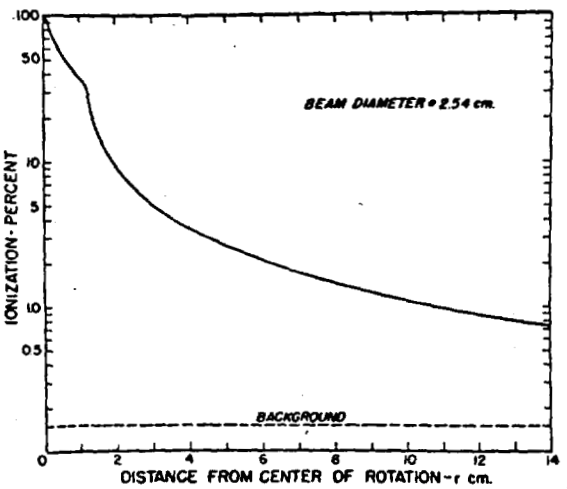

Fig. 8. Ionization distribution in tissue resulting from rotation of a 2.54 cm. diameter beam of 190 mev. deuterons in a plane 360° around a point. The center of rotation coincides with the peak of the Bragg curve. The manner of rotation is indicated on the graph. The curve plotted corresponds to ionization along any radius in the plane of rotation.

peak, simple methods are available to broaden the peak. In principle, a broad peak results from deuterons that have considerable energy distribution. In practice, one may insert a variable thickness absorber wheel in the beam before it reaches the body. As the wheel rotates during exposure, the effect of a broader maximum is obtained. Multiple port irradiation also gives the effect of a broader maximum if the ports are at wide angles.

BEAM INTENSITY

As the parallel beam of ions accelerated in the cyclotron traverses tissue some of the particles are lost from the beam. They are lost partly by multiple elastic scatter-

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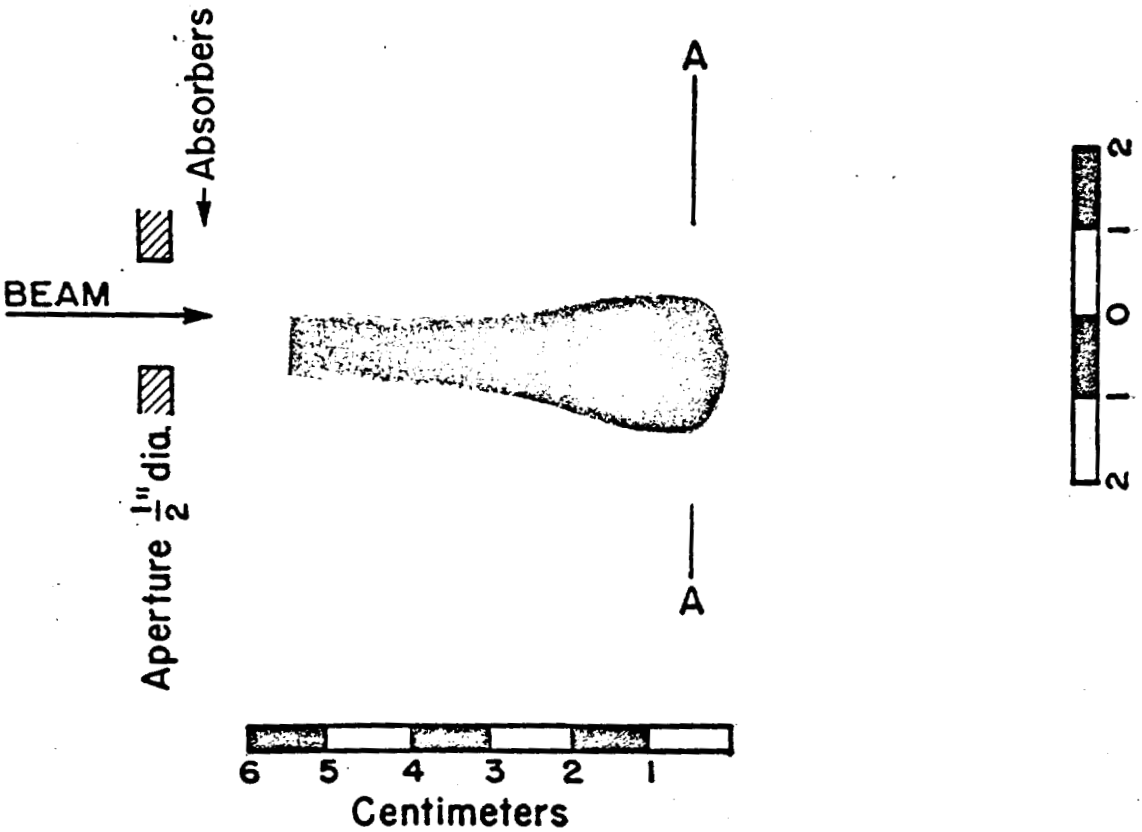

FIG. 9. Radioautograph of end of range of 190 mev. deuterons on roentgen film. The beam emerged through an aperture ½ inch in diameter. The commercial roentgen-ray diagnostic film was immersed in water and rotated slowly through an angle of 60 degrees around axis A–A while the picture was taken.

ing, but mainly by inelastic scattering resulting in nuclear transmutations. Before biological application of the beams was made it was necessary to attempt measurement of the absolute number of particles in the beam as well as their attenuation as it was related to the total ionization. For this purpose the analyzer of Figure 4 was a Faraday cage and a number of measurements were made to determine the number of deuteron particles that penetrated different absorber thicknesses. For polystyrene and aluminum a "Faraday attenuation" curve is plotted in Figure 10. One may notice that most of the particles penetrate almost the entire thickness of absorber, the slight initial slope of the curve being due to inelastic collisions. Near the end of the range, the number of particles drops rapidly but not precipitously because of the small amount of straggling present. Theoretically each particle having the same energy would penetrate the same depth in an absorber were it not for three different processes. The first process is the straggling of energy loss.

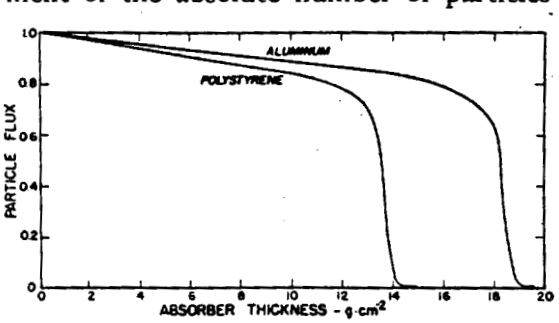

FIG. 10. Flux of high speed deuterons as a function of absorber thickness in aluminum and polystyrene (11.5 per cent H and 88.5 per cent C). The curves are quite similar for different elements and the range for various elements and tissue compositions may be quite accurately determined from the measured stopping powers.

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Different particles traveling in a straight path have random statistical fluctuations in their ionization and rate of energy loss. The second cause for range distribution is multiple elastic scattering of deuterons by nuclei of the absorber. In this process the particles suffer many small impacts, each of them causing a slight change in the direction of the particles. The result is a slight spreading of the beam and a consequent shortening and statistical distribution of their range measured along the beam axis. The third cause of straggling is the loss of particles from the beam due to inelastic interaction of the beam particles with the nuclei of absorber atoms.

It was interesting to compare the measured mean range with the range given in the Range-Energy Tables prepared by W. A. Aron *et al.*[18] On the basis of this comparison the beam energy was determined to be 190 mev., assuming that the tables which were extrapolated entirely from low energy data were correct for the high energy ranges. This is in reasonable agreement with the only other independent method available at the present time for measurement of the beam energy, namely by estimation, from the radius of curvature of the ion path in the field of the focusing magnet.

From the slope of the end of the range distribution curve it is possible to calculate the root mean square fluctuation δR of the range [19]

$$\frac{\delta R}{R_m} \approx \frac{2}{\sqrt{\pi}} \frac{R_0 - R_m}{R_m} \approx 0.017$$

where R_0 is the extrapolated range and R_m is the mean range. This may be compared to an approximate formula for the straggling of monoenergetic particles given by Wilson,[20] and based on Bethe's equation for energy loss.

$$\frac{\delta R}{R} \approx 0.24\, W^{-0.1} E_0^{-1/2} \approx 0.007.$$

Here W is the ratio of kinetic energy to rest energy of the deuterons and E_0 their rest energy expressed in mev.

The experimentally obtained straggling is about twice the theoretical value assumed for monoenergetic particles. By examination of the range energy formula one may conclude that the cyclotron deuterons must be quite monoenergetic. It is estimated that the energy spread of the beam is of the order of 1 mev. (0.5 per cent) or less.

The initial decrease in ion flux at low absorber thicknesses is due to inelastic collisions (Fig. 10). The accurate evaluation of the cross section for inelastic scattering and the angular distribution of the scattered particles is beyond the scope of this paper. However, during the past three years significant work has been done on this problem so that the salient facts are now quite well understood. At high velocities corresponding to a kinetic energy of 100 mev. per nucleon or higher, the nucleus itself becomes partially transparent as shown by Cook *et al.*[21] At low atomic number Z, the nucleus may be regarded as a collection of nucleons, capable of interacting individually with the incident particle. The mean free path of a 110 mev. nucleon in the nucleus is 3×10^{-13} cm., so that at higher Z, multiple nucleon-to-nucleon collisions occur in the nucleus. In a single nucleon-to-nucleon collision the energy loss is usually not more than 25 mev. Whether the process following the collision is the emission of a single particle or several particles depends on the interaction of the excited nucleon with the rest of the nucleus.[22] The yield of stars has been investigated in photographic emulsions with deuterons and high energy helium ions by Gardner and associates.[23] The mean prong number was found to be approximately 3 for each star in the emulsion.

When deuterons are used for tissue irradiation, it is quite possible to predict that the general type of particles in nuclear stars will be preponderantly protons, neutrons and alpha particles. The distance between the proton and neutron composing the deuteron nucleus is so large that often one of the nucleons gets into the target

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nucleus while the other remains outside. This leads to the so-called stripping process in which the deuteron flies apart, thus giving rise to fast neutrons or protons. Either of these moves predominantly in the forward direction. The stripping process was proposed by Serber.[24] From the range of the products of star formation, their wide distribution at all angles, and their expected cross section it is estimated that the star prongs might contribute not more than 1 per cent to the ionization in air of 200 mev. deuterons, and to the particle current measured in the Faraday cage. The ionization and current measurements should thus be only slightly affected by the recoils produced in inelastic collisions. Attempts were made to detect such effects by obtaining differences in ionization when the ion chamber wall material was varied in atomic number. However, since the standard error in ionization measurements was about 1.6 per cent, no significant effects were observed due to ionization from nuclear stars. One may infer from this result that the biological effect of the nuclear stars is also lower than that of primary deuteron ionization though not necessarily lower than 1 per cent.

The inelastic cross section varies inversely with the energy. The slope of the Faraday cage curve was not steep enough for accurate cross section measurement. However, by extrapolation one obtains a figure of 5×10^{-25} cm.^{2} for aluminum above 100 mev. Below 100 mev. the total cross section is greater.

When enough absorber has been placed in the beam to stop all deuterons, there are still some ionizing particles left in the beam. They have about one half of 1 per cent of the ionizing value of the high energy particles. This ionization is chiefly due to recoils due to elastic collisions with the fast neutrons produced by the stripping and other inelastic processes. The ionization at absorber thickness greater than the range of the beam is of the same order of magnitude as general neutron background in the exposure room.

RATE OF ENERGY LOSS

Measurement of the Bragg curve and of the Faraday curve is of interest in radiobiological investigations because the use of these data allows determination of the specific ionization of the particles and from this the rate of energy loss. The specific ionization for single particles may be quite accurately calculated as a function of energy.[18] Due to straggling, multiple and inelastic scattering, the beam ceases to be monoenergetic as it is slowed down in an absorber. Correspondingly, one is able to calculate from the experimental data the mean ionization per particle which takes into account the finite energy spread of the beam at low energies. Figure 11 shows the experimentally obtained mean specific ionization curve in air with aluminum absorbers. A 30-fold increase in specific ionization is obtained as the particles slow down. The increase is steeper than the total ionization curve itself. Specific ionization and rate of energy loss are of great interest in radiobiology since it is known that the relative biological effectiveness of various radiations is a function of these quantities. Provided that one knows the energy required per ion pair produced, the specific ionization may be interpreted in terms of rate of energy loss as well. Assuming that the theoretical values for the rate of energy loss[18] are correct, we determined the value of W, the average energy required per ion pair, by simultaneous ionization and beam current measurement and found it to be 32.5 ev. for dry air at STP.

W is approximately constant for the entire energy range down to 10 mev. deuterons. More recently Bakker and Segre determined W values[25] with 340 mev. protons in a number of gases.

The specific ionization of the doubly ionized 380 mev. α-particles varies in a fashion similar to deuterons along their path; the range of these particles is one-half that of 190 mev. deuterons and the specific ionization four times that of deuterons with the same velocity. Bragg

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curves and Faraday cage curves are available for these particles. It should be pointed out that different sources of the high energy deuterons and alpha particle beams afford means for the experimental study of biological effects on small organisms with a 300-fold variation of mean rate of energy loss. Work along these lines is in progress.

concept and terminology may be applied to a number of radiations. We shall discuss each unit separately.

(1) *The beam current*: (*I*) This may be expressed in ampere units or in terms of particles per second and corresponds to the electric charge of all high energy ions impinging on the biological specimen per unit time. The beam current may be measured directly using a Faraday cage.

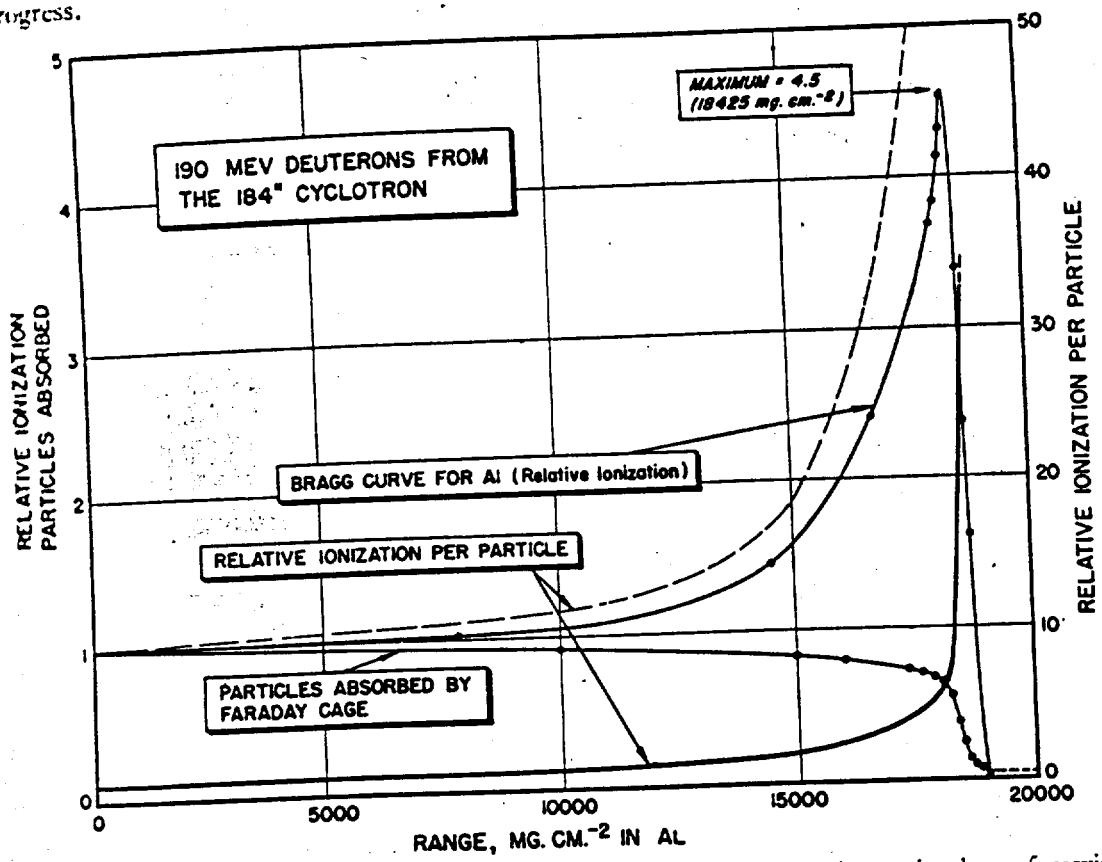

FIG. 11. Relative ionization and relative number of deuterons through aluminum absorbers of varying thickness. The ratio of these gives the mean specific ionization which is plotted in arbitrary units. Observe a sharp increase of the relative ionization per particle at the end of the range.

DOSIMETRY

The use of the traditional roentgen unit is not convenient with high energy ion beams. We are dealing with a radiation that has a very inhomogeneous distribution in space. Six different units of dose were found to be satisfactory in the interpretation of biological effects caused by such beams. Some of these are natural extensions from dosimetry of other radiations. The

In the measurements reported here, the charge Q collected by the Faraday cage has been measured in terms of potential change V caused at the plates of a condenser of known capacity C in time t. The measurement of voltage was made with a slideback voltmeter:

$$Q = CV$$

the current:

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$$I=\frac{dQ}{dt}=C\frac{dV}{dt}. \qquad (1)$$

If the rate of change in potential is measured in volts/sec., and C in farads, one obtains the beam current in amperes. The number of particles which pass a given point per unit time is obtained by dividing I by the particle charge ze in coulombs.

$$\frac{dn}{dt}=\frac{I}{ze}=\frac{C}{ze}\frac{dV}{dt}. \qquad (2)$$

(2) *The beam current density or flux of particles per unit cross section and unit time* (F). The beam current density expressed as amperes cm.$^{-2}$ or as particles cm.$^{-2}$ sec.$^{-1}$ is usually not uniform over the entire cross section of the beam. It has a distribution which reaches a constant maximum at the center of the beam and falls off at the edge. For complete determination of the beam the entire spatial dependence of the current density is needed.

Figure 12 shows flux distributions obtained with the extrapolation chamber at various absorber thicknesses. However, it seems sufficient for most purposes to obtain the peak flux at the center of the aperture since the variation of flux at the edge of the beam is due to scattering and may be estimated for given geometrical conditions. A special ionization chamber was developed for measurement of the flux of particles. This chamber measures the ionization from particles going through an area prescribed by the size of the collecting electrodes.

Let F be the beam current density, F^* the particle flux and i the measured ionization current in an ionization chamber filled with nitrogen and having a sensitive volume v. Assume p_0 to be the specific ionization in terms of ion pairs per particle per cm. of STP nitrogen.

$$F=\frac{i}{vp_0}\ \text{(amp cm.}^{-2}\text{)},$$

$$F^*=\frac{i}{vp_0e}\ \text{(particles cm.}^{-2}\text{ sec.}^{-1}\text{)},$$

(e = charge of electron).

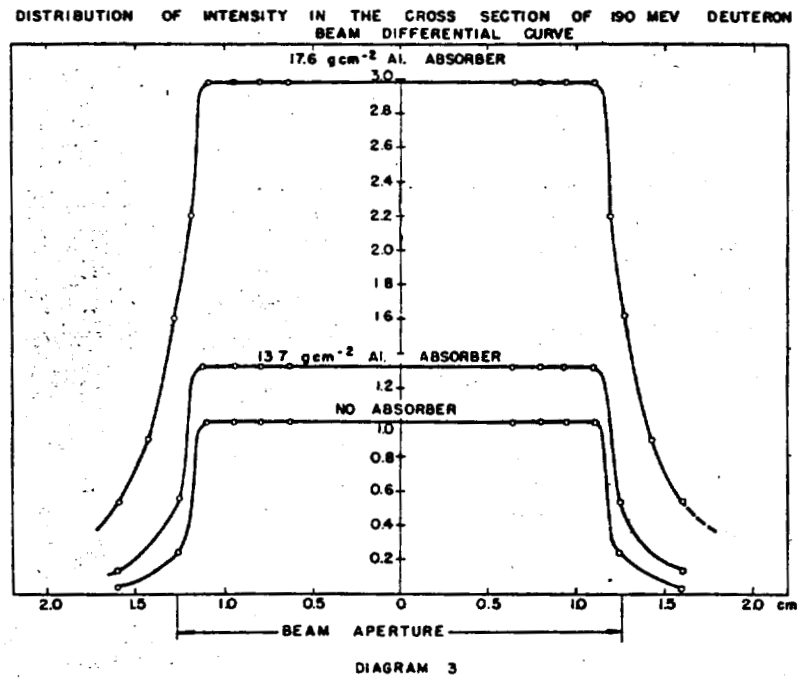

FIG. 12. Distribution of deuteron beam current density at three different absorber thicknesses, in arbitrary units. Beam aperture circular, 1 inch diameter.

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(3) *Specific rate of energy transfer* (R). This is the energy transferred by the beam to a unit mass of tissue of known composition in unit time. It may be obtained by multiplying the particle flux by the rate of energy loss of each particle in the tissue. The specific rate of energy transfer has the same meaning as the dose rate expressed in rep/sec. or gram roentgen/g. sec. units. Conveniently it is measured in terms of mev. g.$^{-1}$sec.$^{-1}$ but it is also easy to express it in terms of other units. From the specific rate of energy transfer of high energy deuterons at a well defined point in the beam, it is possible to calculate specific rate of energy transfer for any other point in homogeneous tissue provided the isodose curves discussed in section 1 are available. For a given aperture size the isodose curves are modified for inhomogeneous tissue only by the variations of density and stopping power of tissue and these depend on tissue composition and geometrical distribution of organs. If the stopping power is known for each point in the irradiated tissue, isodose curves may be approximately calculated for any distribution of tissue without having to measure them out each time in phantoms.

Knowledge of the density of ion chamber gas d_g, and the energy required per ion pair W_g yields the specific rate of energy transfer R_g to the gas.

$$R_g=\frac{i\cdot W_g}{vd_ge}=F^*\cdot r_g. \tag{3}$$

Here r_g is the rate of energy loss (REL) of each particle in ev. for each g.cm.$^{-2}$ of gas traversed.

$$r_g=\frac{W_gp_g}{d_g}=\frac{NZ_g\epsilon_g}{A_g}. \tag{4}$$

Here N is Avogadro's number, Z_g and A_g are atomic number and atomic weight of the chamber filling gas respectively and ϵ_g is the rate of energy loss for each particle per cm.^{2} per electron in the gas. For any other element with constants, Z, A, ϵ the rate of energy loss r is given by

$$r=r_g\frac{ZA_g}{Z_gA}S_e \tag{5}$$

where $S_e=\epsilon/\epsilon_g$ is the relative electronic stopping power. Knowledge of the relative electronic stopping power is thus necessary for determination of the specific rate of energy transfer in tissue from gas ionization measurements. For tissues of complex composition, having $\alpha_1,\alpha_2,\cdots,\alpha_k$ percentages by mass of elements with atomic numbers $Z_1, Z_2,\cdots,Z_k$ we have used the expression

$$r=\frac{r_gA_g}{Z_g}\sum_{j=1}^{k}\frac{\alpha_j}{A_j}S_{ej}Z_j \tag{5a}$$

so that finally the specific rate of energy transfer in tissue, R, from gas ionization measurement, turns out to be

$$R=\frac{iW_gA_g}{vd_geZ_g}\sum_{j=1}^{k}\frac{\alpha_jS_{ej}Z_j}{A_j}=\frac{i\cdot W_gr}{v\cdot d_gr_g}. \tag{6}$$

The nuclear physicist would use R in units of ev. sec.$^{-1}$ $g.^{-1}$, with i in amperes, and W electron volts/ion pair. Multiplication by 1.602×10^{-12} gives R in units of (erg sec.$^{-1}$ $g.^{-1}$) and further division by 93 yields R in units of (rep $g.^{-1}$ sec.$^{-1}$).

The method of averaging stopping power is not completely justified, since some recent experiments[24] seem to indicate that molecular stopping power is not a simple average of atomic stopping powers. However, until more definite confirmation is forthcoming the above figure may be conveniently used. In any case, corrections in stopping power due to molecular interaction would be small. Measurements of stopping power will be discussed in a later section.

(4) *Specific energy transfer* (S). This term corresponds to the total energy received by a gram of tissue during the entire period of irradiation T. It may be obtained by integrating the specific rate of energy transfer over time. It may be expressed in mev./g, ergs/g, rep or gram roentgen/g units.

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$$S=\int_0^T R dt=\frac{W_g}{v_g d_g e}\frac{r}{r_g}\int_0^T i dt=\frac{W_g r \mathcal{Q}}{v_g d_g r_g e}. \quad (7)$$

$\mathcal{Q}$ is the total charge collected by the ion chamber in time T.

(5) *Total number of high speed particles* (n) *and density of particles* ($dn/d\sigma$). The total number of high speed ions is particularly useful when comparisons with the "target" theory of radiation effects are made. Measurement is obtained with the Faraday cage. From (2)

$$n=\int_0^T \frac{dn}{dt}dt=\frac{C\cdot V}{z\cdot e}. \quad (8)$$

Even more useful is the expression of particle density per unit cross section of the beam, $dn/d\sigma$. This is obtained from the specific energy transfer and the mean rate of energy loss of the particles, equations 7 and 5

$$\frac{dn}{d\sigma}=\frac{S}{r}=\frac{\mathcal{Q}W_g}{v_g d_g r_g e}. \quad (9)$$

(6) *The energy transfer* (U). The energy transfer is the energy transferred to the entire body of the animal by the beam in the entire course of treatment. This is measured in terms of ev., ergs, or gm. roentgens. This quantity would be usually obtained by integrating the specific energy transfer, S, for the whole mass m of exposed tissue

$$U=\int S dm. \quad (10)$$

The isodose curves are so much alike that it is sufficient to know the aperture size, the rate of particle flux as measured in the monitoring ion chamber and a spatial distribution of different types of absorbers and tissues. In practice we have used total energy transfer together with the mass of the animal body irradiated as per cent of body mass. Often a simpler expression than (10) may be satisfactory if E is used to denote the energy of the high speed ions as they enter the tissue

$$U\approx n\cdot E. \quad (11)$$

The above expression is only approximate because some particles suffer inelastic collisions and produce secondaries. Part of the disintegration recoils produced will produce ionization in tissue, while the other part may escape as neutron or gamma radiation.

DETERMINATION OF ELECTRONIC STOPPING POWER OF DEUTERONS

The range of the particles was determined in aluminum, the standard substance to which the relative stopping power of other elements was referred. The monitoring ionization chamber was used to measure the beam intensity, and the number of particles going through a given thickness of absorber was measured by the Faraday cage. A complete Faraday cage curve for aluminum is shown in Figure 11, yielding the value of 18.425 g.cm.$^{-2}$ for mean range and 18.707 g.cm^{-2} for the extrapolated range of 190 mev. deuterons. A relatively small part of the aluminum absorber, equivalent to slowing the ions to 170 mev., was then removed and a known thickness of another metal with different

TABLE I

MEASURED AND CALCULATED STOPPING POWER OF VARIOUS ELEMENTS FOR 180 MEV. DEUTERONS

Element	Z	S_Z/S_{AL}	S_Z^*/S_N
H†	1	1.25	1.18
Be	4	1.11	1.047
C	6	1.08	1.02
N*	7	1.06	1.00
O†	8	1.04_5	0.98_6
Al‡	12	1.000	0.943
Fe	26	0.920_5	0.868
Cu	29	0.915	0.863
Mo	42	0.847_5	0.739_5
Sn	50	0.823	0.776
Ta	73	0.767	0.724
Pl	82	0.747	0.707
U	92	0.726	0.685

* The nitrogen value was interpolated from the values for O, and C. The last column was added to make comparisons with ionization chamber measurements easy. The ion chambers are usually filled with nitrogen.

† Calculated from data on water, lucite and polystyrene.

‡ Standard basis of comparison.

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atomic number Z was substituted. The range of the deuterons was now measured through the combined absorber consisting of aluminum and the substituted metal. From these data, equivalent thicknesses of aluminum and the substituted metal were calculated. From this the relative stopping power per electron was obtained. The final data are plotted in Figure 13 where the relative electronic stopping power compared to aluminum is shown as a function of the atomic number Z, Z being plotted on a logarithmic scale. Beginning with the element Fe there is a straight line relationship between the electronic stopping power and the logarithm of Z. Below Fe the relationship is not as simple. Theoretically there is no particular reason why all the points should lie on a completely smooth curve. Table 1 shows the results of the measurements and the calculated stopping power. In the usual theory, the Thomas Fermi Statistical model of the atom is used in calculating the theoretical rate of energy loss. According to this theory the ionization potential, which may be deduced from the stopping power measurements, is exactly proportional to the atomic number at high Z. According to the present experiments there is no strict proportionality with the atomic number; rather the ionization potential is proportional to the 1.1 power of the atomic number. The deviation is not great enough to change the theoretical range and above $Z=25$ the assumption $I=9.5\ Z$ volts still fits the data reasonably well. The discrepancy should be more apparent when billion volt parti-

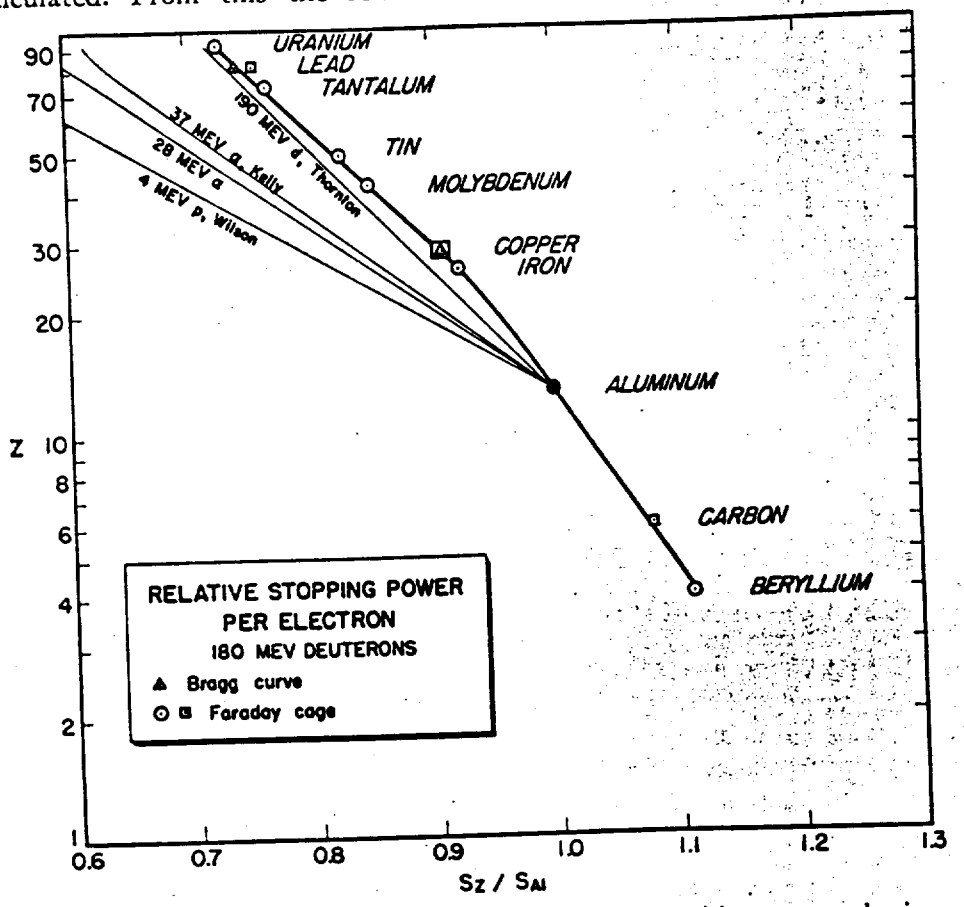

Fig. 13. Relative stopping power per electron of 180 mev. deuterons with respect to aluminum, as a function of the atomic number.

cles are available, and it will play a role in the range energy determination of the high energy particles.

Having obtained the electronic stopping power, it is now possible to calculate the equivalent stopping power per gram of different types of tissue of known composition and density. These values may be used immediately in dosage calculations. Table II gives the values for soft tissue, dry protein and bone. There is some difference in the manner of stopping high energy charged particles compared to low energy roentgen rays. Bone usually absorbs more energy when exposed to low energy roentgen rays than does soft tissue. Materials with high atomic number usually absorb more energy than low Z materials when they are exposed to low energy roentgen rays since the photoelectric absorption coefficient is proportional to Z^3, the Compton and pair production coefficients to Z. In the case of deuterons, protons or alpha particles the energy absorbed per gram of high atomic number material is often less than that per gram of low atomic number material because the stopping power per electron is less for high Z than for low Z. Table II shows that in a deuteron beam bone absorbs actually slightly less energy per gram than a gram of soft tissue placed in the same portion of the beam. In certain therapeutic procedures where bone has to be in the path of the radiation, this circumstance may be of some advantage, since bone is a fairly radiosensitive tissue. The present data add to the information available in the literature at various particle energies consisting of determinations of Wilson[26] for 4 mev. protons, of Kelly and Segre for 15 and 37 mev. alpha particles,[29] Stephan and Thornton for 180 mev. deuterons,[30] and Bakker and Segre[25] for 340 mev. protons.

TABLE II

STOPPING POWER OF 180 MEV. DEUTERONS FOR VARIOUS TISSUES

Medium	Composition in % Mass								Effective Atomic Number Z	Relative Electronic Stopping Power	Relative Mass Stopping Power	Energy Loss of 180 Mev. Deuterons
	H	C	N	O	P	S	Ca	Other Z=16				
Aluminum	—	—	—	—	—	—	—	—	13	0.94	0.91	6.0 mev./g. cm.^{2}
Nitrogen‡	—	—	100	—	—	—	—	—	7	1	1	6.6
Water	11.1	—	88.9	—	—	—	—	—	5.6	1.02	1.14	7.52
Soft tissue* (wet)	10	12	4	73	0.2	0.2	0.01	0.59	5.3	1.024	1.136	7.5
Virus protein* (dry)	7	49	16	25	1	0.5	—	1.5	4.4	1.04	1.03	6.8
Wet bone†	4	17	5	48	5	0.2	20	0.8	4.8	1.03	0.94	6.2

* Composition from ref. 27, p. 7.
† Composition calculated on basis of ref. 28, p. 625.
‡ Relative stopping power assumed to be unity, since the energy loss in nitrogen may be directly estimated from ionization measurement.

RATE OF ENERGY LOSS AND RELATIVE BIOLOGICAL EFFECTS

It is well established that when animal tissues are irradiated, ionizing particles with a high rate of energy loss have a relatively higher biological effect than particles with a low rate of energy loss.[32] The ratio of the doses required to produce the same biological effect (or the so-called relative biological effectiveness, R.B.E.) may be as great as 10 to 1 with fast neutron recoils as compared to roentgen rays. On the other hand, in different biological tissues the R.B.E. may be different for a given particle. In some cases even a decrease of effective-

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ness is found with increasing REL (rate of energy loss). It is worth while to make a comparison of the mean rate of energy loss available at various portions of the deuteron and alpha particle beam with the rates of energy loss of other radiations used at the present time. The rate of energy loss of 190 mev. deuterons per gram soft tissue is about 6.52 mev./g. This rate of energy loss is about the same as the rate of energy loss of 45 kv. electrons. Forty-five kilovolt electrons may be assumed to have the energy of a typical secondary electron from 200 kv. roentgen rays. We thus make the interesting deduction that the relative biological effectiveness of 190 mev. deuterons is expected to be approximately the same as the relative biological effectiveness of 200 kv. roentgen rays. As the deuteron beam penetrates an absorber, the deuterons lose energy but the mean rate of energy loss increases only at a slow rate. When the peak of the Bragg ionization curve is reached, just before the end of the range, the deuterons have a mean energy of 25 mev., and correspondingly the mean specific ionization is 48 mev./g. cm^{-2}. Review of the data recorded in the literature on fast neutron effects indicates that in most of the biological experiments with these fast neutrons the experimenter used neutrons of mixed energy. Most recoils from such neutrons may be estimated to be of relatively low energy, *e.g.*, fast neutrons from a chain reacting pile have a mean energy of approximately 4 mev. Considering the available information, it may be conjectured that the R.B.E. for lethal effect on tissue cells should be not very different from unity at the Bragg ionization peak, but might increase rapidly to a factor of about 10 as the particles slow to a stop. On this basis the R.B.E. of fast deuterons remains close to unity over 95 per cent of their range.

LETHAL EFFECTS OF HIGH ENERGY DEUTERON AND PROTON BEAMS

Since the range of 190 mev. deuterons is about 6 inches in soft tissue and the range of 340 mev. protons is even longer (approximately 28 inches), it was possible to study the lethal effect of whole body irradiation on white laboratory mice. The animals were placed in a beam which was substantially uniform in flux over its diameter of $1\frac{1}{4}$ inches. The particles passed through the entire body with substantially the same specific ionization. The mice were enclosed in plastic tubes of 1 inch diameter and 1/16 inch thickness. Each mouse was placed with the head toward the beam. For one experiment, strain "A" mice were used (480 animals), and for another, Bagg albinos (270 animals). Doses were administered of 180 mev. deuterons, 340 mev. protons, and 200 kv. roentgen rays. The deuteron energy decreased to about 120 mev. at the exit from the mice. Fifty per cent mean lethal doses for a thirty day period were studied. From Table III, it may be seen that there was no significant difference between the three radiations. The weight loss with deuterons and protons was very similar at equal survival ratios to those of roentgen rays. The survival curves had typical shapes resembling data obtained with roentgen rays. The gross symptoms and signs of the mice were typical for radiation sickness. A significant percentage had diarrhea and hemorrhage, which was evidenced by bloody diarrhea. Many of the mice lost weight very rapidly just prior to death, and before death occurred their fur was ruffled. Dr. Paul Rosahn made some histological studies of the various tissue sections obtained from mice irradiated with deuterons at various dose levels. Blood studies were also carried out. These data are being reported in a separate paper.

The results were expected and found to be approximately the same for 200 kv. roentgen rays, deuterons and protons. The timing of roentgen rays and deuterons was different; the roentgen rays were obtained in 60 cycle rectified AC waves; the deuterons in 90 pulses per second each of approximately 10–15 microsecond duration. Some attempt was made to correlate the mean

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dose rate to the lethal dose, and from preliminary data it appears that higher dose rates result in a slightly higher and more rapid lethal effect.[17] However, the many factors which influence the survival of mammals after a dose of radiation makes the last conclusion preliminary and subject to further study. The acute lethal experiments conducted with the high energy deuterons indicate that qualitatively and quantitatively the gross biological effect of high energy nucleons on white mice is quite similar to that of roentgen rays. This is of course not true when the low energy portion of the beam is utilized.

TABLE III

COMPARISON OF ACUTE LETHAL DOSE OF MICE FOR ROENTGEN RAYS, 190 MEV. DEUTERONS AND 340 MEV. PROTONS
50 PER CENT L.D.—30 DAYS

	I	No.	SET	SRET	ET	REL	RBE
Type of Radiation	Mouse strain	of mice in experiment	Specific energy* transfer (ergs/g)	Specific rate of energy transfer (ergs/min)	Energy transfer ergs	Mean rate of energy loss (soft tissue) mev.$^{-1}$ gm.^{2}	Relative biological effect (compared with roentgen rays)
180 mev. roentgen rays	Bagg albino	120	6.6×10^{4}	2.6×10^{3}	1.6×10^{6}	8.0 (approx.)	1
	"A"	120	5.8×10^{4}	2.6×10^{3}	1.4×10^{6}		1
160±30 mev. deuterons	Bagg albino	120	5.5×10^{4}	2.10^{6}	1.4×10^{6}	7.4	approx. 1
	"A"	270	5.6×10^{4}	5.10^{4}	1.3×10^{6}	7.4	approx. 1
315±15 mev. protons	"A"	90	6.2×10^{4}	2.10^{4}	1.4×10^{6}	5.77	approx. 1

* 1 rep = 93 erg/g^{-1}.

PRELIMINARY STUDIES OF RADIATION EFFECTS ON MOUSE TUMORS

It seemed worth while to carry out a few experiments to localize the ionization of the deuterons in some tumors. These experiments have given some indication of the possible future medical usefulness of high energy ion beams.

The choice of the experimental animals was somewhat difficult. It is of advantage to use as large an animal as possible for two reasons: (1) The size of the tumor at the time of irradiation should be small compared to the size of the animal. If this is the case the tumor may be reached by a pencil of radiation without having to irradiate too large a part of the body of the animal. (2) The size of the tumor should be larger than 0.6 cm. because the beam will scatter out to at least this diameter as it passes through the body of the animal, even if very small beam apertures are used. Both of these conditions favor the use of rabbits over rats or mice. The Brown-Pearce carcinoma available in rabbits, however, spontaneously regresses and fails to cause lethal effects in a large percentage of the animals. Since clear-cut evidence of the radiation effect was needed, mice were used in the first experiment. The data reported here refer throughout to Strong A strain mice carrying a transplantable mammary carcinoma.[21] This strain and tumor originally given to us by Dr. Strong

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have been carried on for over fifteen years in the Donner Laboratory and with care there are 100 per cent "takes" among the transplants and 100 per cent of the mice having such tumors die from the carcinomas. At the beginning of these experiments it was quite clear that one could not hope for a 100 per cent regression of tumors after the treatment since several conditions had to be rigorously fulfilled. The tumor had to be irradiated over its entire volume; at the same time the body should not receive more than a moderate dose. These conditions are only partially satisfied in the mice where the skin lying over the tumor will unavoidably receive much radiation. Metastasis of the tumor also might influence the outcome. Using small numbers of mice (there was only limited cyclotron time available), the tumor lethal dose was first established. This was done by pulling the entire tumor, enclosed in a skin fold, away from the body of each animal and endeavoring to direct the beam in such a way that only the tumor and the skin fold would be hit, the rest of the body being avoided. Table IV shows the results, and it was found that specific energy transfer of 6.7×10^5, 9.8×10^5 and 13×10^5 ergs/g. can cause complete regression in about one-half of the animals, in agreement with the observations of Lawrence *et al.*,[32] for 200 kv. roentgen rays and 8 mev. neutrons. 3.3×10^5 erg/g. appeared to have retarded the tumor growth only for a limited time period. Figure 14 indicates the weight loss of some of these animals and their survival time as compared to controls.

Table IV

RESULTS OF DEUTERON IRRADIATION OF MAMMARY CARCINOMA IN "A" MICE
(Body of the Mice Shielded and the Tumor Exposed)

Group	Peak Specific Energy Transfer in Tumor erg g^{-1}	Per Cent Body Mass Exposed	Energy Transfer ergs	Number of Animals	Permanently Recovered with Complete Regression of Tumor Per Cent	Died Apparently Due to Tumor Growth Per Cent	Died Apparently Due to Radiation Effects Per Cent
I	Controls	0	0	40	2.5	97.5	0
II	3.3×10^5	7	0.54×10^6	5	0	100	0
III	6.7×10^5	7	1.08×10^6	19	42	53	5
IV	9.8×10^5	7	1.6×10^6	18	33	50	17
V	13×10^5	7	2.1×10^6	19	50	44	6
		Tumors Exposed Through the Body of the Mice					
VI	9×10^5	20	2.5×10^6	20	25	60	15
VII	11×10^5	20	3.1×10^6	20	20	18	62

The principle which we hoped to demonstrate in a practical way was that by the use of deuterons, protons, or alpha particles it is possible to administer a larger amount of energy to a tumor than to the normal tissues of the animal lying between the tumor and the radiating device. Since the mouse tumors were transplanted under the skin, in the next experiments the mice were placed in such a way that the deuteron beam had to pass through their lungs first before reaching the tumors. The regression dose of the tumor was several times the lethal dose for whole body irradiation of the animals, and therefore it was decided to further enhance the effectiveness of the treatment by a technique equivalent to multiple port irradiation. The tumors of the animals were fixed in space and the animals themselves were rotated slowly around the tumor, describing an arc of 120 degrees. This allowed distribution of the beam in the

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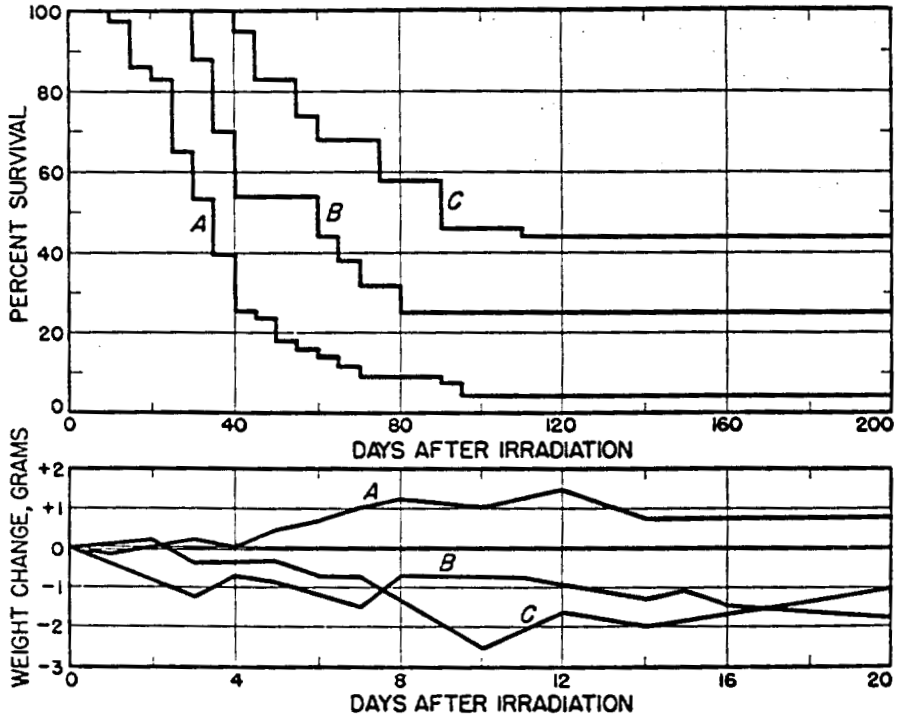

FIG. 14. *Upper Graph:* (A) Survival of A mice with transplanted mammary carcinoma, not treated with radiation. (B) Survival of tumor mice treated with deuterons through their body (Group V, Table IV). (C) Survival of tumor mice treated with deuterons passing only through tumor and the skin enclosing it (Group III, Table IV).

Lower Graph: Weight loss of Groups A, B, C after irradiation.

animal body outside of the tumor and also increased the probability that the most ionizing part of the beam would hit the tumors uniformly. The mice were placed in a lucite tube in a vertical position, anesthetized, and partially immersed in water at body temperature. The tumor was aligned in the center line of the cylindrical water bath. Absorbers were placed in the path of the deuteron beam to bring the peak of ionization to the tumor site. The specific rate of energy transfer was about 2.5×10^5 ergs/g. per minute and each mouse received treatment of only three or four minutes' duration. Two separate experiments were performed. In each of these, 20 mice were irradiated and 20 tumor-bearing control mice passed through

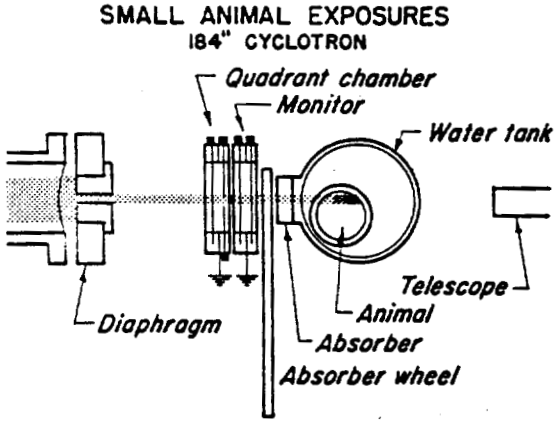

FIG. 15. Method of local irradiation of small animals. The animal is anesthetized and placed in a small lucite cylinder. The cylinder is immersed in a lucite water tank. By rotation and adjustment of the relative positions of the cylinder holding the animal and the water tank, and by adding external absorbers the peak of the Bragg curve can be aligned to any part of the body. During irradiation it is possible to slowly rotate or rock the water tank, thus enhancing the ratio of depth dose to surface dose.

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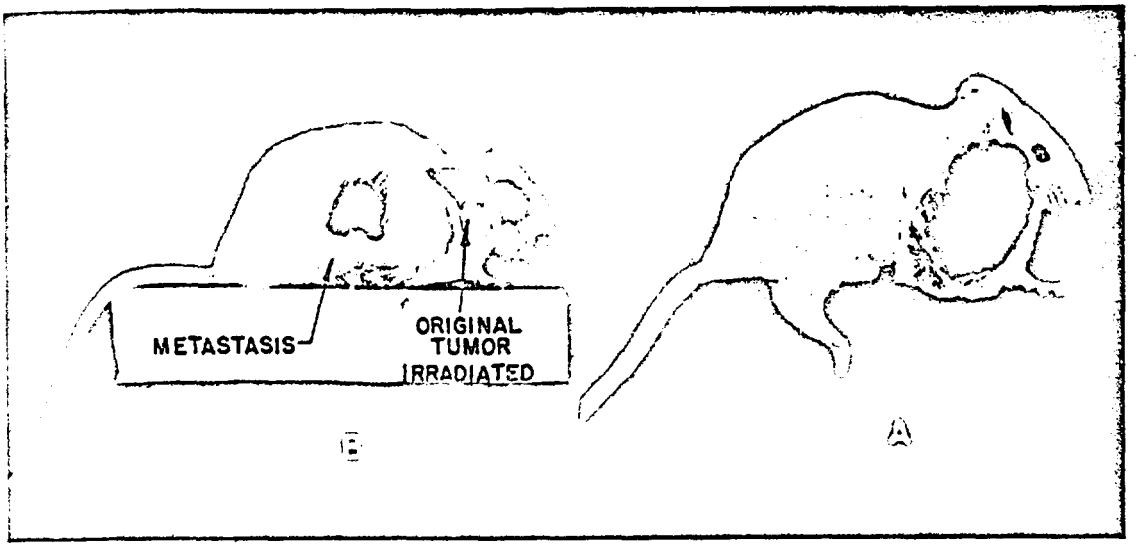

Fig. 16. (*A*) Control mouse, unirradiated, thirty days after transplantation of mammary tumor. (*B*) Tumor mouse treated with deuterons through the body on the tenth day after tumor transplantation. The ray was misdirected and part of the tumor, a direct extension or a metastasis, continued to grow rapidly.

the same handling but received no irradiation. The specific energy transfer was 9×10^5 ergs/g. at the site of the tumor in the first experiment, and 11×10^6 ergs/g. in the second experiment. The beam aperture was adjusted to fit the size of the tumors of the individual mice.

The effect on the irradiated mice (see Table IV) in each instance was quite uniform. Tumor tissues exposed to the most ionizing portions of the beam exhibited rapid regression, in some instances quite complete ten days after irradiation, leaving only scar tissue. At no time thereafter was there any tumor growth observed in any of the mice at or near the central spot of irradiation. A good number of the mice, however, in the treated group still showed continuing tumor growth, resulting apparently from two different causes: (1) The beam was not aligned perfectly in a number of instances and parts of the tumors not affected by the beam continued to grow. (2) There were metastases of the original tumors out of the field of irradiation. In some cases these tumors were along the path of the trocar used for transplanting the tumor, and possibly they represented the deposition of cell fragments at the time of transplantation. Nevertheless, 5 of the first 20 treated animals and 4 of the second group of 20 mice survived the treatment with no ill effects. Altogether 9 animals out of 40 treated survived at least six months after irradiation and their tumors completely regressed.

In Figure 16 a photograph of a typical unirradiated tumor mouse is shown, thirty days after tumor transplantation. Another animal is also shown where the treatment failed since the deuteron beam was misdirected. Figure 17 shows 2 animals twenty days and three months after irradiation. Absence of the tumors is noted; they were replaced by scar tissue. The skin of these animals was epilated and reddened about ten days after radiation treatment. Some of the areas treated became ulcerated, others exhibited hemorrhagic blebs. In cases where no metastases developed, these animals recovered from the skin effects in two or three months. At the end of three months, the skin appeared normal in color, the epidermis somewhat thickened at the site of irradiation, and in most of the animals regrowth of hair occurred.

The irradiated tumor animals lost weight but regained it within a few days after

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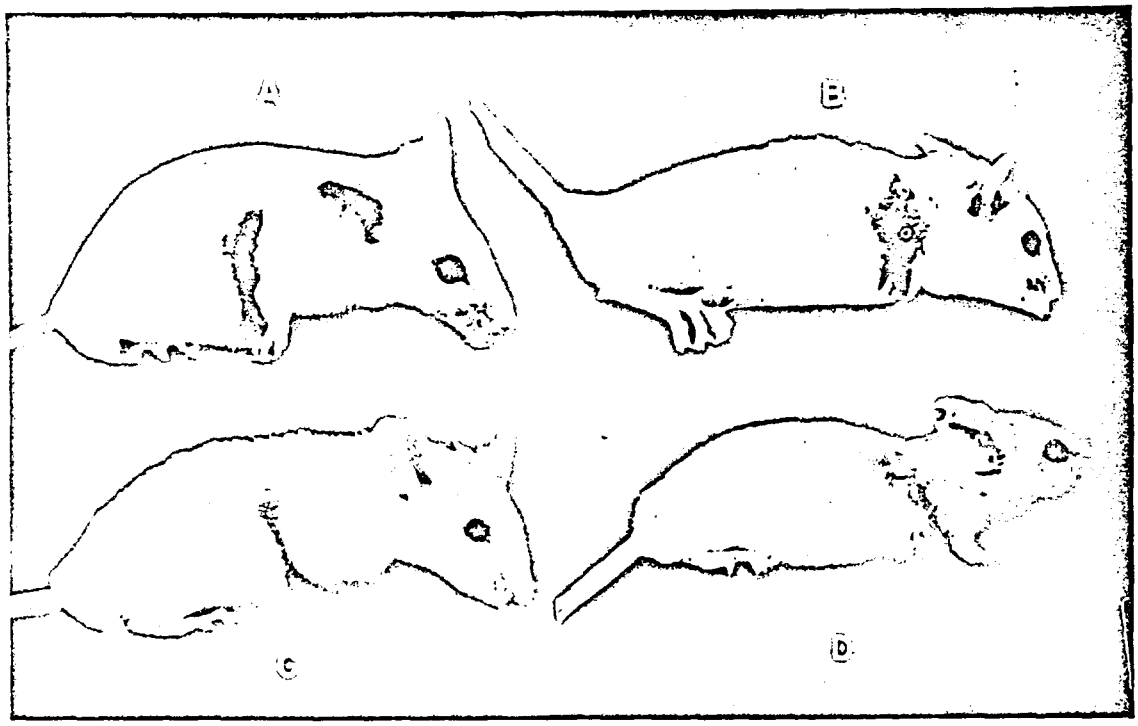

FIG. 17. Tumor mice successfully irradiated with deuterons, the beam passing through their body before reaching the tumor. (*A*) (*B*) Twenty days after irradiation. The tumors are gone, leaving epilated areas and scar tissue. (*C*) (*D*) The same mice three months later. The hair is slowly regrowing over the irradiated areas.

irradiation. In the few animals studied, white and red blood cell counts were temporarily decreased.

Postmortem studies of the animals which died showed in some cases hemorrhage into the lungs; in others, the lungs were partially replaced by fibrous tissue. Other animals apparently died due to unchecked growth of the tumors which had not been accurately irradiated. Some mice in which successful regressions were obtained died as late as nine months after irradiation from late radiation effects without any particular weight loss or previous warning of lethal effect.

Among the group of mice irradiated by the deuterons in Groups II to V of Table IV and where the tumors had regressed, tests were made to determine whether or not the same animals would "take" the same tumor again. It has been reported by many previous workers[33] that mice in which complete tumor regressions were achieved by irradiation become temporarily immune to later transplantation of the same tumor. Twenty-five of the animals that experienced successful regressions were selected and two months after irradiation of the first tumors, retransplants were made. These retransplants did not take in 18 of the 25 animals. These transplants were in an area of the animal body which was entirely unaffected by irradiation. In the other 7 animals the transplants were successful and tumors increased in size rapidly, causing a lethal effect within a few weeks. When retransplantation was attempted in another group of mice after a lapse of four months from the time of irradiation more (60 per cent) of the retransplants were successful. This indicates that the immunity produced was temporary in nature.

Another attempt at irradiation of tumors through the animal body was repeated on

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20 white rats with transplanted lymphosarcomas. The percentage results duplicated the data reported for the mice.

DISCUSSION OF THE ANIMAL STUDIES

The ease with which the dosimetry and the exposures for lethal effect were made and the relative facility with which a significant number of highly radioresistant tumors regressed in the mice and rats indicate the advantages of the use of high energy ion beams in certain special problems of experimental radiology and possibly eventually in radiation therapy. The tumor experiments with the mice were carried out with a relatively crude technique, and due to the smallness of the test animal's body, it was unavoidable that a relatively large dose was given to some of the vital organs of the animals. In the case of larger animals or humans, when a relatively small tumor mass is irradiated, the irradiation could be carried out with very little dose to the surrounding vital normal tissues. Since dosimetry can be easily controlled, even if the proper area is not entirely covered in a single irradiation treatment, the radiologist could correct for this by giving a series of small doses to the tumor. However, the preliminary experiments performed here indicate that the use of directed particle beams would be contraindicated if the tumor contours were not accurately known and if the tumor were of a rapidly metastasizing type. In any event it seems clear that the value of intense local radiation treatment also depends on the radiation sensitivity of the normal tissues surrounding the tumor and of the tissues elsewhere in the path of the beam. The availability of ion beams with advantageous depth dose characteristics should stimulate research work in the field of early diagnosis of inoperable tumors and their accurate localization.

CURRENT WORK WITH THE BEAM OF THE 184 INCH CYCLOTRON

The physical and biological tests described above were completed during the middle of 1949. Based on the results achieved, a modest program was initiated on the study of the biological effects of these radiations on small animals and microorganisms. One of the important radiobiological problems that may be studied with the aid of the high energy ion beam is the effects of irradiations on local regions of the animal body. In collaboration with Lieutenant Victor Bond *et al.* of the United States Navy Radiation Laboratory in San Francisco, some data have been secured on the lethal effects produced when a small part of the body volume, approximately 5 per cent, in various locations is irradiated.*

In collaboration with Beukema, Ansley and Reinhardt of the Department of Anatomy of the University of California, some work was done on arresting bone growth in the young white laboratory rat when certain areas of the extremities around the joints are irradiated.[34] This study, as yet unfinished, furnished a dramatic demonstration for the sharp delineation that is possible between irradiated and unirradiated tissues. With the permission of Dr. Reinhardt we reproduce here a histological section of the tibia of a rat (Fig. 18) which was irradiated twenty-six days previously by a beam of deuterons which was passed through a circular aperture 5/8 inch in diameter. The beam was directed to the knee joint of this animal and the boundary of the beam is indicated by dotted lines on the section. The specific energy transfer was 1.85×10^6 erg/g. In the section (linear magnification of $140 \times$) the demarcation line of the beam is easily discernible. Near the knee joint the bone marrow is completely depleted of cells and there is no production of new cells. Marked decalcification and other osseous changes are also seen. Beyond the demarcation line the bone marrow and the bone appear to be normal. The sharpness of the dividing line indicates the sharpness of the edge of the beam. This study might possibly

* A report of this work has been submitted for publication.

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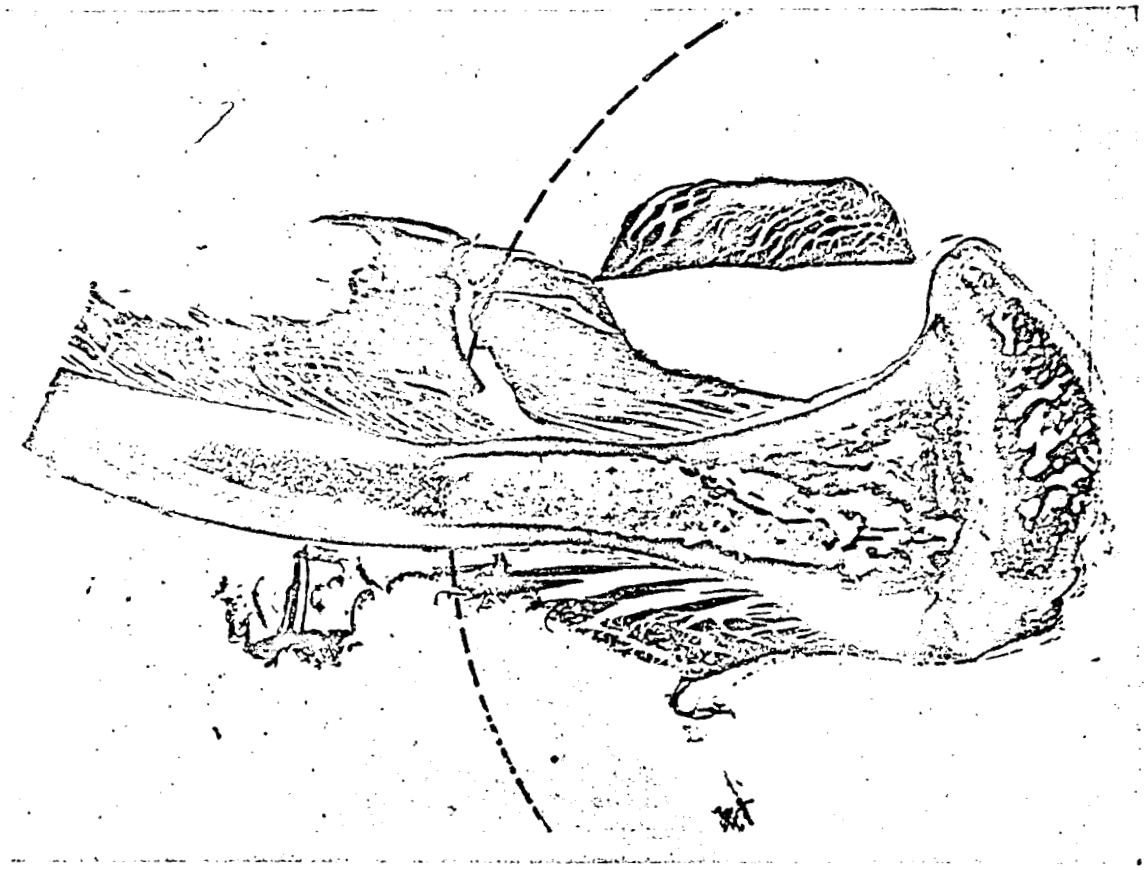

FIG. 18. Histopathological section of rat tibia thirty-six days after irradiation with a radiation field ⅜ inch in diameter. The boundary of the radiation field is indicated by a dotted line. Note the sharp line of transition between treated and normal marrow. The untreated marrow has normal appearance and is full of cells, while the treated area is aplastic containing many free crenated red blood cells and much fluid. The line of transition is similarly sharp for the osseous changes. This section was prepared by Professor Wm. R. Reinhardt and John R. Beukema.

answer the question as to how much each joint of the animal contributes to the growth of the particular limb. It may possibly give some answers to the question of the regeneration of bone marrow and bone from radiation effects and may be a tool in the study of enhancing healing from radiation damage.

When one irradiates a well defined portion of the body, it is important to have a record of the exact areas irradiated. A convenient method used in this laboratory follows:

A roentgenogram of the animal is taken. Without disturbing the film, the animal and film are transported without changing their respective positions to the position where the cyclotron beam exposure is made. The beam is turned on for a short time and the ions pass through the animal body and the film, resulting in a radiograph of the beam cross section. The beam spot on the film is superimposed on the roentgenogram of the animal, and it indicates the region of the animal body which will be irradiated by the beam. This technique is being currently used in attempts to irradiate selectively the pituitary gland of rats with a 0.3 cm. diameter deuteron beam directed laterally through the head. The purpose of this study is to detect the effect of irradiation of the pituitary gland on the

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production of various pituitary hormones. This work is being carried out in collaboration with Donald Van Dyke of the Institute of Experimental Biology and Rex L. Huff of this laboratory.

A set of experiments is being carried out concerning the biological effects of the cyclotron beam on unicellular organisms. Some of these organisms were chosen for the specific properties which are particularly useful in some phases of radiobiological research. The first exposure of single cells was made in collaboration with Norman H. Giles of the Biology Division, Oak Ridge National Laboratory, in which *Tradescantia* pollen was exposed to deuterons and alpha particles of various specific ionizations in order to obtain the relative biological effect as a function of the rate of energy loss for the chromosome breaks produced in these cells.

Particularly promising is the study of the mechanism of the effect of radiation on cell division of yeast cells. This study was initiated with Professor R. E. Zirkle of the University of Chicago during the summer of 1949. An account of further similar investigations was given at the Oberlin Symposium sponsored by the National Research Council.[35] R. L. Dobson of this laboratory has studied the relative biological effect as a function of the rate of energy loss on other microorganisms, notably on the bacterium *E. coli*.[36]

In the present paper the authors have endeavored to show that there are potential applications of this new radiation in the fields of experimental radiotherapy, in the local irradiation of animals for the study of the effect of radiation on various organs, and in radiobiological investigations using unicellular organisms. The studies on unicellular organisms are particularly suitable for demonstration of the mechanism of the biological effects of radiation. Since a number of high energy accelerators are under construction, there should be greater opportunities in the future for utilizing their unique properties for medical and biophysical investigation.

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SUMMARY

The physical properties and isodose curves of 190 mev. deuterons have been described. It is shown that the deuteron beam has unique radiological properties: straight and deep penetration in tissue with small scattering and maximum dose near the end of the range of the beam. The deuteron beam is suitable for effective and intense irradiation of small volumes deep within the body of animals or humans. Detailed accounts of measurements of the ionization, range, stopping power and dosimetry of the ion beam are given. Methods for total and partial body irradiation of small animals are illustrated and results of the acute lethal effects and the effects of local irradiation of mouse tumors are described. Possible application to radiotherapy is pointed out.

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REFERENCES

1. Stone, R. S., Livingston, M. S., Sloan, D. H., and Chaffee, M. A. Radio frequency high voltage apparatus for x-ray therapy. *Radiology*, 1935, *24*, 153–159; 298–302.
2. Dessauer, F., Lion, K., and Gökmen, M. Versuche mit der Rotationsbestrahlung. *Strahlentherapie*, 1937, *60*, 546–556; Dessauer, F., and Mutherem, G. Die Rotationsbestrahlung, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1937, *56*, 218–222.
3. du Mesnil de Rochemont, R. Zur Dosenberechnung bei der Rotationsbestrahlung. *Strahlentherapie*, 1939, *66*, 593–608.
4. Hawley, S. J. Rotation therapy: theory and

1169800

clinical applications. *Radiology*, 1948, *51*, 205–213. (For a recent review see this article.)

5. LAWRENCE, J. H., and LAWRENCE, E. O. Biological action of neutron rays. *Proc. Nat. Acad. Sc.*, 1936, *22*, 124–133.
6. STONE, R. S., LAWRENCE, J. H., and AEBERSOLD, P. C. Preliminary report on use of fast neutrons in treatment of malignant disease. *Radiology*, 1940, *35*, 322–327.
7. ADAMS, G. D., ALMY, G. M., DANCOFF, S. M., HANSON, A. O., KERST, D. W., KOCH, H. W., LANZL, E. F., LANZL, L. H., LAUGHLIN, J. S., QUASTLER, H., RIESEN, D. E., ROBINSON, C. S., and SKAGGS, L. S. Techniques for application of betatron to medical therapy. AM. J. ROENTGENOL. & RAD. THERAPY, 1948, *60*, 153–157.
8. QUASTLER, H., ADAMS, G. D., ALMY, G. M., DANCOFF, S. M., HANSON, A. O., KERST, D. W., KOCH, H. W., LANZL, L. H., LAUGHLIN, J. S., RIESEN, D. E., ROBINSON, C. S., JR., AUSTIN, V. T., KERLEY, T. G., LANZL, E. F., MCCLURE, G. Y., THOMPSON, E. A., and SKAGGS, L. S. Techniques for application of betatron to medical therapy. AM. J. ROENTGENOL. & RAD. THERAPY, 1949, *61*, 591–625.
9. QUASTLER, H., and CLARK, R. K. Biological evaluation of 20 million volt roentgen rays. I. Acute roentgen death in mice. AM. J. ROENTGENOL. & RAD. THERAPY, 1945, *54*, 723–727.

   CHASE, H. B., QUASTLER, H., and SKAGGS, L. S. Biological evaluation of 20 million volt roentgen rays. II. Decoloration of hair in mice. AM. J. ROENTGENOL. & RAD. THERAPY, 1947, *57*, 359–361.

   LUCE, W. M., QUASTLER, H., and SKAGGS, L. S. Biological evaluation of 20 million volt roentgen rays. III. Recessive sex-linked lethals in *Drosophila melanogaster*. AM. J. ROENTGENOL. & RAD. THERAPY, 1949, *62*, 555–558.

   QUASTLER, H., and LANZL, ELIZABETH F. Biological evaluation of 20 million volt roentgen rays. IV. Efficiency and dosage range. AM. J. ROENTGENOL. & RAD. THERAPY, 1950, *63*, 566–574.

   LUCE, W. M., QUASTLER, H., and LANZL, E. F. Biological evaluation of 20 million volt roentgen rays. V. Bar effect in *Drosophila*. AM. J. ROENTGENOL. & RAD. THERAPY, 1950, *64*, 963–967.
10. SKAGGS, L. S., ALMY, G. M., KERST, D. W., LANZL, L. H., and UHLMANN, E. M. Development of betatron for electron therapy, with introduction on therapeutic principles of fast electrons. *Radiology*, 1948, *50*, 167–173.

    UHLMANN, E. M., and SKAGGS, L. S. Principles of fast electron therapy in cancer. AM. J. ROENTGENOL. & RAD. THERAPY, 1949, *61*, 232–235.
11. WACHSMANN, F. Ausblick auf die Anwendungsmöglichkeiten der Elektronenschleuder in der Medizin und bisherige Versuchsergebnisse mit ultraharten Strahlungen. Roentgen Congress, Stockholm, June, 1949.

    PAUL, W., and SCHUBERT, G. Physikalische Vorgänge und biologische Wirkungen in mitschnellen elektronen bestrahlten Objekten. *Naturwiss.*, 1950, *37*, 156.
12. TRUMP, J. G., MOSTER, C. R., and CLOUD, R. W. Efficient deep tumor irradiation with roentgen rays of several million volts. AM. J. ROENGENOL. & RAD. THERAPY, 1947, *57*, 703–710.
13. MARINELLI, L. D., TRUNNELL, J. B., HILL, R. F., and FOOTE, F. W. Factors involved in experimental therapy of metastatic thyroid cancer with I^{131}. *Radiology*, 1948, *51*, 553–557.
14. WILSON, R. R. Radiological use of fast protons. *Radiology*, 1946, *47*, 487–491.
15. BROBECK, W. M., LAWRENCE, E. O., MCKENZIE, K. R., MCMILLAN, E. M., SERBER, R., SEWELL, D. C., and THORNTON, R. L. Initial performance of the 184-inch cyclotron of the University of California. *Phys. Rev.*, 1947, *71*, 449.
16. POWELL, W. M., HENRICH, L. R., KERNS, Q. A., SEWELL, D., and THORNTON, R. L. Electromagnetic deflector for the beams of the 184-inch cyclotron. *Rev. Scient. Instruments*, 1948, *19*, 506–512.
17. Preliminary reports of this work were given at the meeting of the American Association for Cancer Research, Detroit, April 16–17, 1949; at the International Congress of Radiology, London, July 23–30, 1950; and Atomic Energy Commission Reports, AECD 2099-A, Tobias, C. A., Anger, H., Weymouth, P. P., and Dobson, R. L. The radiological use of high energy deuteron beams, May 28, 1948, and UCRL 193, Tobias, C. A., Rosahn, P., Lewis, Margaret, Anger, H., and Lawrence, J. H. Biological use of high energy deuterons. July, August, September, 1948.
18. ARON, W. A., HOFMANN, B. G., and WILLIAMS, F. C. Collection of range vs. energy and rate of energy loss vs. energy curves for heavy particles in various media. Atomic Energy Commission Report UCRL 121, Revised February 26, 1949.
19. LIVINGSTON, M. S., and HOLLOWAY, M. G. Range and specific ionization of alpha particles. *Phys. Rev.*, 1938, *54*, 18.
20. WILSON, R. R. Range, straggling and multiple scattering of fast protons. *Phys. Rev.*, 1947, *71*, 384.
21. COOK, L. J., MCMILLAN, E. M., PETERSON, D. M., and SEWELL, D. C. Cross section of nuclei for 90 Mev neutrons. *Phys. Rev.*, 1949, *74*, 7.

1169801

22. Serber, R. Nuclear reactions at high energies. *Phys. Rev.*, 1947, *72*, 1114.

23. Gardner, E., and Peterson, N. Stars in emulsions initiated by deuterons. *Phys. Rev.*, 1949, *75*, 364.

24. Proceedings of the Oberlin Conference, National Research Council. In press. (This article contains a review of the problem.)

25. Bakker, C. J., and Segre, E. Stopping power and energy per ion pair production for 340 Mev protons. Atomic Energy Commission Report, UCRL 850, August 3, 1950.

26. Wilson, R. R. Range and ionization in measurements on high speed protons. *Phys. Rev.*, 1941, *60*, 749–753.

27. Lea, D. E. Actions of Radiations on Living, Cells. Cambridge University Press, London, 1946.

28. Bodansky, M. Introduction to Physiological Chemistry. Fourth edition. John Wiley & Sons, Inc., New York, 1938.

29. Kelly, E. L. Experimental determinations of stopping powers using alpha-particles of 15 to 37 Mev. Atomic Energy Commission Report, UCRL 208. Also in *Phys. Rev.*, 1949, *75*, 1006–1007.

30. Stephan, W. J., and Thornton, R. L. Range measurements of 200 Mev deuterons in various materials. Atomic Energy Commission Report, AECD 2147, October 20, 1947.

31. Lawrence, J. H., Horn, R., and Strong, L. C. Radiation studies on mammary carcinoma in mice. *Yale J. Biol. & Med.*, 1937, *10*, 145–154.

32. Axelrod, Dorothy, Aebersold, P. C., and Lawrence, J. H. Comparative effects of neutrons and x-rays on 3 tumors irradiated in vitro. *Proc. Soc. Exper. Biol. & Med.*, 1941, *48*, 251–256.

33. Goldfeder, Anna. Relation between radiation effects and cell viability as indicated by induced resistance to transplanted tumors. *Radiology*, 1942, 426–431; see also Goldfeder, Anna. Further studies on relation between radiation effects, cell viability, and induced resistance to malignant growth. II. Effects of roentgen rays on Bagg-Jackson mouse carcinoma 755 irradiated in vitro and in situ. *Radiology*, 1945, *44*, 283–292; see also Goldfeder, Anna. Relationship between morphology and x-ray effects in implants of mouse sarcoma 180 irradiated with 5,000 and 60,000 roentgens (in air). *Radiology*, 1945, *45*, 49–55.

34. Beukema, J. R. Study of biological effect of deuteron irradiation upon growing bone of young rats. On file, Anatomy Department, University of California, Berkeley, California.

35. Tobias, C. A. Proceedings Oberlin Conference; also UCRL 960, Biological studies of radiation effects, evidence of a combined target, intermediate action mechanism of radiation effects, 1950, 43–69.

36. Dobson, R. L. Effects of radiation on Escherichia coli. Thesis, University of California, Berkeley, California; also in process of publication as a UCRL report entitled: Lethal radiation effects of x-rays, deuterons, and alpha particles on the bacterium Escherichia coli. 1951.

37. Glasser, O., Quimby, Edith, H., Taylor, L. S., and Weatherwax, J. L. Physical Foundations of Radiology. P. B. Hoeber, Inc., New York, 1947.

1169802