Radiological Use of Fast Protons

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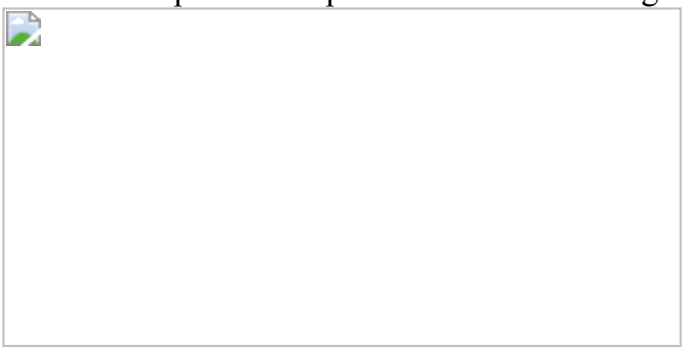
Except for electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators.

Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 MeV (million electron volts) and perhaps as high as 400 MeV. ***The range of a 125 MeV proton in tissue is 12 cm., while that of a 200 MeV proton is 27 cm. It is clear that such protons can penetrate to any part of the body***.

The proton proceeds through the tissue in ***very nearly a straight line,*** and the tissue is ionized at the expense of the energy of the proton until the proton is stopped. The dosage is proportional to the ionization per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

Let us examine the properties of fast protons somewhat more quantitatively. Perhaps the most important biological quantity is the specific ionization, or number of ions per centimeter of track. This quantity is not difficult to calculate. The results of such calculations are shown in Figure l, where the range of protons in tissue is plotted for protons of various energies.

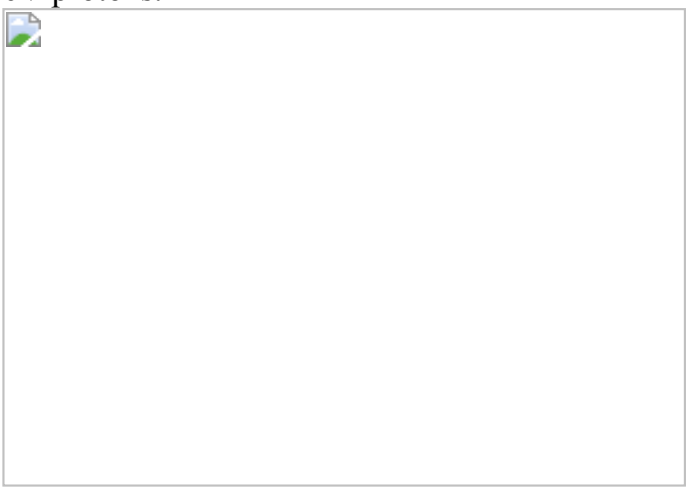


In the same figure, the specific ionization is plotted as a function of the range in tissue. For purposes of calculation, tissue has been assumed to have the molecular formula (1): C0.5H8O3.8N0.14, and to be of unit density, i.e., 15 per cent protein and 85 per cent water. The calculations can be easily extended to other materials and densities.

The range of a proton in air in meters is given by the convenient formula R=(E/9.29)^1.8 where the energy is expressed in MeV. The range in tissue is 1.11 X 10^-3times the range in air. The stopping power of other substances may be found in Livingston and Bethe: Rev. Mod. Physics 9: 246,1937. The physical calculations of this paper will be submitted to the Physical Review for publication.

The accuracy is perhaps 5 per cent. However,exact values for various tissues can be quickly measured as soon as the fast protons are available. Fig. 1. Curve I is the range-energy relation in tissue. Curve II shows the specific ionization as a function of the residual range of a proton in tissue. Figure 1 shows, for example, that if we want to expose a region located l0 cm. below the nearest surface, it will be necessary ionization over the last to have protons of 115 MeV. If a depth of 15 cm. were required, then 140 MeV pro- tons would be needed. The specific ionization curve needs a little

interpretation If we interpret the abscissae as the residual range, then there should be little difficulty in visualizing the specific ionization at various depths within the body. As a particular example, let us consider 140 MeV protons.



In Figure 2, the dotted line is a depth-dose curve obtained by plotting the specific ionization taken from curve II of Figure 1 against the depth of proton in the tissue. Thus, at the surface, the residual range is 15 cm., and curve II of Figure 1 shows that the specific ionization for a proton of 15 cm. range is 0.15 million ion pairs per centimeter. This point has been adjusted to 100 per cent in Figure 2. When the proton has proceeded into the tissue 7 cm., its residual range is 8 cm. and the ionization of a proton of 8 cm. range is 0.2 million ion pairs per centimeter or 133 per cent of the surface dose.

The rest of the curve can be obtained in the same way, and we see that the curve rises sharply in the last few centimeters. The average ionization over the last centimeter is about six times that at the surface. In the final half centimeter of a proton track, the average dose is sixteen times the skin dose.

The full curve is perhaps more realistic, however, and it will be explained later. It is well known (2) that ***the biological damage depends not only on the number of ions produced in a cell, but also upon the density of ionization.*** Thus the biological effects ***near the end of the range will be considerably enhanced*** due to greater specific ionization, the degree of enhancement depending critically upon the type of cell irradiated. At this time we might inquire about the current of protons required for an irradiation. I shall use the roentgen equivalent dose, as it particularly is amenable to calculation for this application. One roentgen equivalent dose (r.e.d.) of protons will have been received at a certain point in the tissue when 83 ergs of energy have been absorbed per gram of tissue. In the last centimeter of range a proton loses 30.1 MeV (energy of a proton of 1.0 cm. range; see curve I of Figure 1). Since 1 MeV is equal to 1.6 millionths of an erg, each proton loses 48 millionths of an erg in the last centimeter. Hence, to produce 1 r.e.d. averaged over the last centimeter of depth requires 48 X 10^6 = 1.72 mi11ion protons per square centimeter. To produce 1,000 r.e.d. will require 1.72 billion protons per square centimeter. This corresponds to a current of 2.75 X 10^-10 amp./cm^2 of protons for a one-second exposure or 4.6 X 10^-13 amp./cm^2 for a ten-minute exposure.
More generally the r.e.d. at a point x cm below the surface is given approximately by the formula:

where R is the total range of the proton in tissue in mm, j is the current density or protons in amperes/cm^2., and t the exposure time in seconds. The formula is not accurate in the last millimeters of range.

The machines now under construction should have little difficulty in producing such currents. In fact, it is expected that they will yield currents millions of times as great. It will be simple to collimate proton beams to less than 1.0 mm. diameter or to expand them to cover any area uniformly

Let us now become a 1ittle more technical and consider secondary effects. First, the energy loss of the proton is a statistica1 effect due essentially to the production of ions along its path; hence, not all protons of the same energy will stop at the same distance beneath the skin. This effect is called range straggling and is easy to calculate. The results of such calculations can be summarized by saying that the longitudinal width in which most protons come to rest is about 1 per cent of the initial range . The protons come to rest so that the distribution of their end-points is given by:

where x is the distance below the surface, and a is given by:

where N is the atoms per cm^3, Z is the atomic number, z is the ion charge number, Eo is the rest energy of the ion in MeV, and R is the range in cm.

The effect of this on the depth dose curve is qualitatively shown in Figure 2. As a result of straggling, the full curve obtains instead of the dotted one. Fig. 2. The dotted curve shows the relative dose due to a since 140 MeV proton. The full curve shows qualitatively the depth dose curve for a beam of 140 MeV protons in tissue.

A second effect is due to the many small angle scatterings of the proton as it passes the nuclei of the atoms of the tissue. This is called multiple scattering, and its effect is to spread the end of the beam out transversely. It is also easy to calculate, and it turns out that the transverse width which an infinitely narrow starting beam would have at the end of its range is about 5 per cent of the initial range.

The transverse distribution of the end-points of the protons is given by:

where y is the distance from the average end of the range measured perpendicular to the initial direction of the beam, and B is given by:

The numerical constant should be determined more accurately by experiment. Both effects are small, but they do indicate the limitations of precision available.

A third effect is that due to the nuclear absorption and scattering of the protons. The exact behavior of protons in nuclear reactions at such high energies as considered here must be determined by experiments to be carried out in the future. Present experiments using high-energy neutrons give good estimates of the radii of most nuclei (3). Probably whenever a fast proton hits the nucleus it will be captured and its energy will appear in several slower protons, alpha particles, or neutrons. In any case, the probability of a proton impinging on a nucleus after traveling 10 cm. in tissue will be about 25 per cent. The effect tends to decrease the specific ionization at the end of the range by 15 to 30 per cent. Inasmuch as the specific ionization is several times greater at the end of the range than it is at the beginning, this will not be serious.

A similar effect is that due to elastic scattering of the protons by nuclei. The probability of this type of scattering is essentially the same as that of absorption. In this case, however, the proton is not stopped but continues at the same energy but in a different direction. The effect, then, is to diffuse about 20 to 40 per cent of the beam. For fairly broad beams this would not be noticeable because such scattering will be predominantly forward.

The above should be the principal effects, and we see that our original picture of a proton beam proceeding without spreading until it is stopped at high. specific ionization in the tissue is only slightly modified. It will be possible to treat a volume as small as 1.0 c.c. any. where in the body and to give that volume several times the dose of any of the neighboring tissue. The exact behavior of protons of the energy considered here will become known only when such protons are available for experiment.

In treating large tumors, for example, one will want to cover the whole volume with the very high ionization density which obtains over the last few millimeters. This can easily be accomplished by interposing a rotating wheel of variable thickness, corresponding to the tumor thickness, between the source and the patient.

The exposure can be monitored precisely simply by placing a shallow ionization chamber between source and patient. Absolute determinations of the dosage can be determined by measuring ionization currents in gases of the elements of tissue or in a gas which mocks up the molecular formula of tissue.

What makes the problem of dosage measurement so simple is the absence of the wall effects encountered in x-ray or neutron exposure measurements. This is because the high-energy proton produces its secondary electrons at such low energy that their range is essentially zero.

The above results are easily generalized to other particles. Range and specific ionization of deuterons or alpha particles can be determined from Figure 1 for protons. If the proton energy ordinates are multiplied by two, as well as the range, curve 1 then holds for deuterons. Thus a 200 MeV deuteron has 16 cm. range. The specific ionization remains the same, however, and a deuteron of 16 cm. range makes 0.14 X 10^6 ion pairs per cm. For alpha particles both ordinates are multiplied by four, but the range is left unchanged. Thus a 400 MeV alpha particle has a range of only 8 cm., but its specific ionization is 0.8 X 10^6, four times as great as for a proton of the same range. The intense specific ionization of alpha particles, when considered in the light of Zirkle's results, will probably make them the most desirable therapeutically when such large alpha particle energies are attained. For a given range, the straggling and the angular spread of alpha particles will be one-half as much as for protons. Heavier nuclei, such as very energetic carbon atoms, may eventually become therapeutically practical.

One naturally asks what are the advantages of fast protons over high-energy electrons such as those from a betatron (4). This question can be answered only by medical workers, and the answers will probably be different for different kinds and sizes of tumors. Certainly the differences between fast electrons and protons are onlly quantitative. The specific ionization for protons is much greater, and the concentration of ionization in a given volume is also greater because the straggling and spreading of electrons is worse. On the other hand, electrons of sufficient energy can be produced by more modest equipment.

Finally, I would like to emphasize the danger which will be lurking near the proposed high-energy machines. We have seen that a current density of a few times 10^-10 amp./cm^2 for one second could have lethal effects. The particles can penetrate the metal walls of the machines, and if less than one billionth of the proposed currents of about one microampere is scattered in the wrong direction, then workers may be in danger. This becomes particularly apparent when one considers that the range in air of a 150 MeV proton is about 150 meters. On the other hand, the range of such a proton in lead is only a few inches, and with thoughtful precaution accidents can be averted.

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