Protons for radiotherapy: a 1946 proposal

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The current enthusiasm for the medical application of charged particles has peaked at a time when nuclear physics research has lost some of its glamour, but nevertheless particles for radiotherapy are a spin-off from the halcyon days of nuclear physics. In the early years of the 20th century, beams of charged particles were used in nuclear disintegration experiments to produce artificial radioactive materials. This was the precursor of the nuclear age. Higher and higher energies were called for and made possible, largely by the invention of the cyclotron in 1931. These accelerators, invented and built for the research of nuclear physics, were later adapted for cancer treatment.

Robert Wilson was born in Wyoming, USA, and went to graduate school at the University of California Berkeley, USA, with Ernest Lawrence, the inventor of the cyclotron. In 1943, he was recruited to lead the cyclotron group at Los Alamos National Laboratory (NM, USA), working on the Manhattan project, but they had no cyclotron, so the US government bought the one from Harvard University (Cambridge, MA, USA; built in 1937) for US$1 with the promise to replace it after the war.

Wilson wrote his seminal paper proposing protons for radiotherapy in 1946, after leaving Los Alamos and moving to Harvard to design and build their new replacement accelerator.[1] He came from a strong Quaker background, and it is said that he was motivated to give some time to this medical application as "atonement for involvement in the development of the bomb at Los Alamos".[2]


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.

These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible.

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 1, 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): [illegible] 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.[2] 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.

Figure 1 shows, for example, that if we want to expose a region located 10 cm. be-

[1] Accepted for publication in July 1946.

[2] The range of a proton in air in meters is given by the convenient formula [illegible] where the energy is expressed in Mev. The range in tissue is [illegible] times the range in air. The stopping power of other substances may be found in Livingston and Bethe: Rev. Mod. Physics 9: [illegible], 1937. The physical calculations of this paper will be submitted to the *Physical Review* for publication.

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Key findings of the 1946 paper by Wilson

- Proton energies needed to treat human cancer, namely about 125 to 200 MeV, were readily available with the technology of the day
- The beam currents needed to result in treatments lasting no more than a few minutes were readily attainable
- The proton depth dose curve is characterised by a sharp Bragg peak near the end of the particles range, where most energy is deposited, with no dose beyond
- A rotating wheel of variable thickness was proposed to spread out the Bragg peak over a large tumour volume, which is still the most commonly used technique
- The number of ionisations per cm of track, and therefore the biological effectiveness, is considerably greater at the end of the particle range compared with the incident particle

Wilson pointed out that protons have advantages over X-rays for the treatment of cancer, because of their physical dose distribution. The dose deposited by a beam of mono-energetic protons increases slowly with depth, but reaches a sharp maximum near the end of the particles range, in the so-called Bragg peak. The beam has sharp edges, with little side-scatter, and the dose falls to zero at the end of the particle's range. The possibility of precisely confining the high-dose region to the tumour volume while minimising the dose to the surrounding normal tissue is the attractive feature of charged particle beams. Unfortunately, the paper had little immediate effect in the radiotherapy community at the time.

Patients were first treated with protons at accelerators built initially for physics research, but which had become obsolete as bigger and better accelerators were built elsewhere. The earliest efforts were at the Lawrence-Berkeley National Laboratory (CA, USA) in 1954[3] and in Uppsala, Sweden, in 1962; only a small number of patients were treated at these facilities.[4] In the 1960s, a collaboration was formed between the Harvard cyclotron and physicians from the Massachusetts General Hospital (MA, USA), led by Herman Suit, with the first patient treated in 1973. By the time that the cyclotron was closed in 2002, over 9000 patients had received proton treatment.

Currently, several dozen purpose-built hospital-based facilities are in operation, or under construction, in the USA, Europe, and Japan.[5] Most involve protons, but some use heavier ions such as carbon. Proton facilities typically cost about $125 million, with heavier ions involving much higher costs. Such facilities might well revolutionise radiation oncology, mainly because of the decrease in healthy tissue morbidity associated with the improved dose distribution.

Conflicts of interest

The author declared no conflicts of interest.

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