A Brief History of Neutron Therapy: Introduction

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Interest in treating cancer patients with neutrons began shortly after their discovery by Chadwick in 1932. This came about because, at around the same time, Earnest O. Lawrence in California and the team of Cockroft and Walton at the Cavendish Laboratory were developing accelerators capable of energies sufficient to trigger nuclear transmutation. Quite rapidly, the two laboratories developed bigger and more powerful machines and by 1933 were producing neutrons with energies in the megavolt range and at fluences sufficient to conduct radiobiological experiments. In the next few years, Lawrence, together with his brother John, conducted experiment with neutron beams on animal tissues, while L. H. Gray and his colleagues were conducting their own investigations in England using plants. The experiments conducted by both teams appeared to show an increased response to irradiation with neutrons relative to x rays. The Lawrences' experiments also seemed to show a therapeutic gain in that the response of tumors exceeded that of normal tissue.

Excitement over these early results led to enthusiasm for treatment of human patients, and in 1938 the first human clinical trial was started. As is described in the subsequent papers, this was the beginning of the first cycle of excitement, followed by disappointment, and then cautious optimism in regard to neutron therapy.

Neutrons of energies in the range of about 2 MeV to 70 MeV are referred to as "fast" neutrons, and therefore the accompanying papers discuss fast neutron therapy, or FNT.

Neutrons from radioactive sources have been used for brachytherapy; in particular, californium-252, a neutron emitter, was used for intracavitary treatments for several diseases. Clinical trials were encouraging, but because brachytherapy with conventional sources is very effective, proving superiority of neutron sources was elusive. The added cost and complexity of obtaining, storing and disposing of neutron sources ultimately led to a decline in enthusiasm for the modality.

Another modality involving neutrons is boron neutron-capture therapy (BNCT). As with both other neutron-based treatments, interest in BNCT began soon after the discovery of the neutron, when it was learned that neutrons were absorbed more easily by certain elements and compounds than others. Hydrogen is an efficient absorber of neutrons, and hydrogen-rich materials are used for shielding where neutrons are produced. Some other elements, boron in particular, have much higher cross-sections for low-energy neutrons (so-called thermal, or epithermal neutrons). A neutron interaction with a boron nucleus can result in the emission of an alpha particle which travels a short distance and deposits a large amount of energy. If the boron atom happens to be inside, or on the surface of, a tumor cell, the damage can be targeted effectively. Meanwhile, the dose to surrounding tissues, which ideally do not contain boron, is minimal. Early clinical trials once again followed the cycle of great excitement, followed by great disappointment. In the early days, drugs did not exist to direct the boron-containing compound to the tumor cells, and consequently normal tissues, particularly blood vessels, received high doses. Today, however, new agents are being developed as well as improved accelerators that can make BNCT viable, and there is a resurgence of interest in this modality.

Neither BNCT nor neutron brachytherapy are addressed by the following articles, although both might be suitable topics for publication in a future History Edition.

Instead, the papers that appear here focus on FNT. The first article follows its development from the early discoveries and the initial excitement following the first biological experiments. The US National Cancer Institute was founded during this period and grants from the NCI supported early clinical trials. As the paper reveals, the excitement generated by the positive results of the early biological experiments was followed by disappointment that came after the first clinical trials. Ultimately, however, there was a wave of renewed interest as improved knowledge encouraged further investigation.

The second paper explores the technological developments that followed some encouraging clinical trials that took place in the 1960s. These developments included improved sources of neutrons, including a move from reactors to cyclotrons of various designs, the development of alternate targets, and the construction of improved delivery systems. Overall, more than 40 treatment facilities were built in 13 countries, several of which were still operating into the current decade. The significance of these developments is explored and some of the reasons for the success and failure of the facilities provide important lessons for the future.

The third and final paper describes recent advancements and improvements to the technology for FNT. The equipment needed to generate higher energy neutron beams was either developed specifically for radiation therapy or was adapted from research accelerators. More grants from the NCI became available to support the construction of

treatment facilities and fund clinical trials. Improved collimation technologies that had been developed for photon beam therapy were introduced to enhance FNT. Treatment planning systems also were improved, using capabilities developed for photons. And while encouraging results were seen for several rather rare and radio-resistant tumors, the cost of maintaining FNT facilities was, in many cases, unsustainable. A single FNT facility remains in operation today where the benefits of high-LET neutron beams continue to be demonstrated.

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