MEDICAL CYCLOTRONS

In 1932 Ernest Lawrence and Stanley Livingston envisaged a device for basic research on the atomic nucleus; today modern versions of their device provide healing radiations at many medical centers.

Henry G. Blosser

Each day in Detroit and Seattle and a score of other cities around the world, dozens of cancer patients report for neutron treatments of tumors resistant to conventional photon-based radiation therapy. Few, if any, of these patients know that the healing radiations are being produced by a cyclotron operating in accord with basic principles first promulgated some 60 years ago in a journal, the *Physical Review*, which they also know nothing of. And Ernest Lawrence and Stanley Livingston, as they wrote their pioneering 1932 paper,[1] spoke of the relevance and need for such a device in the study of the atomic nucleus, but at least in their earliest papers, no thought of a future benefit in the treatment of cancer is considered.

Now, with the help of superconductivity, it is possible to build a cyclotron with twice the energy of Lawrence's largest conventional cyclotron, the 200-ton Crocker 60-inch, and yet small enough and light enough to mount directly on a rotating gantry so that the complete cyclotron moves around the patient. Figure 1 shows the first such superconducting therapy cyclotron, set up for testing at the National Superconducting Cyclotron Laboratory in East Lansing. This cyclotron was moved to Harper Hospital in Detroit in July 1990 and has been in use for patient treatments since September 1991. Figure 2 shows an older, but highly effective, room temperature neutron therapy facility which has been in use for some ten years at the University of Washington Hospital, in Seattle.

In addition to neutron therapy facilities, approximately 100 cyclotrons are at present in use in hospitals and medical isotope production centers around the world, producing short-lived diagnostic isotopes such as carbon-11 (with a halflife of 20 minutes), nitrogen-13 (11 minutes), oxygen-15 (2 minutes) and fluorine-18 (110 minutes) on site in hospitals. In addition a vast volume of longer-lived medical isotopes are produced by cyclotrons located in commercial production centers and thereafter transported for end use in hospitals and clinics. In an alternate cancer therapy application, "descendants" of the original cyclotron, the synchrocyclotron and the synchrotron, are used to provide proton beams for cancer therapy. (Protons are especially effective in situations where the tumor site requires extreme dose localization to avoid critical, radiation-sensitive nearby structures.)

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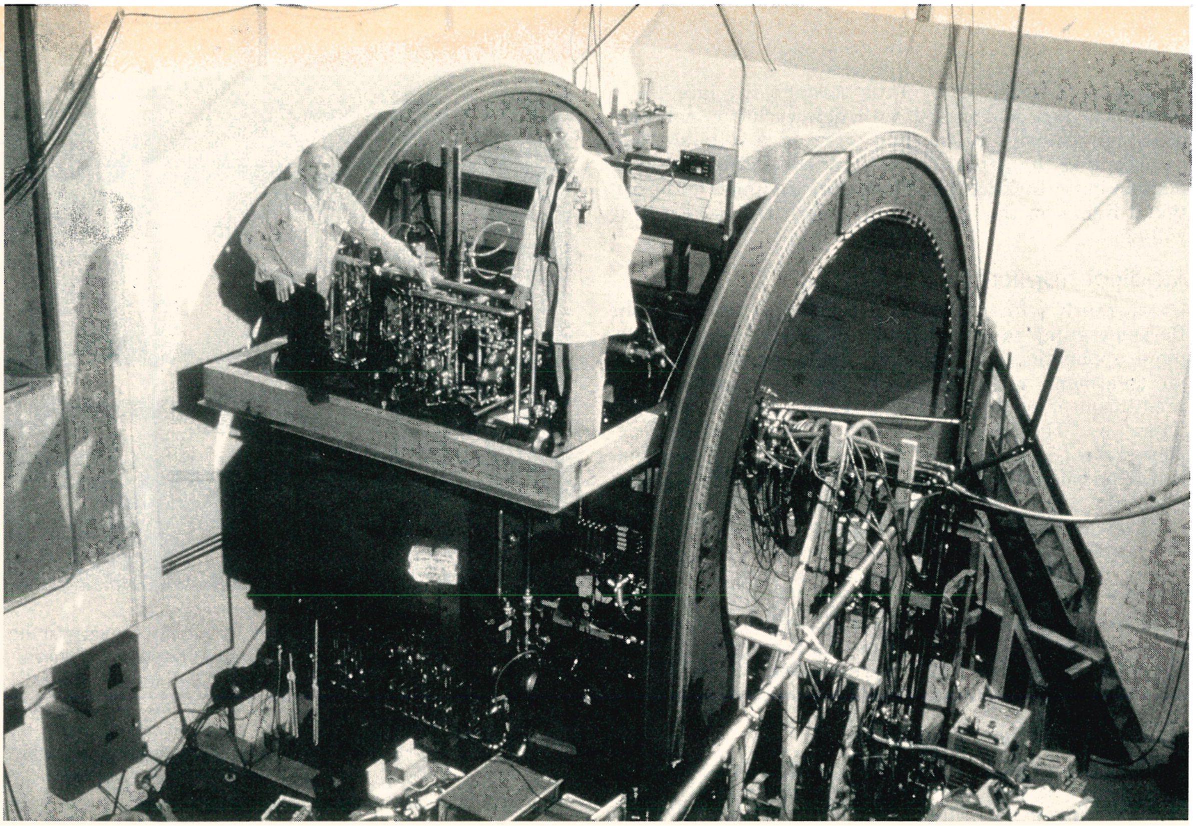
The basic cyclotron concept

All of the important applications of the cyclotron principle build on the initial concept first experimentally reported by Lawrence and Livingston in their 1932 *Physical Review* paper.[1] The essential feature of the idea is to repetitively reuse the same accelerating voltage by providing a magnetic field to bend the particles back and forth across a single accelerating gap, reversing the voltage on the gap in just the time that the ions require to complete their 180° bend and return to the gap. Figure 3 reproduces a dramatic figure from the 1932 paper: the first published cyclotron "tuning curve." The two sharp peaks in the plot of beam current vs magnetic field correspond to the 1/1 and the 1/2 values of the charge-number-to-mass-number spectrum created by feeding hydrogen gas into a discharge region in the center of the cyclotron. At these values, the famous Lawrence relationship for the orbital angular velocity, $\omega = qB/m$ (where q and m are the charge and mass of the ion, and B is the magnetic field) is satisfied: The period of the orbital motion of the ions just matches the period of the applied radiofrequency accelerating voltage, and the ion current dramatically increases!

Now, 60 years later, the cyclotron continues to be a very important accelerator system, with important roles both in fundamental research and in the area of practical applications. This longevity results from the broad applicability of the original cyclotron resonance principle and from a series of important further advances in the basic cyclotron principle, nearly all of which also trace to ideas originally reported in articles in the *Physical Review*.

The concept improves

In their 1932 paper Lawrence and Livingston already recognized the difficulty posed for the pure cyclotron principle by contradictory demands on the shape of the magnetic field (1) to maintain a constant angular velocity as the energy (and therefore the mass) of the accelerated particle increased, and (2) to provide restoring, or focusing, forces to hold divergent particles in or near the acceleration plane. If the magnetic field was shaped to provide focusing, the particles would slide in phase relative to the accelerating voltage as their mass increased and would eventually be decelerated (the mass increase



The Harper Hospital Cyclotron, set up for testing at the National Superconducting Cyclotron Laboratory. William Powers, the MD who headed the hospital's Radiation Oncology Center in the cyclotron construction years, and Blosser (left) are standing on the cyclotron. The pair of large steel rings allows the cyclotron to rotate through a full 360° arc around a patient positioned on the axis of the ring system. **Figure 1**

exactly following Einstein's $E = mc^2$ relationship). If the magnetic field was shaped to keep the orbital frequency constant, or "isochronous" (that is, a field which increased with radius to match the $E = mc^2$ mass increase), it would defocus the particles, causing them to strike the poles of the magnet and thus also be lost. In 1936 Hans Bethe and Maury Rose, in a subsequently widely quoted *Physical Review* letter,[2] quantified this problem. Their concluding paragraph states:

> The only way to obtain higher energies [in the cyclotron] seems to be to increase the voltage on the dees [the name usually used for the accelerating electrodes in cyclotrons, because of their shape]. But even this will increase the energy limit only moderately, *i.e.* just as the square root of the dee voltage. Therefore it seems useless to build cyclotrons of larger proportions than the existing ones.

Just one year later a paper from L. H. Thomas appeared in the *Physical Review*[3] with the first sentences of the abstract stating:

> Bethe and Rose maintain in a recent letter and paper that a maximum energy for the beam from a cyclotron is fixed by the incompatibility of the conditions for resonance and focusing when the relativity increase of mass with velocity is taken into account. It is shown below that, while this result holds for a radially symmetrical magnetic field, it is not necessarily true in general; and that for a field varying with polar angle there is an additional focusing effect.

Thomas's paper thereafter proceeds to define and analyze the central concept underlying the further evolution of cyclotrons in the latter half of the 20th century. The essence of the Thomas concept was to introduce alternating strong and weak azimuthal regions into the cyclotron magnet (so that the magnet pole resembles a pie with alternate slices removed). The alternating strong and weak regions of field cause the particle orbits to weave in and out with respect to a circle. The radial component of the particle velocity in the weaving-in-and-out motion, crossed with the azimuthal component of the magnetic field (which has to be present out of the central plane of the magnet in regions where the field is changing in strength), produces an axial force component directed toward the central plane at both the entrance and the exit of each hill region; this force component can be made arbitrarily strong and can therefore override the defocusing force components resulting from a field shape which holds the orbital frequency accurately constant.

The Thomas concept lay dormant through the years of the great war and into the 1950s, and its first experimental development occurred as part of a classified project at the Lawrence Berkeley Laboratory in the late 1940s, later declassified and reported in the *Review of Scientific Instruments* by Elmer Kelly and coworkers.[4] The delay in developing the cylindrically asymmetric, or "isochronous," cyclotron (these cyclotrons are also often referred to as "sector focused" cyclotrons, and sometimes as "azimuthally varying field," or AVF, cyclotrons) was undoubtedly in part due to the skepticism of experimentalists as to the validity of the extensive mathematical development of Thomas. Thus through the late 1930s Lawrence pressed forward with new cyclotron concepts based on achieving higher and higher dee voltages, that is, accepting the general validity of the Bethe–Rose formalism but attacking the values they assumed for operational limits on the critical parameter, the accelerating voltage.

Medical applications begin

Concurrently with pressing toward higher energies, the Berkeley group (and Lawrence personally) began to explore applications of cyclotrons for neutron production, for treatment of cancer using neutron beams and for production of medically useful radioisotopes. The first paper[5] on "The Biological Action of Neutron Rays" appeared in *The Journal of Radiology* in 1937 and was based on the use of neutrons produced in the 37-inch cyclotron. The first human patient was treated with neutrons in Berkeley on 26 September 1938, and exploratory cancer treatments continued until February 1943 (using in the later years the beams from the 60-inch Crocker cyclotron). A popular article in the September 1941 issue of *Popular Mechanics*[6] described the progress of work on the 184-inch cyclotron and heavily emphasized the medical benefits which were expected to be derived from the beams produced by this giant new cyclotron.

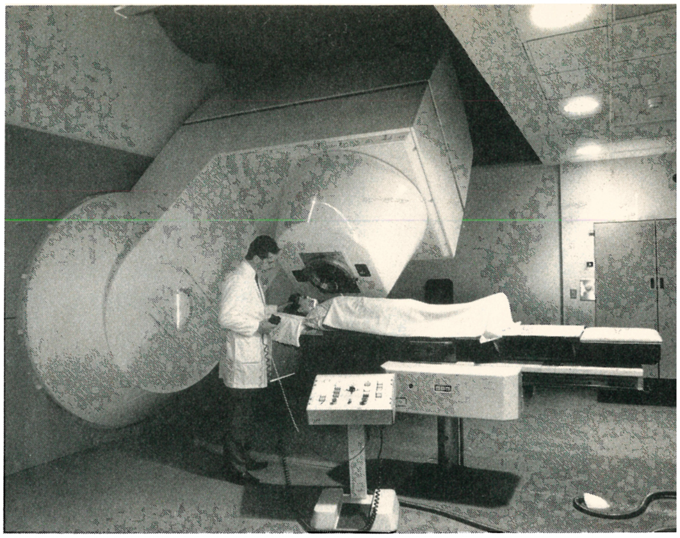
Further cyclotron evolution

In the war years the Berkeley cyclotron program was interrupted so that the magnets could be used for the development of apparatus to be used in the Oak Ridge calutrons. After the war, as work on the 184-inch resumed, the new concept of frequency modulation was put forward by V. I. Veksler and by Edwin McMillan, the latter in an article in the *Physical Review*.[7] In such a cyclotron, an azimuthally symmetric magnetic field decreases with radius as needed to provide axial focusing, and the mass increase is compensated by slowing down, that is, modulating, the frequency of the voltage on the accelerating gaps. (This changes the acceleration to a batch process, as opposed to the continuous-wave, or cw, mode of the original cyclotron, and the maximum intensity is thereby greatly reduced.) Reginald Richardson and coworkers moved quickly to experimentally test the FM, or "synchrocyclotron," principle and reported their successful results in a 1947 *Physical Review* article.[8] In recent conference presentations Richardson has described Lawrence's excitement when the synchrocyclotron concept was shown to work experimentally, including his stopping and sending back a truck which was about to deliver parts for the giant million-volt dees being put together for the 184-inch cyclotron: With the FM principle, only a small dee voltage would be needed, and Lawrence was undoubtedly pleased to move away from the challenge of achieving 1 million volts on a dee.

In the late 1940s, the advance of cyclotrons occurred mainly in the synchrocyclotron arena, and energies climbed into the region where proton beams could penetrate the human body to depths adequate to reach a number of important human tumors. Robert Wilson pointed out[9] the likely benefit of protons in radiotherapy as a consequence of the well-defined range of the protons, as contrasted with the exponential attenuation of either photons or neutrons. Following his suggestion, exploratory cancer treatments with proton beams began on the Harvard synchrocyclotron in the early 1960s and continue at present. Some 6000 persons have now been treated at that facility.[10]

In the meantime, in the early 1950s appreciation of the significance of Thomas's azimuthally-varying-field suggestion as a way of avoiding the reduced intensity and generally poor quality of the beams from synchrocyclotrons was increasing. (Central to the effort to apply Thomas's ideas was the work of the Kelly group at Berkeley mentioned above and a follow-up study at Oak Ridge[11] which marked my own first involvement with cyclotrons.) In addition, the Midwestern Universities Research Association had come into being, and in a seminal *Physical Review* paper of 1958,[12] a MURA group added the concept of "spiral sectors" to the array of tricks available for providing strong axial focusing. In a spiral-sector cyclotron magnet, the crests of the magnet hills bend to the right or left as viewed from the magnet center. (An often used recipe for the angular location of the hills is the logarithmic spiral $\theta = ar$, where a is an arbitrary constant and r is the radius.) With the hills spiraled, one edge becomes more strongly focusing and one edge becomes defocusing, but the net result of separated focusing and defocusing lenses, as is well known, is still stronger "alternating gradient" focusing.

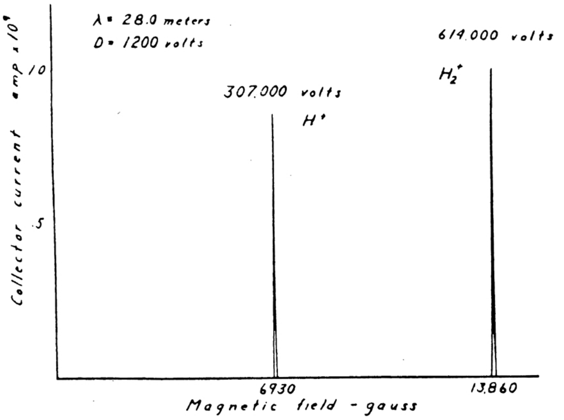
Many cyclotron physicists quickly came to appreciate the clear benefits of blending a MURA spiral into an isochronous cyclotron of the general Thomas concept to give both high energy and high intensity. In 1958 an enthusiastic group of cyclotron specialists came together at Sea Island, Georgia, for the first of a continuing series of international conferences on sector-focused cyclotrons.[13] Over the next few years, the conceptual basis of the cyclotrons of the last 25 years was rather thoroughly formulated.



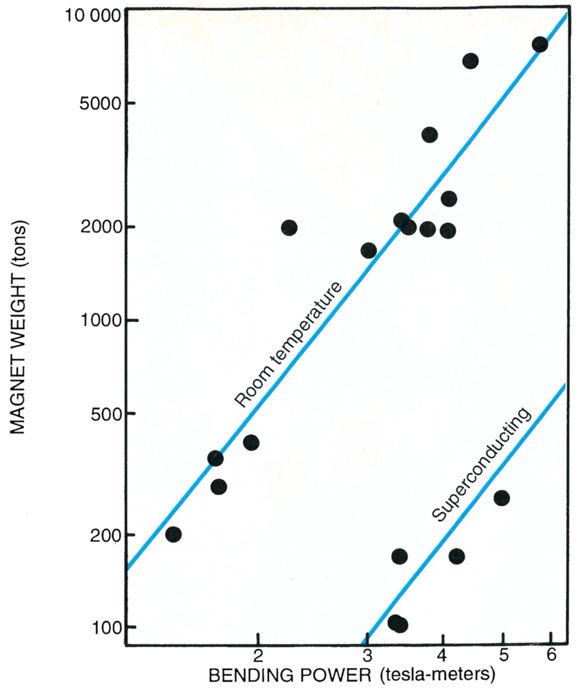
Preparing a patient for neutron therapy at the University of Washington Medical Center in Seattle. This therapy system uses a room temperature cyclotron located in a separate shielded room and a system of moving magnets that can direct the neutron beam at the patient from any angle. The cyclotron and rotating gantry system were manufactured by Scanditronix Inc of Uppsala, Sweden. (Courtesy of University of Washington Medical Center.) **Figure 2**

Superconductivity and neutron therapy

The last important contribution to the scientific basis of today's medical cyclotrons came in 1961, in a *Physical*



'Ion current to Faraday collector as a function of the magnetic field with oscillations of 28 meters wave-length applied to the accelerating electrodes"—the first published cyclotron "tuning curve." (From ref. 1.) **Figure 3**



Comparison of magnet weight vs bending power for the large cyclotron magnets of the world. I have drawn trend lines through points for room temperature and superconducting cyclotrons. For a given bending power, the trend lines differ by a factor of 17, illustrating the great impact of superconductivity in reducing the weight of cyclotrons. **Figure 4**

Review Letter from Bell Laboratories announcing the discovery of high-field (or "hard") superconductivity.[14] In the beginning, the effectiveness of using this technology in cyclotron magnets was inhibited by the unreliable properties of commercial quantities of early high-field superconductors. By the 1970s most of these problems had been overcome and large superconducting coils for bubble chambers were a reality.[15] Groups at Chalk River, East Lansing and Milan moved forward with adaptation of this technology to greatly reduce the size and cost of cyclotrons. Most dramatically, the overall weight of large cyclotrons was reduced by nearly 20-fold, to about 5% of previous levels, as is shown in figure 4, which plots the weight of the large cyclotrons of the world versus the maximum bending power, or $B\rho$, of the magnet. Noting this reduction, Bruce Bigham and Harvey Schneider of Chalk River pointed out[16] that cyclotrons appropriate for neutron therapy would now be small enough and light enough to mount directly on a rotating gantry. In the early 1980s, William Powers, a leading radiation oncologist, persuaded the management of Detroit's Harper Hospital to provide funding for such a cyclotron. This cyclotron, constructed in a collaborative program with Michigan State University, is the one shown in figure 1 and is now in regular use as a major therapeutic component in Detroit's Comprehensive Cancer Care Center.

Another medical accelerator

As we have seen, scientific and technical concepts outlined in *Physical Review* articles of 30 to 60 years ago have led to medical cyclotrons, an important set of instruments functioning to improve and prolong human life. The selection of medical cyclotrons as this article's focus allowed a moderately in-depth review of the selected topic, but omits another important medical technology that also evolved from experimental concepts reported in the *Physical Review* and other scientific journals in the 1930s, namely the medical linear accelerator. These medical linacs are now the primary source of the beams of high-energy photons which are the dominant radiation modality in routine use for the treatment of cancer in radiation therapy–radiation oncology departments throughout the world. Thus also in this application, research reported in the *Physical Review* has led to a set of instruments of great value in improving and prolonging human life.

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