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MEDICAL CYCLOTRONS

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Particle accelerators were initially developed to address specific scientific research goals, yet they were used for practical applications, particularly medical applications, within a few years of their invention. The cyclotron's potential for producing beams for cancer therapy and medical radioisotope production was realized with the early Lawrence cyclotrons and has continued to grow with more technically advanced successors - synchrocyclotrons, sector-focused cyclotrons and superconducting cyclotrons. While a variety of other accelerator technologies was developed to achieve today's high energy particles, this contribution will chronicle the development of one type of accelerator, the cyclotron and its medical applications. These medical and industrial applications eventually led to the commercial manufacture of both small and large cyclotrons and facilities specifically designed for applications other than scientific research.

1. Introduction

The discovery by Rutherford in 1919 that nuclear disintegration could be caused by bombarding nitrogen with alpha particles from a naturally occurring radioactive substance precipitated an intense effort to produce ever more energetic nuclear particles to probe and understand matter. The result has been an exciting period of development of a variety of machines (particle accelerators) to produce charged particles of increasingly high energies to probe the nucleus. This development, which started with simple electrostatic linear accelerators in 1924 and the Lawrence cyclotron in the 1930's, continues today with the commissioning of the LHC at CERN [1]. Particle energies have increased over the last 80 years to nearly 10^7 times that available from naturally decaying elements, and have allowed a rich, if not yet complete, understanding of the makeup of matter and the Universe.

Many different methods for producing high energy nuclear particles were proposed and developed since Rutherford's call for "a copious supply" of more energetic particles in 1919. These methods are discussed

in previous review articles in Vol. 1 of this journal [2]. This contribution will focus on one method of acceleration, the cyclotron, particularly in relation to the precipitant development of the medical applications spawned by it—applications which continue to expand today.

From its inception in 1930 by E.O. Lawrence [3] through its many design variations to increased particle energy and intensity for research, the cyclotron has been used for a variety of biological, medical and industrial applications. Soon after the first experimental demonstration of the cyclotron resonance principle by Ernest Lawrence and Stanley Livingston [4] [5], new radioisotopes produced by high energy particles were discovered and used for the study of both biological processes and chemical reactions. Lawrence developed the cyclotron for nuclear physics research, yet he was very much aware of its possible applications in medicine. An interesting and comprehensive historical review of the development and growth of medical applications for cyclotron produced beams and radio-

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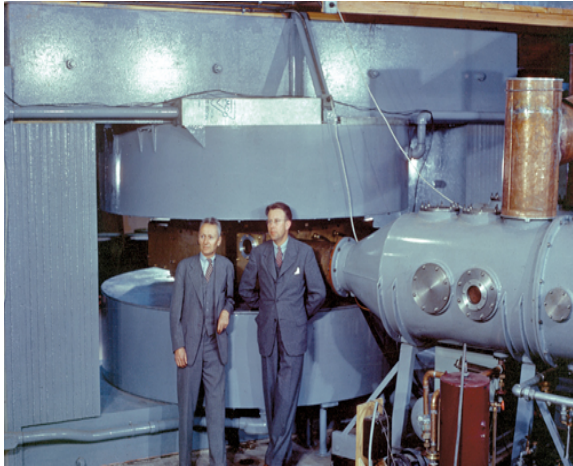


Fig. 1. Donald Cooksey and Ernest Lawrence (right) at the completed 60-inch cyclotron in the Crocker Laboratory.

isotopes initiated at Berkeley by E.O. Lawrence and his colleagues can be found in [6].

The earliest medical applications of cyclotron beams began at the University of California, Berkeley when Lawrence brought his brother John to join Lawrence's group in 1935 [7]. John Hundale Lawrence, a physicist with an M.D. from the Harvard Medical School (1930), quickly demonstrated the worth of cyclotron produced radioisotopes in disease research [8]. He became the Director of the Division of Medical Physics at the University of California at Berkeley. In 1936 he opened the Donner Laboratory to treat leukemia and polycythemia patients with radioactive phosphorus (^{32}P) [9]. These were the first therapeutic applications of artificially produced radioisotopes on human patients. By 1938, the Berkeley 27-inch (later upgraded to 37-inch) cyclotron had produced ^{14}C , ^{24}Na , ^{32}P , ^{59}Fe and ^{131}I radioisotopes, among many others that were used for medical research [6].

Lawrence believed in the promise of accelerator-produced radioisotopes as a possible weapon against disease and heralded these biomedical applications to appeal to local philanthropists to fund his accelerator development programs. Philanthropies at the time donated more money to medicine, public health, and biology than to physics. His appeals attracted funding for the 200-ton multi-use Crocker 60-inch (magnet pole) diameter cyclotron in 1938, which was commissioned in 1939, ostensibly, as a "medical" cyclotron. One might consider the Crocker machine to be the first cyclotron built specifically for medical research and applications. A photo of the completed cyclotron is shown in Fig. 1.

John Lawrence and Cornelius Tobias, another student of Ernest Lawrence, used this cyclotron to research one of the earliest biomedical uses of radioactive isotopes. They used radioactive nitrogen,



Fig. 2. E. O. Lawrence (seated), the inventor of the cyclotron, and his brother, J. H. Lawrence, the "Father of Nuclear Medicine", at the console of the Crocker 60-inch cyclotron.

argon, krypton, and xenon gases to provide diagnostic information about the functioning of specific human organs. Their research discovered the nature of the decompression sickness known as the "the bends," experienced by many military aviators when flying at high altitudes without pressurized suits [10]. A photo of the Lawrence brothers at the console of this cyclotron is shown in Fig. 2.

In other activities, Dr. John Lawrence and Dr. Robert Stone were the first to use hadron therapy to treat cancer using the Crocker 60" cyclotron. They began clinical trials treating cancer with neutrons in 1938, just six years after the discovery of the neutron by Chadwick in 1932. Neutron radiation damage is done primarily by nuclear interactions, interactions that are now known to have a high linear-energy-transfer (high LET). With high LET radiation such as neutron radiation, the chance for a damaged tumor cell to repair itself is very small [11]. A photo of a patient being prepared for a neutron treatment is shown in Fig.3. This initial work was terminated because the cyclotron was needed for the war effort during World War II. However, after the war, a renewed interest in neutron therapy precipitated clinical trials at several facilities around the world in the 1970's. Except for the early trials at Berkeley, most of the later trials were conducted using accelerators other than cyclotrons. By the 1980's, neutron therapy was no longer used for routine cancer treatment.

Robert Wilson, yet another graduate student of Lawrence, realizing the advantages of the hadron Bragg peak, proposed the use of high-energy protons and other

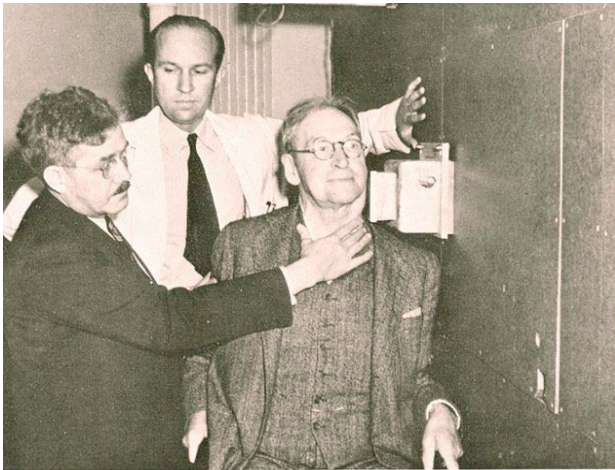


Fig. 3. John Lawrence and Robert Stone setting and preparing a patient for neutron irradiation at the 60" Crocker cyclotron in 1938.

charged ions to treat deep-seated tumors in the human body [12]. The basic physics that makes hadron therapy so attractive is the manner in which high energy ions lose energy while passing through matter. Energetic ionizing (charged) particles lose energy slowly through atomic interactions as they penetrate matter until near the end of their range, where they give up the last 85% of their energy. This energy loss profile is illustrated in Fig. 4 for a 160 MeV proton beam. The large energy loss peak at the endpoint (blue curve) at 15 cm into the body is called the Pristine Bragg Peak. Protons are known today as low LET radiation. However, the depth that an energetic proton will penetrate into the human body varies predictably with energy, such that most of the proton energy can be delivered precisely in a tumor at any depth by selecting the appropriate energy. Beams of lower energies and intensities can be directed at the tumor so as to cover the whole depth of the tumor. This is shown in Fig. 4 for a 9 cm Spread Out Bragg Peak or SOBP (Red Curve). The radiation damage to the body during entry is significantly less than in the tumor. Since the beam stops in the tumor, very little damage is done behind it. An energy deposition profile for a 10 MeV photon (grey curve) is also shown on the same scale in Fig. 4 for comparison—illustrating higher entry and exit doses to the patient together with a smaller energy deposition in the target (tumor) area. The energy loss profile for a neutron is similar in shape to that of a photon, hence these particles damage both cancerous and healthy tissue. The proton, though a low LET particle, has the advantage that it can concentrate its energy in the tumor.

Wilson's proposal led to the routine use of high energy ion beams for the direct treatment of localized (cancerous) tumors within the human body. Today there

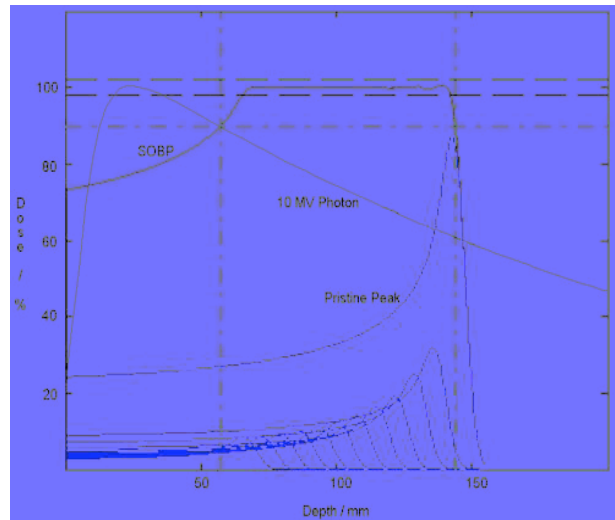


Fig. 4. Energy loss profiles for a 160 MeV proton beam compared with a 10 MeV Photon. A 160 MeV proton Pristine Bragg peak (Blue curve) and a combined energy 9 mm Spread Out Bragg peak (SOBP) made of a series of lower energy proton beams (Red Curve) are shown.

are over 30 operating Ion Beam Therapy (IBT) facilities around the world, many of them designed and built by commercial vendors, with several more planned or under construction. Over 60% of these facilities use one commercial cyclotron design as the source of energetic ions required for the treatment [13].

Through these and other pioneering work, John Lawrence became known as the "Father of Nuclear Medicine and the Donner laboratory is recognized as its birthplace" [14]. The cyclotron development activities at the Berkeley Radiation Laboratory became the crucible for the growth of nuclear medicine and hadron therapy as an indispensable part of modern health care. Accelerator produced radioisotopes are now routinely used for imaging diagnostics or to treat diseases. Human organs can be readily imaged, and disorders in their function revealed. "It is estimated that 15 to 20 million nuclear medicine imaging and therapeutic procedures are performed every year around the world, and demand for radioisotopes is increasing rapidly. In developed countries (about a quarter of world population) the frequency of diagnostic nuclear medicine procedures performed is approximately two per 100 persons per year, and the frequency of therapy with radioisotopes is about one tenth of this" [6].

In the sections that follow, the development of the cyclotron, from the classical design invented in 1930 by Lawrence to the relativistic superconducting machines of today, will be briefly reviewed; and, the medical applications that each new capability inspired will be presented. While virtually all the advances in cyclotron design and performance were accomplished in the pursuit of scientific research, there was a persistent

demand for access to them for applications in medicine and industry. The rapid advances in cyclotron performance quickly made earlier designs obsolete for research, and many of these were given over to medical research and applications work. This growing demand eventually (~1970) made the commercial manufacture of cyclotrons dedicated to these applications viable. These commercially developed and manufactured machines and their medical applications will be given special attention.

2. A Brief Review of Cyclotron Development

2.1. The Classical Cyclotron

The classical cyclotron (also called “conventional” or “Lawrence” cyclotron) invented by Lawrence in 1930 was quite simple in concept and construction. The underlying physics principles are that charged ions (protons, electrons, etc) are accelerated with electric fields and contained or focused by magnetic fields. Lawrence’s brilliant insight was that the orbit period of a particle of charge q , mass m and velocity v traveling in a circle in a uniform magnetic field B normal to the particle velocity is constant; only the radius R of the orbit increases with the particle momentum (mv) [15] [16].

$$R = mv/qB \quad (2.1)$$

The particle orbit period t is given by;

$$t = 2\pi m/qB \quad (2.2)$$

Hence, a constant frequency sinusoidal oscillating voltage on the accelerating cavities, called dees because of their shape, matching the cyclotron resonance condition ($\omega = qB/m$) accelerates the particles twice per revolution, causing them to increase their orbit radius as they gain energy. The repetitive dee gap crossing of the recirculating beam allows it to be accelerated to high energies with relatively low dee voltages, thus eliminating the need for the high voltages used on the competing technologies of the time, the Van de Graaff [17] and Cockcroft-Walton linear accelerators [18].

The ideal kinetic energy gain per revolution in a cyclotron for a synchronous particle of charge q is given by:

$$T = 4qV_0 \quad (2.3)$$

For a peak dee voltage V_0 of ± 2 kV, a particle of charge q receives an 8 keV kinetic energy gain per revolution, i.e., each time it crosses the gap between the dees (every

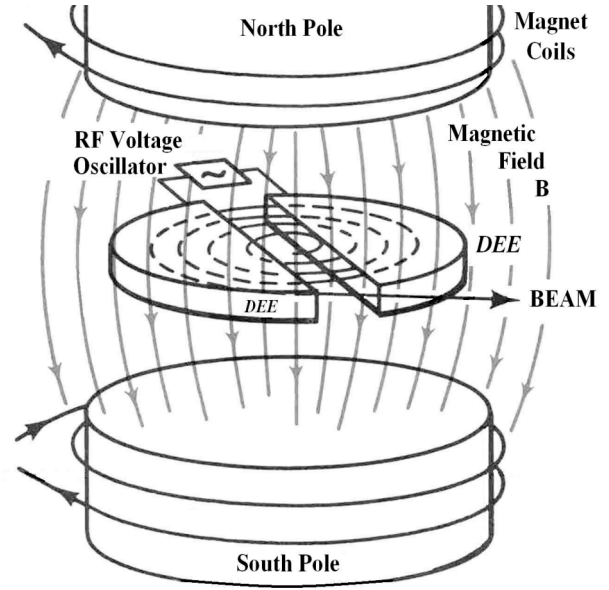


Fig. 5. A three dimensional exploded view of the major cyclotron electromagnetic components as invented by Ernest Lawrence in 1930.

180° of rotation) it receives and energy gain of 4 keV. A proton traversing 300 orbits would gain a maximum of 2.4 MeV. A classic schematic showing the major electromagnetic components of a conventional cyclotron is shown in Fig. 5.

2.1.1. Orbital Stability

A critical design issue for all particle accelerators is the orbital stability of the circulating beam during acceleration. The particles must remain focused into small bunches in all three spatial dimensions and orbit oscillations about the magnet mid-plane and equilibrium orbit must be small enough to keep beams from getting lost on the magnet poles or dee structures. Electric and magnetic restoring forces must be built into the accelerator to keep the beam centered in the orbit. Also, the magnetic field must be constant to a high precision to maintain a constant orbit frequency that matches the constant RF electric field frequency throughout the many revolutions of the acceleration cycle. This later condition, called “isochronism,” insures that the particles arrive at the acceleration gap when the RF voltage is near its peak value V_0 . The two requirements of beam focusing and isochronism compete with one another in the classical cyclotron and ultimately limit the maximum energy of this initial design.

2.1.2. Focusing

Beam focusing and orbit stability in a cyclotron requires a small restoring force to push a divergent circulating beam back into the mid-plane equilibrium

orbit. The magnetic field of a classical cyclotron shown in Fig. 5 tends to bulge out and decrease slightly with radius because of leakage near the pole outer edges. The resulting magnetic field thus has a small radial component (B_r) that applies weak axial and radial forces to the circulating beam. The slight field decrease with radius is too small to provide the necessary focusing forces to keep the beam in the machine throughout the acceleration cycle. Lawrence's team added iron "shims" to the magnet pole tips to produce a more rapid field fall-off with radius to provide the required focusing forces. The shims, shown in Fig. 6, increase the pole gap from the center outward with radius to reduce the field in a controlled way. The field decrease with radius for a classical cyclotron is;

$$B_r = -nB_0z/R \quad (2.4)$$

where n is a constant defined as the "Field Index." The resulting radial and axial focusing forces are:

$$F_r = -mw^2(1-n)r \quad (2.5)$$

$$F_z = -mw^2nz \quad (2.6)$$

For values of $0 < n < 1$, these forces keep the beam focused and cause it to make small oscillations about the magnet mid-plane during acceleration. The orbit oscillation frequencies are called "Betatron Tunes" and are given by;

$$\nu_r = w(1-n)^{1/2}/2p \quad (2.7)$$

$$\nu_z = w(n)^{1/2}/2p \quad (2.8)$$

where again $w/2p$ is the particle orbit frequency [19]. The resulting oscillation period of a deviant particle about the equilibrium orbit in both the axial and radial directions is smaller than the orbit frequency, the definition of a weak focusing accelerator. The

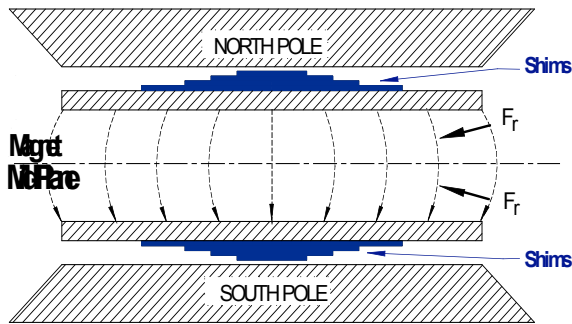


Fig. 6. A cross-sectional view of a cyclotron magnet pole gap showing the field shaping shims (blue) installed to provide a stable circulating beam during acceleration.

mathematical formalism for the above equations can be found in reference [16].

2.1.3. Isochronism

For a constant sinusoidal rf accelerating voltage $\pm V_0$, a synchronous particle arriving at the dee gap at the maximum voltage receives a kinetic energy gain per revolution given in equation 2.3, as shown for three consecutive orbits (blue dots) in Fig. 7. The only force maintaining the particle in synchronism with the accelerating voltage is the magnetic field, which must be maintained to a very high precision ($\sim 0.1\%$) for particles making hundreds of turns. Variation in the magnet gap or the magnet excitation current will cause the particle orbit period to deviate from the synchronous value. For a field constrained to decrease with radius as required for focusing, the particle orbit periods will be longer than the synchronous orbit, and will hence arrive at the dee gap at increasingly later times (red dots) relative to the rf period, causing the particles to become increasingly out of phase with the rf electric field. This is referred to as "Phase Slip," i.e., the particles slowly slip out of phase with the rf accelerating voltage with each passing turn. Two things happen when this occurs. First, the accelerating voltage experienced by the particle is less than V_0 , i.e.;

$$V = V_0 \cos\theta \quad (2.9)$$

where θ is the rf phase angle traversed during a single particle orbit. The resulting kinetic energy gain per turn would then be:

$$T = 4qV_0 \cos\theta \quad (2.10)$$

The lower energy gain per turn causes the particles to make a larger number of orbits in the cyclotron to reach the maximum design energy. In the worst-case scenario, the particles will eventually arrive late enough after many turns to receive no acceleration or even deceleration. Second, an increase in the particle bunch spatial size and time width during acceleration, also shown in Fig. 7. Both effects cause beam intensity loss during the acceleration process.

Yet a third effect of acceleration in any cyclotron that causes the particles to lose synchronism with the fixed frequency rf electric field is that the particle mass $m(t)$ increases with velocity according to Einstein's theory of relativity. As the particle velocity $v(t)$ increases with time, the particle mass $m(t)$ increases according to;

$$m(t) = m_0/(1 - \beta(t)^2)^{1/2} \quad (2.10)$$

where m_0 is the particle mass at rest, $\beta(t) = v(t)/c$ and c

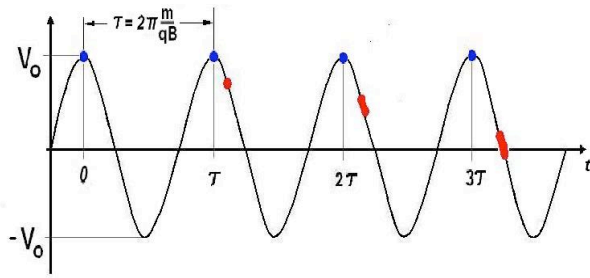


Fig. 7. Sinusoidal RF accelerating voltage illustrating Isochronous acceleration (blue) and “phase slip” due to a decreasing magnetic field with radius (red) for three revolutions.

is the speed of light. A 20 MeV proton’s mass is 2% higher than one at rest according to eq. (2.10). This mass increase further increases the orbit period (eq. 2.2) adding to the loss of synchronism. To compensate for the relativistic mass increase with energy, the field must increase with radius in proportion to the particle mass increase—exactly the opposite of what is required for focusing. Using high dee voltages to reduce the number of turns required to achieve maximum energy can mitigate the competing requirements of relativity, focusing and isochronism. Even with this, the maximum proton energy capability of the classical cyclotron originally invented by Lawrence can be shown to be approximately 20 MeV. This situation lasted until about 1958 for the classical cyclotron design.

In the years following the development of the first practical cyclotron (11”, 1.2 MeV p) in 1932, several larger cyclotrons were constructed at Berkeley and many machines were subsequently built around the United States and the world. At Berkeley, Lawrence built the 27” (3.6 MeV p, 1932), 37” (8 MeV d, 1937) and 60” Crocker (16 MeV d, 1939) cyclotrons and started the construction of the 184” cyclotron. Designed for 340 MeV protons, this machine would not have worked as a classical cyclotron for the reasons just described, but was modified to operate as a synchrocyclotron. Lawrence’s graduate students and other scientists from Berkeley started the construction of many research cyclotrons at other institutions based on the classical Berkeley designs. By the late 1930’s, machines were built at Cornell (S. Livingston), Columbia, Indiana University (Franz Kurie and L. J. Laslett), Princeton, MIT (S. Livingston) Rochester, and Yale, just to name a few of the approximately 24 cyclotrons operating or under construction at academic institutions around the United States by the mid 1940’s [20]. Cyclotrons were also built in Sweden (Stockholm, 32”), Japan (Reiken, 26”) and Europe. Some of these machines were used for medical and scientific studies well into the 1960’s.

2.2. The Synchrocyclotron

One obvious solution to the classical cyclotron energy limit is to reduce the frequency of the rf accelerating voltage with time in synchronism with the increase in the particle orbit period caused by the effects, primarily relativity, described above, i.e;

$$\omega_{rf}(t) = qB/m(t) \quad (2.11)$$

This “frequency modulated” (fm) operation requires a single beam bunch to be accelerated with the phase of the accelerating particles shifted to be between 40° and 60° after the voltage peak as shown in Fig. 8. The synchronous accelerating voltage V_s is then less than V_0 . When a particle is out of phase with $w_{rf}(t)$, i.e, has an orbit period either smaller (θ_{min}) or larger (θ_{max}) than the synchronous value (θ_s), it receives a energy gain less or greater than $4qV_0 \cos\theta_s$. This causes the particles orbit period to move back toward the synchronous value over several orbits, acting like a feedback loop. Consequently, the particle orbit period will oscillate about the synchronous value during the acceleration cycle, a process called Phase Stable Acceleration. The phase angle range ($\theta_{min} - \theta_{max}$) of the particle motion is referred to as an “RF Bucket.” The principle of “Phase Stability” was postulated simultaneously by Veksler [21] and McMillan [22], and is also the fundamental principle for acceleration in a synchrotron. Phase stable acceleration also allows the particles to accelerate through small magnetic field anomalies in the cyclotron caused by pole tip machining errors and poor magnet excitation current regulation. One drawback of the synchrocyclotron is that once a beam bunch is captured and accelerating, the next bunch cannot be accelerated until the first is accelerated to full energy and the rf frequency reset to the injection value. The

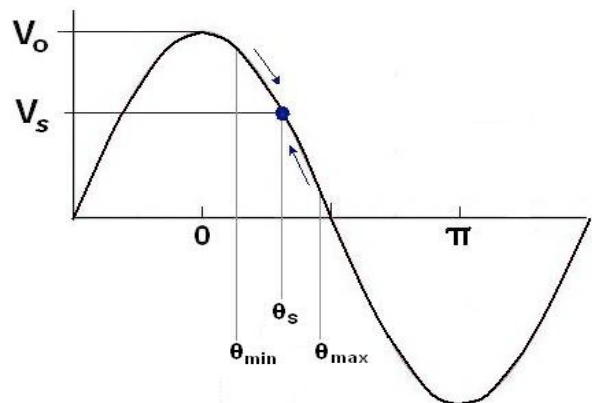


Fig. 8. RF acceleration cycle illustrating the principle of Phase Stable Acceleration in a synchrocyclotron. The area between θ_{min} and θ_{max} is the “RF Bucket”.

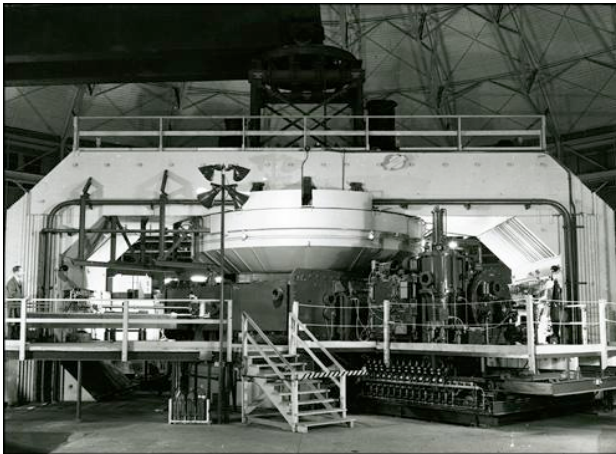


Fig. 9. The Berkeley 184" synchrocyclotron, 1946.

resulting extracted beam has a pulse period several thousand times the rf accelerating frequency, compared to the classical cyclotron pulse period of twice the accelerating RF frequency—significantly reducing the average extracted beam intensity.

The principle of phase stable acceleration was first demonstrated when the 37" Berkeley cyclotron was converted to a synchrocyclotron in 1946 [23]. The 184" cyclotron at Berkeley, shown in Fig. 9, was then quickly redesigned to operate as a synchrocyclotron capable of accelerating protons to 350 MeV. Following these successes at Berkeley, 14 large synchrocyclotrons were constructed around the world that produced proton beams of up to 1 GeV (Gatchina) in energy [24].

2.2.1. Early Proton Therapy Medical Developments

The higher beam energies (>100 MeV Protons) of the synchrocyclotron gave medical researchers the opportunity to study and test proton beam therapy as originally proposed by Robert Wilson in 1946 [12]. John Lawrence was the first to treat cancer patients with high energy protons in 1954 using the Berkeley 184" synchrocyclotron by irradiating the pituitaries of 30 patients with metastatic breast cancer [25].

Another of the early synchrocyclotrons, the Harvard synchrocyclotron commissioned in 1949 (160 MeV p), shown in Fig. 10, would go on to become a dedicated proton source for a pioneering program of Ion Beam Radiation Therapy for cancer from the 1960's until its decommissioning in 2002. Robert Wilson established many of the design parameters for this machine while he was an associate professor at Harvard, during which he published the famous paper proposing the use of high-energy protons for the treatment of deep seated tumors in the human body [12]. After a distinguished

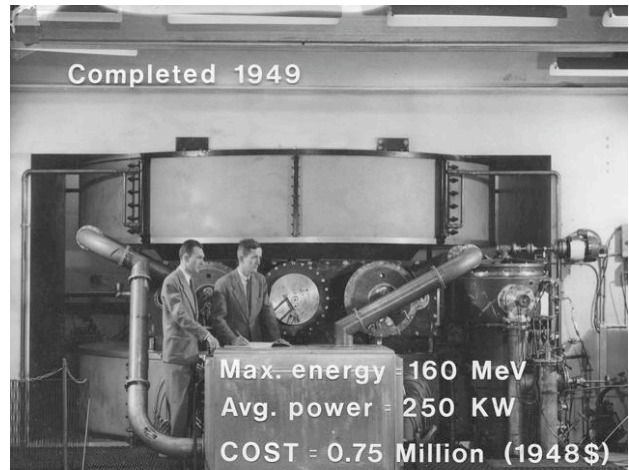


Fig. 10. Photo of the Harvard 160 MeV synchrocyclotron just prior to its commissioning on June 15, 1949, with Professors Norman Ramsey (R, Cyclotron laboratory Director) and Lee Davenport (Associate Director). This machine was shut down on June 20, 2002.

career in nuclear and medical research, the Harvard accelerator was used to begin a study of the treatment of various neurological lesions with high-energy protons in the 1960's in collaboration with the Massachusetts General Hospital (MGH) neurosurgery department. This collaboration resulted in the development of several important beam manipulation techniques (double scattering, range modulation), treatment protocols and patient immobilization techniques for proton radiotherapy that are still in routine use today [26]. 9,115 patients were treated using the Harvard synchrocyclotron from 1961 until its decommissioning in 2002.

Another of these early synchrocyclotrons performed preliminary studies of Proton Beam therapy from 1957 to 1968. On December 9, 1951, a synchrocyclotron with a radius of 90" and a maximum energy of 200 MeV for protons was commissioned at the Gustaf Werner Institute (GWI) in Uppsala, Sweden with Ernest Lawrence in attendance. This machine was used for radio therapeutic research and clinical tests with 185 MeV proton beams from 1957 to 1968. These are but a few examples of how early physics driven accelerators were used for medical research and applications, a trend that still continues to this day.

2.3. The Thomas (Isochronous) Cyclotron

The major disadvantage of the synchrocyclotron, low average intensity pulsed beams, was overcome by the development a third type of cyclotron known as the isochronous cyclotron which is capable of accelerating a continuous stream of particle bunches at a constant orbit frequency to high energies. The approach to addressing

the relativistic mass increase of eq. (2.10) is to allow the field to increase radially at the same rate as the relativistic mass increases during acceleration. The radial field variation of the axial component of the magnetic field must be;

$$B_z = B_0 \left[1 - (Z/A)^2 (r/a)^2 \right]^{1/2} \quad (2.12)$$

where $a = E_0 / ecB_0$. With this radial field variation, the cyclotron frequency is constant and independent of energy.

2.3.1. The Radial Ridge Cyclotron

The high energy isochronous cyclotron was not considered in the early days of cyclotrons because the increasing field violated the conditions necessary for axial stability ($0 < n < 1$) of the classical and synchrocyclotrons discussed earlier. A method to overcome the weak focusing properties of the required radially increasing field was proposed in 1938 by Llewellyn Thomas [27]. Thomas proposed to use an azimuthally varying magnetic field to provide edge focusing for particles entering and exiting the high and low field regions of the magnet. This was accomplished by dividing the cyclotron magnet pole faces into regions of high fields, called ‘‘Hills’’ (H), and low fields, called

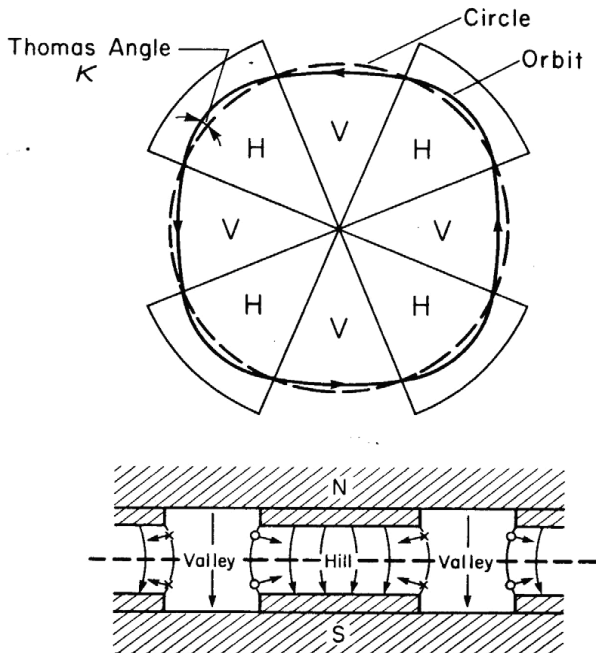


Fig. 11. Schematic of a four sector radial ridge cyclotron magnet showing the non-circular orbits, the Thomas angle and the regions of high (H) and low (V) fields.

‘‘Valleys’’ (V), such that the average radial field of the cyclotron increases with the energy according to eq. (2.13) to maintain a constant orbit period. The simplest example of this is the four sector radial ridge cyclotron magnet pole face depicted schematically in Figs. 11 and 12.

The azimuthally varying magnetic field makes the protons travel in non-circular orbits causing them to pass through the interface between the high and low fields at an angle k , referred to as the ‘Thomas’ angle. The radial components of the fields at the interface can be made strong enough to produce adequate radial and axial focusing forces to maintain beam stability throughout the acceleration cycle. These forces are proportional to the Thomas angle k and the ratio of the high and low field values, which must be calculated during the design of the accelerator. An ion traversing a pole gap with an axial variation in pole height sees a net axial focusing force back towards the cyclotron median plane, as shown in Fig. 10. A photo of a commercially available isochronous 24 MeV proton cyclotron using radial ridge pole tips is shown in Fig. 13 [28].

While the benefits of fixed frequency and CW (continuous dc beam) operation were clear, it took a while for this ‘Thomas’ cyclotron to be adopted. The first operational isochronous cyclotron was a three sector radial ridge electron machine constructed and operated at Berkeley during the 1950s. This major development was deemed classified and therefore not made public until 1956 [29]. The first isochronous proton cyclotron, a 3 radial sector machine with a pole

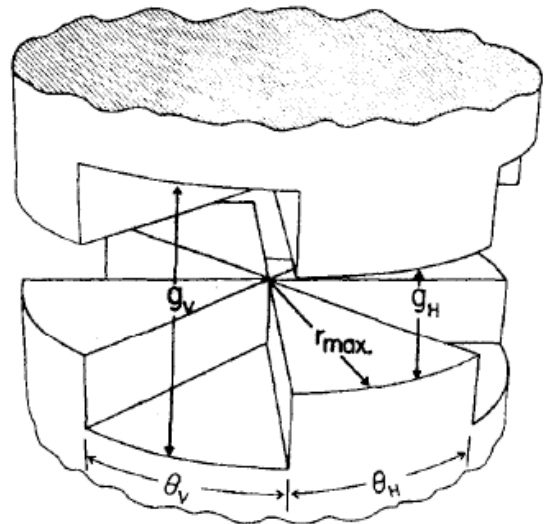


Fig. 12. An isometric view of the pole tip geometry for a four-sector radial pole tip gap variation needed for a Thomas Cyclotron. The ‘Valley’ and ‘Hill’ pole tip gaps g_v and g_h are shown.

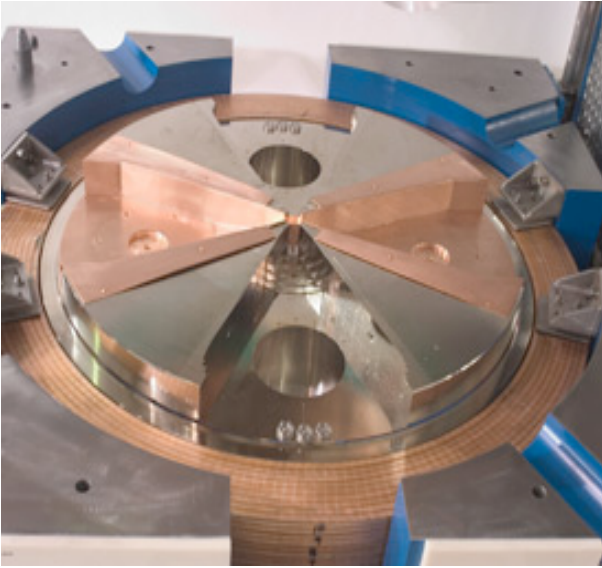


Fig. 13. Photo of the lower pole tip of an Advanced Cyclotron Systems TR 24 radial ridge cyclotron. This cyclotron delivers up to 1 amp of 15 to 24 MeV protons to produce PET or SPECT Isotope.

diameter of 86 inches, was built at DELFT in 1958. This machine accelerated protons to 12.7 MeV [30]. Another demonstration of such focusing was the Thomas shimmed classical cyclotron at Los Alamos National Laboratory [31].

The slow adoption of Thomas's 1938 proposal seems to be due both to the fact that the orbit dynamics of this machine needed to be absorbed by the cyclotron builders, and also that the existing cyclotrons of the 1930-40s were simply adequate for the nuclear research in progress. The priorities of WWII once again had a role in the slow development of this concept. Eventually the demand for higher energies and intensities for nuclear science forced the development of the isochronous cyclotron. By 1959, there were two isochronous cyclotrons in operation and another 13 in various stages of design and assembly.

The pole field variation required to provide the Thomas focusing may be done with a sine wave or square wave pole gap variation, and with radial or spiral ridge pole shapes. From the beginning, a distinguishing feature of isochronous cyclotrons was that a quantitative beam dynamics simulation was required to verify the field design, and indeed one of the first uses of the new digital computers in the 1950s was for the design of an isochronous cyclotron. The complete theoretical basis of the isochronous cyclotron, in which it is seen that Thomas focusing is an example of the general principle of Alternating Gradient Focusing, is shared with another accelerator type, the Fixed Field Alternating Gradient accelerator (FFAG), and was developed principally by members of the MURA Group in the mid-1950s led by

Symon. [32]. From the late 1950s onward most new cyclotron projects were based upon this isochronous cyclotron type.

2.3.2. The Spiral Ridge Cyclotron

The energy capability of the radial ridge design is limited to about 45 MeV by the small Thomas angle that can be achieved, which limits the strength of the axial focusing forces that can be obtained. This constraint was removed by the introduction of spiral, rather than radial ridge pole tip sectors. The spiral angle magnet pole sectors caused the circulating particles to cross the pole edges at an angle greater than the Thomas angle, producing a stronger axial focusing force. The spiral pole tip shape can be adjusted during the design process to select the strength of the focusing required for orbit stability. This process could not be done empirically, but required the use of digital computers, which became available to scientists in the late 1950s. The radial and spiral ridge cyclotrons belong to a cyclotron group referred to as isochronous, azimuthally varying field, and sector-focused cyclotrons. One of the largest spiral ridge cyclotrons, TRIUMF, was made in Vancouver, B.C. This accelerator, a 6 sector cyclotron shown in Fig. 14, accelerated H^- ions to 520 MeV and is physically the largest cyclotron ever built (pole diameter of 17.17 m) because the maximum field was limited to 6 kG to prevent magnetic striping of the H^- ions during the acceleration process [33].

The development of the sector-focused cyclotron required sophisticated machining and fabrication techniques, and was initially available only for scientific research. However, the efficiency and compactness of

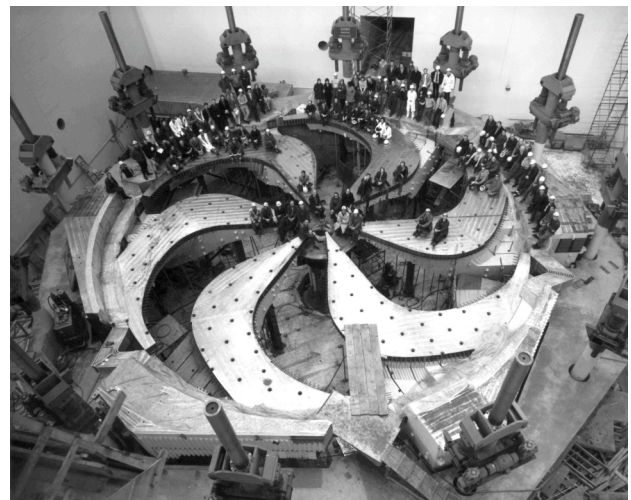


Fig. 14. TRIUMF spiral ridge cyclotron pole magnets shown during construction.

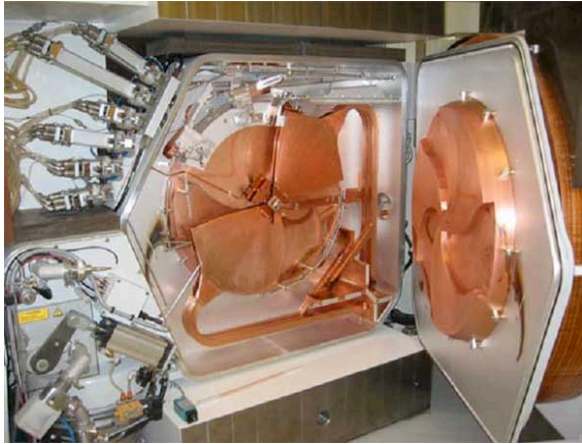


Fig. 15. A four sector isochronous cyclotron magnet pole tips with spiral edges

the design made these cyclotrons ideal for the production of medical isotopes for SPECT and PET. Today, with the omnipresence of accelerator design computer codes, the sector-focused cyclotron has become an immensely practical high energy, efficient and relatively low cost machine that has made the applications of high energy particle beams a common commercial commodity used for the production of a large number of medical imaging, diagnostic and therapeutic applications. One example of a commercial cyclotron employing the spiral ridge pole design is the General Electric 14 MeV proton “PETrace” isotope production cyclotron [34], shown in Fig. 15. These commercial machines will be discussed later in *Section 3*.

2.3.3. Separated-Sector Ring Cyclotron

The separated sector cyclotron is the logical extension of the sector-focused design where the valleys are eliminated and the cyclotron is constructed from individual magnets spaced in the form of a ring. Willax proposed this design in the 1960s [35]. The first two machines of this design were constructed at PSI in Zurich, Switzerland (590 MeV Protons) [36] and at Indiana University (IUCF) in Bloomington, Indiana (200 MeV Protons) in the 1970s [37]. Each cyclotron was designed for a different particle and energy range, have different numbers of dipole magnets (8, 4 respectively) and employ different pole shape designs (spiral and radial pole edges), as shown in Figs. 16 and 17, which illustrates the flexibility of the ring cyclotron design. The PSI and IUCF cyclotrons, the first of their type, became operational for the first time in 1975.

The separated sector cyclotron has several practical advantages over the sector-focused designs. The RF accelerating dee structures can be removed from the

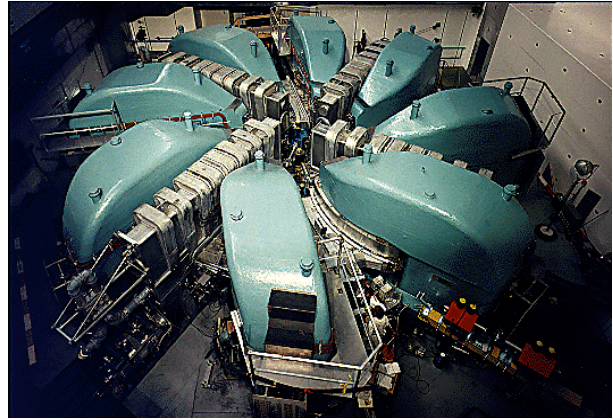


Fig. 16. PSI K600 8 sector isochronous cyclotron. Four accelerating structures located between the spiral ridge magnets that produce an energy gain of 2.9 MeV per revolution. This machine holds the world record for beam intensity extracted from a cyclotron (2 mA protons).

magnet gap and relocated between the individual magnets, making their design more efficient and powerful. Several high power accelerating dee structures can be located symmetrically between the magnets that accelerate the beam twice per dee passage, or twice the number of dee structures used, resulting in multi-MeV energy gains per revolution. Four accelerating structures located between the spiral edge magnet sectors, as seen in Fig. 15 for the PSI eight sector cyclotron, produce an energy gain of 2.9 MeV per revolution throughout the acceleration cycle. Beam extraction efficiencies

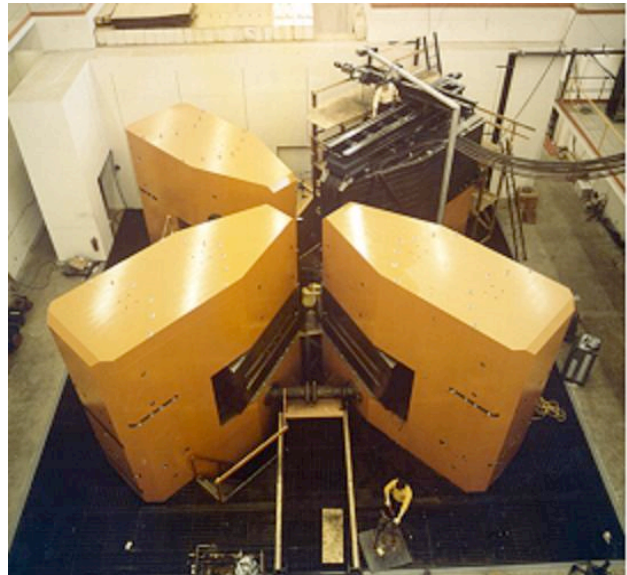


Fig. 17. The Indiana University K220 four sector cyclotron is shown during construction. Two of the four gaps between the magnets

contained accelerator structures that give up to 0.8 MeV energy gain per turn.

approaching 100% can be achieved. The beam injection and extraction devices can also be removed from the magnet gaps and placed in the spaces between the magnets. With all this hardware removed from the magnets, the magnet gap can be reduced to no more than that required for beam orbit containment. Since the electrical power required to generate the resonant magnetic field increases as the square of the magnet gap, the magnet operating efficiency can be made very high. It also produces a sharper field edge between the high and low field regions of the ring, providing increased axial focusing needed for the higher energy beams.

Another example of the versatility of the separated sector design is the IUCF cyclotron. This accelerator was originally constructed as a variable energy (20 through 370 MeV) and multi-particle (p, d, ^3He , ^6Li) research machine. To achieve this wide range of particles and energy, the magnet pole faces were augmented with a set of 21 trim coils that could shape the magnetic field as a function of radius to match the relativistic requirements of each particle and energy selected. The field increase from injection to extraction required for 220 MeV protons was 25%, while the field could essentially be constant with radius for low energy helium and lithium beams. The trim coils required as much power to operate for high energy proton beams as the main magnets themselves. This facility is yet another example of a research cyclotron completing its scientific mission and then being dedicated to medical and industrial applications. The IUCF facility was converted into a Proton Therapy cancer treatment facility (MPRI) in the years between 2000 and 2006 and the cyclotron was reconfigured to operate as a 205 MeV fixed energy proton source [38]. This cancer treatment facility, which continues to operate today, will be discussed in more detail in *Section 3*.

The separated sector cyclotron is neither compact nor generally suited for practical medical applications because of its size and complexity. These high energy and intensity machines were designed for scientific research, and have higher performance capabilities than required for medical use. Nevertheless, most of the 13 large separated sector ring cyclotrons [24] devote some of their time to the development or application of hadron therapy. Indeed, places such as PSI, IUCF and NAC have helped pioneer some of the more advanced applications of hadron radiation therapy

2.4. The Superconducting Cyclotron

In the late 1960s and early 1970s, large scale superconducting magnets, based upon NbTi conductors

operating at liquid helium temperatures, began to appear in advanced scientific applications including bubble chamber magnets, fusion experiments and Magneto Hydro Dynamic (MHD) devices. As the set of technical developments that made possible these new superconducting magnetic devices, which operate at fields as high as 3-4 Tesla, became more widely known, cyclotron designers began to consider their possible role in isochronous cyclotrons. One of the vexing problems of isochronous cyclotron design had been that at the practical limit of magnetic excitation levels of resistive copper windings, typically less than 2 Tesla, the iron in the cyclotron had a wide range of saturation magnetizations that could not be modeled with the tools available, and hence model magnets were needed to verify and optimize the orbit properties of new cyclotron designs. Fraser and colleagues at Chalk River Nuclear Laboratories were the first to realize that for operations above 3T, there could be a simultaneous improvement in magnetic field accuracy due to the likelihood of full saturation of the iron poles, while significantly reducing size and overall cost for a given energy [39]. Cyclotrons have a unique scaling of the final energy (T), radius (r) and field (B), for a given ion of charge $Q = Ze$ and mass Am_0 :

$$T = \left(\frac{Q^2}{A} \right) \frac{e^2}{2m_0} r^2 B^2 \quad (1) \quad (2.13)$$

Eq. (2.13) shows that for a given final energy and ion, increasing the field results in a decrease in the size of the cyclotron, and this scaling holds for all 3 cyclotron types. A significant argument for the development of the superconducting cyclotron proposed by Blosser and Johnson was to construct a compact hadron therapy cyclotron suitable for hospital use [40]. In the 1980s, superconducting magnets were used to exploit this scaling law to realize compact heavy ion isochronous cyclotrons at fields around 5T [41]. The first superconducting cyclotron, a K500 heavy ion accelerator shown schematically in Fig. 18, was successfully fabricated at Michigan State University (MSU). This accelerator is still in service for research today as an injector for a larger K1200 cyclotron built at MSU.

A total of 9 superconducting isochronous cyclotrons operating at fields in the range of 3-5T were built for heavy ion nuclear science from 1981 through 1992. All of these machines are still operating, and are almost an order of magnitude more compact than equivalent energy conventional resistive magnet cyclotrons. Since cyclotron sub-systems and facility overall size scale

with the cyclotron size, this effect also had a dramatic effect

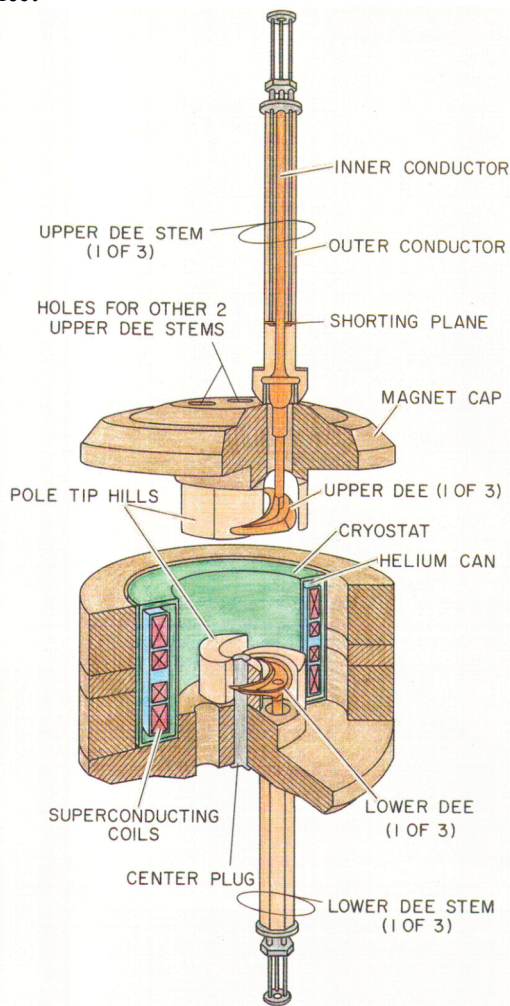


Fig. 18. The MSU K500 cyclotron is a 3 sector, spiral hill superconducting isochronous cyclotron. It has a peak field of 5.5T. It is a variable energy heavy ion accelerator and was the first operating accelerator of any kind to employ a superconducting magnet.

on the overall facility costs. Further, since the magnets are superconducting and the RF systems are now more compact, overall power and cooling requirements are again significantly decreased.

In the 1980s, studies of cyclotrons with fields beyond 5T were made, but the magnet technology was viewed as limiting, as was the engineering complexity of higher field isochronous machines. One of the major difficulties with the very high-field magnets was the strength of the materials required to stably contain the coils and related structure. Successful studies were performed for a superconducting synchrocyclotron [42] and for an 8T cyclotron magnet [43]. However, through the late 1990s, resistive cyclotron magnet designs

remained at 1-3T field levels and superconducting magnet designs remained around 3-5 T.

While dedicated medical cyclotrons are discussed in

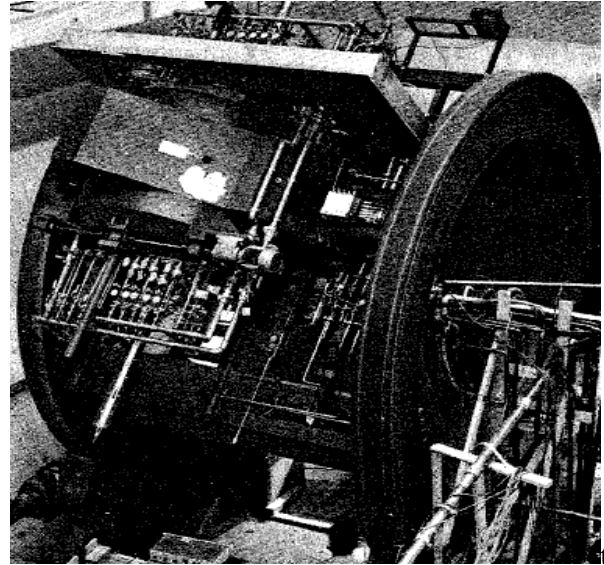


Fig. 19. The 50 MeV Harper Grace Deuteron cyclotron for neutron beam radiotherapy. The 4.6 m O.D. gantry rings allowed this cyclotron to rotate +/- 180 degrees around the reclining patient with the liquid helium cooled magnet fully energized but the beam stopped during rotation

detail in *Section 3* below, we note one unique superconducting cyclotron designed and fabricated at MSU for clinical medical use here. Studies were initiated at MSU in 1984 for a 50 MeV compact superconducting deuteron cyclotron for Neutron Beam Radiotherapy [44]. This cyclotron, shown in Fig. 19, was mounted on a pair of gantry rings in an available spectrometer pit at MSU National Superconducting Cyclotron Laboratory (NSCL) for testing and had an internal beryllium target that yielded a neutron spectrum peak at 25 MeV with an order of magnitude more neutrons per deuteron than a same energy proton beam [45]. It was built jointly by NSCL and the MedCyc Corporation, commissioned at NSCL in April 1989, and installed the next year at Harper Grace Hospital in Detroit, Michigan [46]. Neutron radiotherapy never caught on as a mainstream oncology technique, but this machine was in clinical operation until 2008, when the neutron radiotherapy program at Harper Grace was discontinued.

3. Commercial Medical Cyclotrons

The original cyclotron concept, invented by Lawrence in 1931, has been developed over the last 8 decades into machines that can provide any ion and energy desired for research or applications given the practical limit of cost. The applications of cyclotron beams in medicine

and industry have grown from the first investigations of John Lawrence in the 1930s to the point where commercial cyclotrons are designed and built to specifications to meet a large array of user applications, including industry, national security and medicine.

In general, most of the commercially available isotope production machines are room temperature sector-focused cyclotrons employing either radial (< 30 MeV) or spiral ridge sector magnets. The hadron therapy facilities in operation today use a variety of decommissioned high-energy research accelerators (IUCF for example), a few specially built accelerators, and an ever-growing assortment of commercially available treatment facilities. Indeed manufacturers are now marketing complete isotope production and hadron therapy facilities to hospitals around the world. In this section, an attempt will be made to highlight some of the medical applications and the commercial manufactures of the medical cyclotrons. Given the large and increasing number of these machines operating today around the world, the authors will undoubtedly miss some of these.

3.1. Medical Isotope Production

Phillips introduced the first commercial cyclotron for medical isotope production in 1966 [47]. This 28 MeV proton cyclotron demonstrated that cyclotrons could be a cost effective source of medical isotopes. Cyclotrons have been the main accelerator source of medical isotopes ever since, with hundreds of units deployed by many companies. The Philips cyclotron produced 15 MeV deuterium and 38 MeV ^3He beams. Prior to the commercial isotope production cyclotron, most radioisotopes were produced in research nuclear reactor.

Cyclotron produced medical isotopes are used in planar (2D) imaging studies with the gamma camera, and computed tomography (3D) such as Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), and PET/CT. Generally a compound labeled with a radioactive tracer, prepared in a modular chemistry unit from an irradiated target material, is introduced in vivo. The tracer element, a gamma ray emitter, travels through the body and collects in specific parts of the body depending upon the chemistry of the compound, which can then be imaged for clinical diagnostic purposes or treatment. For instance, Iodine collects in the thyroid glands and tumors. In the simplest case, Planar Imaging, single emitted gamma rays are imaged with a gamma camera, showing a 2D distribution of the tracer radioisotope at active sites in the body. SPECT is similar to planar imaging in that multiple 2D images are obtained by rotating the gamma camera around the patient and then

a 3D image is computer generated. The primary SPECT isotopes used for medical imaging produced by cyclotrons are: $^{99\text{m}}\text{Tc}$ for bone, myocardial and brain scans; ^{123}I for tumor scans and ^{111}In for white blood cells.

PET differs from SPECT in that the tracer elements are short lived positron emitters, i.e., ^{11}C , ^{13}N , ^{15}O , and ^{18}F , which are used to study brain physiology and pathology [8]. Positrons readily annihilate with any free electron in the body yielding a pair of 511 keV photons. The two 511 keV photons are emitted at nearly 180 degrees from each other. Timing can be used to determine the location of the positron annihilation event and thus 3D images can be constructed with computer analysis. The timing also improves the signal-to-noise ratio and fewer events are needed to construct the image. PET/CT and PET/MRI are used to co-registered anatomic and metabolic information simultaneously from PET and CT or MRI data. The main PET tracer is FDG, a glucose analog molecule labeled with Fluorine-18 and produced typically in an 18 MeV proton cyclotron.

A representative (i.e., very incomplete) list of the manufacturers of medical isotope production cyclotrons is provided in Table 1, which illustrates the variety of beams and energies available to the medical community for isotope production [48]. One of the earliest commercial cyclotrons was the CS-15 H^+/D^+ machine marketed by the Cyclotron Corporation in Berkeley, California. Several of the accelerators listed were designed and manufactured by a single firm. The TR-30 and CS-30, for example, was designed originally by the accelerator group at TRIUMF but was then marketed and sold under the names listed by the companies listed in Table I. From this list, it is obvious that in the years after 1975, the sale and use of these isotope production machines grew at a very rapid pace.

The majority of medical isotope production cyclotrons accelerate H^+ ions. The reason for this is that a simple beam extraction process is used. Some of the H^+ ions impinging on a thin internal target, called a "stripper foil," set at an internal radius and have their 2 electrons removed ("stripped" away) and the resulting H^+ ions follow a reverse curvature orbit (with respect to the H^+ ions) and are directed out of the cyclotron. The remaining un-stripped ions continue to accelerate to a larger radius where they can be stripped at a higher energy. Multiple thin "stripper foils" can be inserted at several radii within the cyclotron, making it possible to simultaneously extract several H^+ beams of different energies from a single cyclotron. H^- Cyclotrons operate at magnetic fields of 1T or less to avoid Lorentz stripping, i.e., magnetic removal of the extra electron attached to the proton [49].

The IBA Cyclone 30, introduced in 1986 and

TABLE I
Representative List of Commercial Cyclotrons Used for Isotope Production

Manufacturer	Model	Particle	Energy (MeV)	Intensity (μA)	First Available
Advanced Cyclotron Systems 7851 Adlerbridge Way Richmond, BC (EBCO)	TR 13	H^-	13	100	1994
	TR 14/TR19	H^-	14 – 19	300	
	TR 24	H^-	15 – 24	300	
	TR 30	H^-	15 – 30	1000	1990
	TR 30/15	H^+, D^-	30/15	1000	1994
Ion Beam Applications s.a. Chemin du Cyclotron 3 B-1348 Louvan-la-Neuve, Belgium	Cyclone 3	D^-	3.5	100	
	Cyclone 10/5	H^+, D^-	10/5	100	1988
	Cyclone 18 ⁺	H^+	18	2000	1994
	Cyclone 18/9	H^+, D^-	18/9	100	1992
	Cyclone 30	H^-	30	500	1986
Scanditronix Wellhofer. AB Stalgatan 14 Uppsala, Sweden	MC 16	H^+, D^- $^3\text{He}, ^4\text{He}$	17 /8.3 12.4 /16.5	50	1990
	MC 32 NI	H^+, D^-	16-32/8.5-16	60	1990
	MC 35	H^+, D^- $^3\text{He}, ^4\text{He}$	7.5-35/3.8-18 5.6-47/7.5-16.5	75	
	MC35, 40	H^+, D^+	8-40/20	75	1979
	MC50	H^+, D^+	50/25	50	1989
	MC60PF	H^+	60	35	1984
General Electric www.GEhealthcare.com	MINItrace	H^-	9.6		1993
	PETtrace	H^+, D^-	16.5/ 8.4		1993
Siemens (CTI) www.Siemens.com/healthcare	RDS Eclipse	H^-	11.0	100	1987
	RDS 112				
	RDS 111				
The Cyclotron Corporation* 950 Gilman St. Berkeley, CA	CS-15	H^+, D^+	15/8	60	1967
	CS-22	H^+, D^+	22/12	50	1970
	CS-28	H^+, D^+	24/14	50	1974
	CS-30	H^+, D^+	26/15	60	1973
	CP-42	H^-	42	200	1980
Sumitomo Heavy Industries, Ltd 2-1-1 Yato-cho Ranashi City, Japan	HM-18	H^+, D^-	18/10	70	1991
	480 AVF	H^+	30	80	1985
	750 AVF	H^+	70	55	1985
	930 AVF	H^+	90	10	
Japan Steel Works, Ltd Muroran, Japan	BC168	H^+, D^+	16/8	70	1982
	BC1710	H^+, D^+	17/10	70	1981
	BC2211	H^+, D^+	22/11	70	1989
	BC3015	H^+, D^+	30/15	70	1985



Fig. 20. The widely deployed IBA Cyclone 30 Isotope production cyclotron accelerates protons from 18-30 MeV, also simultaneously accelerating deuterons (9-15 MeV) and features dual isotope production targets.

shown in Fig. 20, was a big step forward. It produced significantly higher H⁺ currents per unit wall plug power and had two independent stripper foils and isotope production targets [50]. Beam intensities up to 1 mA are now available from these accelerators. Today, isotope production cyclotrons are available commercially in energies from 5-90 MeV from EBCO, SHI, GE, Japan Steel Works, IBA, and Siemens (formerly CTI). Most of these later generation cyclotrons are variable energy and particle, can have multiple extracted beams, and come complete with built in target stations and computer control systems designed to permit operation by trained technical personnel who are not required to be expert accelerator designers or builders.

3.2. Ion Beam Therapy Cyclotrons

The 1946 suggestion of Robert Wilson [12] to use high energy protons to kill deep seated tumors in the human body, became a reality beginning in the late 50s, and has grown into a well establish protocol for curing a host of otherwise untreatable cancers, as well as a preferred method of curing other cancers while reducing radiation damage side-effects. This cancer-fighting technique is referred to as “hadron therapy” or “ion beam therapy” (IBT) and is most effective in eliminating well localized cancerous tumors located within the human body, particularly in the head and neck areas. This section, like those above, is not intended to describe the full range of medical applications for IBT, but seeks to describe the required properties of the treatment beams and delivery systems, and list the present commercial suppliers of applicable cyclotron-based IBT facilities.

The basic physics that makes hadron therapy so attractive is the manner in which high-energy particles (protons, deuterons, pions, and heavier ions) lose energy while passing through matter, as described in Section I. The peak in the energy loss profile at the end of an energetic particle’s range, illustrated in Fig. 1, is called the Bragg peak. The depth of penetration of the ion beam into the body depends precisely upon the particle type and energy used for the IBT treatment, as well as the density of the area to be penetrated. This energy loss property allows the physician to precisely target a tumor located within the human body while sparing radiation damage to the healthy tissue around it. A 160 MeV proton beam will penetrate 15 cm into the human body. Successive beams of lower energies and intensities can be directed at the tumor so as to uniformly irradiate the whole depth of the tumor. Beam apertures and Lucite compensators are used to map the lateral shape and distal (rear) edge of the tumor. These devices are shown in Fig. 21. A contour map of the area radiated by a proton beam using this technique is also shown, with the red area being the highest concentration of radiation delivered to the body. The green circle represents a sensitive organ that should not receive damaging radiation, illustrating the capability of this treatment protocol to spare healthy tissue. These very basic techniques have been improved over the years with precise beam scanning and intensity modulation techniques that are used to give a precise 3-dimensional conformal map of the tumor with the treatment beam.

The majority of the existing hadron therapy facilities today use protons, but a few are able to use heavier ion beams such as helium, carbon and neon. IBT using pion beams has also been conducted. The ion beam property used to compare the radiobiological effectiveness of hadron treatment is its Linear Energy Transfer (LET) to the tumor. Ionizing radiation destroys the ability of cells to divide and grow by damaging their DNA strands. Activated radicals

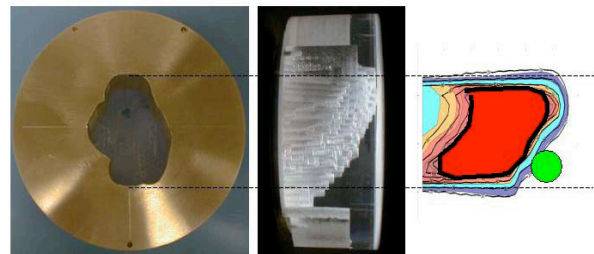


Fig. 21. Brass Beam Aperture and Lucite compensator used together with the SOBP to confine the maximum ionizing energy of a proton beam to a tumor.

produced from atomic interactions is the primary cause of radiation damage by photons, electrons, and protons. These types of radiation are called low linear-energy-

transfer (low LET) radiation. Neutrons and heavy ions have a high LET compared with protons and photons.

All these ions have been used for hadron therapy in the past. There is much debate among clinicians about the relative effectiveness of the various ions species in curing cancerous tumor diseases, although a few very general facts are agreed upon by most:

- Most localized cancers can be effectively treated with low LET protons or with photons.
- About 10% of tumors have a high resistance to low LET treatment and these can often be successfully treated with the higher LET heavy ion beams such as carbon.
- Carbon ions have better dose distributions (less lateral scattering and collateral damage to adjacent healthy tissue) than protons.
- More study is required to accurately determine the most effective treatment protocols.

The facility costs are the primary reason that there are thousands of photon cancer treatment facilities today. Commercially available photon radiation treatment facilities, based on low energy electron linear accelerators, are well within the budget of most hospital facilities. There are currently about 30 operating IBT facilities in the world, of which only a few have a heavy ion capability. Yet, regardless of the techniques used, all IBT facilities require an ion beam source, and a particle accelerator such as a cyclotron, that can deliver a precise beam energy and intensity.

3.2.1. Proton Therapy Treatment Facilities

A 230 MeV proton beam will penetrate 32 cm into the human body, a depth large enough for most human applications; hence, this has become the canonical energy for all proton therapy accelerators. The early trials in the development of IBT by John Lawrence, the scientists at the GWI, Sweden and the Harvard synchrocyclotron facilities were discussed in *Section 2.2*. This work was done with research cyclotrons or cyclotrons converted for medical applications at the end of their useful physics research life. The first hospital based proton therapy treatment facility in the United States, The John M. Slater Proton Treatment and Research Center, was installed at the Loma Linda University Medical Center in San Bernardino, California. The facility was the first specifically designed for use as a Proton Therapy Treatment Facility. The accelerator, a 370 MeV proton synchrotron, and beam delivery systems, including the 360° rotating gantries, were designed at the Fermi National Accelerator Laboratory in Batavia, Illinois by

Fred Mills and Frank Cole [51]. While this paper is not discussing synchrotron accelerators, this facility is worth mentioning here, as it was a milestone for the acceptance of IBT as a superior treatment protocol for several cancers in the United States. Several proton therapy facilities around the world had been operating for several years, particularly in Europe and Japan, but the primary impediment to the use of proton therapy was in the U.S. due to cost.

The second proton therapy facility to begin operations in the U.S. was the Northeast Proton Treatment Center (NPTC), a new commercially built IBT facility installed at the Massachusetts General Hospital in Boston [52]. This facility, recently renamed the Francis H. Burr Proton Therapy Center, replaced the pioneering and aging Harvard synchrocyclotron proton therapy facility that had been in operation in conjunction with the Harvard Medical School since 1961. The new treatment facility was designed and built by Ion Beam Applications (IBA) in Belgium [53] (the same company that manufactures the “Cyclone” series of isotope production cyclotrons listed in Table I). The facility, consisting of a 230 MeV superconducting cyclotron, a beam delivery system and 3 treatment rooms (two of which house 360° rotating gantries), is the first commercially built, installed and operating hadron therapy facility in the world. A photo of the cyclotron, an IBA C235, and a layout of this treatment facility are shown in Figs. 22 and 23. The IBA facilities typically consist of 3 to 4 treatment rooms. Since the commissioning of this facility, IBA has installed a total of 13 additional facilities world wide, 60% of the total

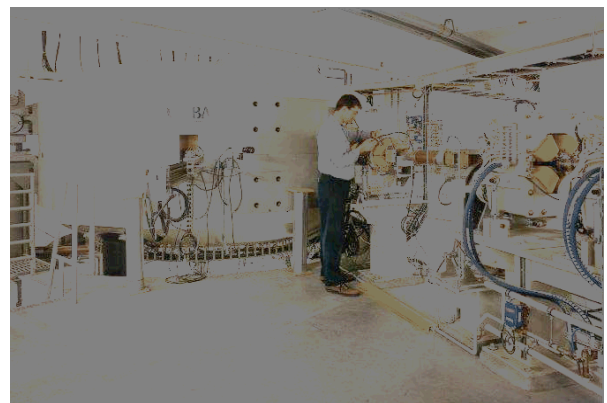


Fig. 22. An IBA Cyclone 230 superconducting cyclotron manufactured for IBT. Compare the size of this 230 MeV proton cyclotron with the 220 MeV Indiana University room temperature proton cyclotron shown in Fig. 17 using the men in the respective pictures.

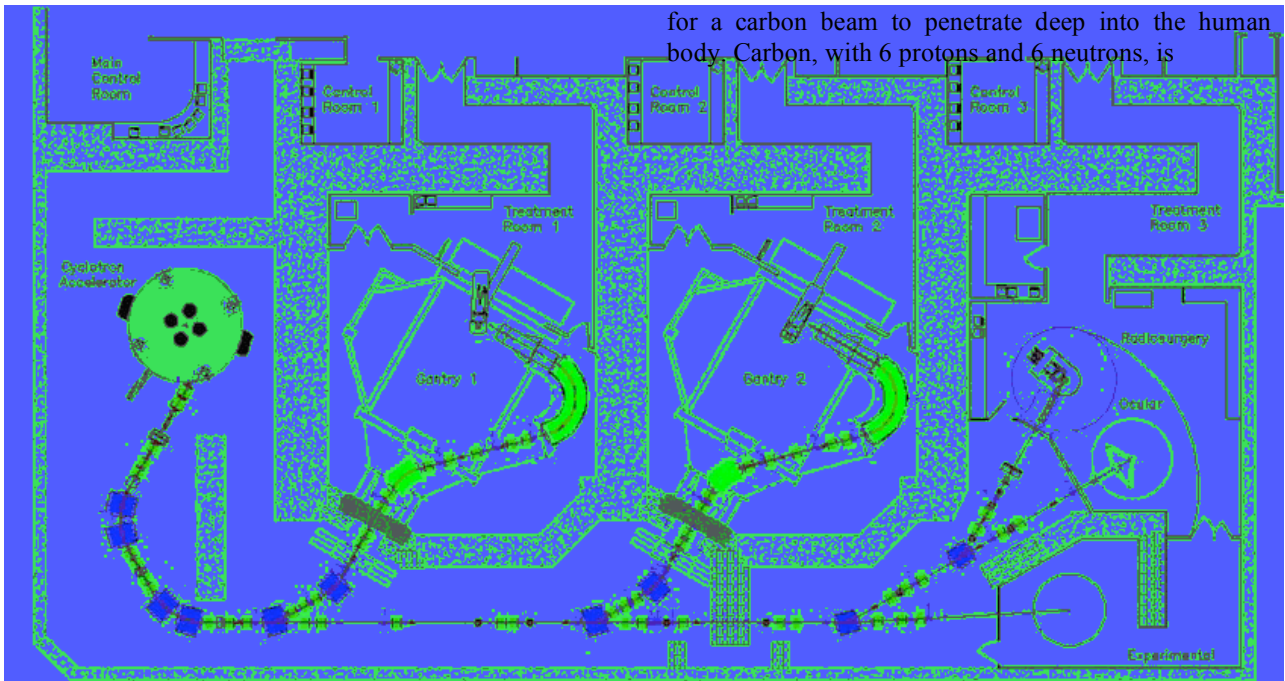


Fig. 23. Facility layout of the NPTC Proton Therapy Treatment center showing the relative locations of the cyclotron, beam delivery systems and 3 treatment rooms.

number of commercial proton therapy facilities (30) installed or under construction world wide as of 2009.

Yet another company, Varian Medical Systems in Palo Alto, California, is marketing a proton therapy system based on an Accel 250 MeV proton superconducting synchrotron, shown in Fig. 24. This cyclotron was based on the design for a superconducting cyclotron by H. Blosser, the inventor of the superconducting cyclotron. Varian acquired Accel Corporation in 2007, and fabricated the machine now installed at PSI Switzerland that is being used for IBT [54].

3.2.2. Heavy Ion Beam Facilities

There are currently four IBT facilities around the world that use heavy ions (carbon) for IBT [55]. Two of these facilities are located in Japan, which has 7 operating IBT facilities. There are another 6 additional IBT facilities under construction in Japan, and 3 of these will be heavy ion facilities. An additional 3 carbon IBT facilities are presently under construction in Europe and one is under construction in China.

All of the existing carbon IBT facilities use a synchrotron accelerator to produce the energy required

for a carbon beam to penetrate deep into the human body. Carbon, with 6 protons and 6 neutrons, is

approximately 12 times more massive than a proton, and thus requires significantly higher energies to penetrate deep into the human body than protons. For a charge to mass ratio (q/a) of $\frac{1}{2}$, a fully stripped 320 MeV/amu carbon beam will penetrate 15 cm into the body. Consequently all of the present carbon facilities presently use high energy synchrotrons to produce the required energy carbon beams for IBT. These are relatively large and complex facilities compared to the commercial proton IBT centers.

IBA from Belgium, has designed a high-field (4.5 T)

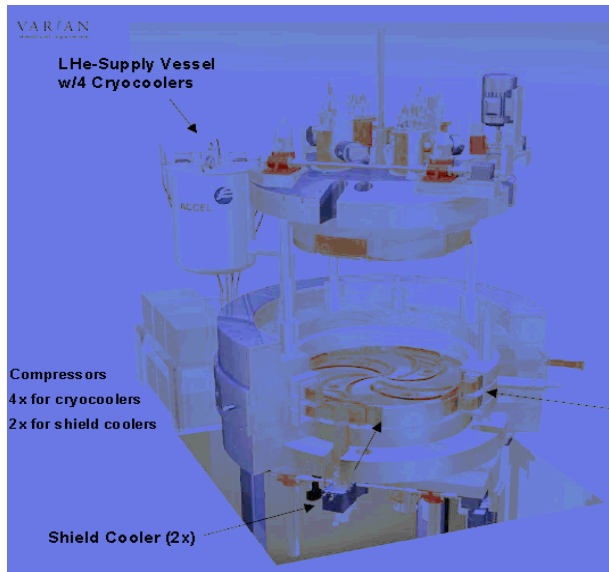


Fig. 24. 3D schematic of the Accel superconducting 250 MeV proton cyclotron. Now being marketed by Varian Corporation. superconducting cyclotron to accelerate ions with $q/a = \frac{1}{2}$ (H_2^+ , He, Li, B, C, Ni, O, and Ar) to 400 MeV/amu. This cyclotron, called the C400, is based on the IBT C235 design but with higher magnetic fields and a larger diameter (6.4 m vs. 4.7 m). The machine will be able to provide 265 MeV protons as well as 400 MeV/amu heavy ions, making it an all purpose accelerator for IBT applications within a very small footprint [56] and a serious competitor to the synchrotron as a practical and affordable source of ions for hadron therapy. The first of these accelerators will be installed in Caen, France. A schematic of the C400 design is shown in Fig. 25.

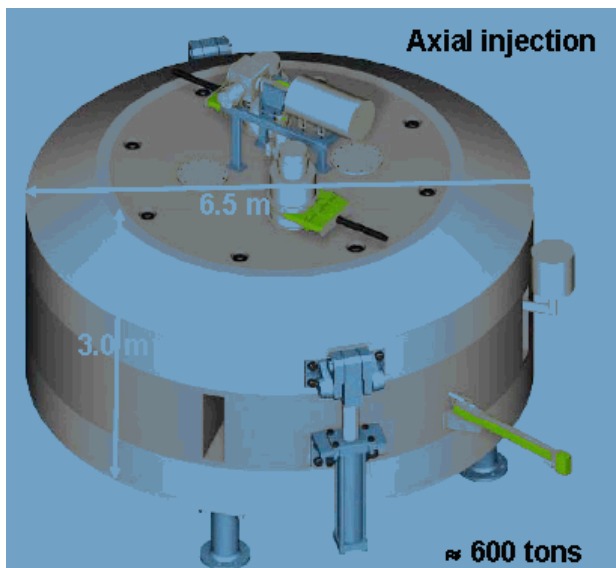


Fig. 25. A schematic of the IBA C400 superconducting heavy ion cyclotron showing some dimensional characteristics.

3.2.3. Commercial Hadron Facilities and Vendors

There are only a few vendors of completely designed and operational hadron therapy facilities and they are listed in Table II. Three of the vendors are the major, heavy industrial corporations in Japan: Mitsubishi, Hitachi, and Sumitomo. Of these, Sumitomo is the only company marketing cyclotrons for both Pet isotope production (see Table I) and hadron therapy. Three of the vendors listed market facilities based on superconducting cyclotrons.

It is risky to count the hadron facilities operating or under construction today since the number changes rapidly. Nevertheless, there are presently 30 operating proton therapy centers around the world, with an additional 14 facilities under construction or planned. Of the 30 existing facilities, 16 listed in Table III use

Table II
Commercial Hadron Therapy System Vendors

Manufacturer	Accelerator Type	Maximum Energy/ Particle
Ion Beam Applications, Belgium	S.C. Cyclotron	235MeV/P
Varian, Inc, Palo Alto, CA, U.S.A.	S.C. Cyclotron	250 MeV/P
Still Rivers, Inc, Boston, MA, U.S.A	S.C. Synchrocyclotron	235 MeV/P
Optivus Proton Therapy Loma Linda, CA	Synchrotron	370 MeV/P
Mitsubishi Heavy Industries, Japan	Synchrotron	370 MeV/P
Hitachi, Japan	Synchrotron	250 MeV /PP
Sumitomo Heavy Industries, Japan	S.C. Cyclotron	235 MeV/P

cyclotrons as the high energy particle source. Of these, 13 facilities were manufactured and installed by IBA (Ion Beam Applications, s.a, Belgium) using the IBA C235 superconducting cyclotron. A 14th facility marketed by Sumitomo Heavy Industries, in collaboration with IBA, uses the Proteus C235 cyclotron design.

4. Future Accelerators for Medical Applications

4.1. New High Field Compact Medical Cyclotrons

In 2003-2004, Timothy Antaya introduced a superconducting synchrocyclotron design with 9T fields for proton beam radiotherapy [57]. The purpose of this effort was to use the field scaling of Eq. 2.12 to produce a compact cyclotron that would enable the development of a low-cost, single-room Proton Beam Radio-Therapy Treatment (PBRT) system. To be feasible, the compact cyclotron would have to be gantry mounted and have a final proton energy of at least 250 MeV. A synchrocyclotron-type accelerator was chosen because: (a) the prior design study at 5T [43] could be used as a guide, (b) it was possible to demonstrate quickly how the beam dynamics of synchrocyclotron would scale at high field, (c) the intensity requirements for PBRT, namely a proton beam intensity of 20-40 enA, are easily achievable in a synchrocyclotron, (d) the anticipated simplicity and inherent robustness of a weak focusing-

The National Cancer Center	Seoul, South Korea
National Cancer Center Hospital East	Kashiwa City Chiba Prefecture, Japan

cyclotron would be ideally suited to the requirements of a non-specialist operated clinical PBRT system, and (e) this field level, while high for accelerators, was far from the limits of the technology for high field superconducting magnets. In order to complete this 9T synchrocyclotron design, it was necessary to develop a quantitative computational beam dynamics model for weak focusing-phase stable cyclotrons [58]. In addition, it was necessary to establish feasible magnet and RF engineering solutions for such high field cyclotrons [59]. Finally, advances in cryogenic engineering and components allowed the engineering of an orientation-independent superconducting cyclotron magnet that is

Table III.
Current List of IBA Proton Treatment Facilities

Facility Name	Location, Country
Northeast Proton Therapy Center (NPTC)	Massachusetts General Hospital Boston, MA, U.S.A.
Midwest Proton Radiotherapy Inst. (MPRI)	Indiana University Bloomington, Indiana U.S.A.
Univ. Florida Proton Therapy Center (UFPTCI)	University of Florida, Jacksonville, FL, U.S.A.
Procure 1 Proton Therapy Center	Oklahoma City, OK, U.S.A.
Procure 2 Proton Therapy Center	Warrenville, IL, U.S.A.
Roberts Proton Therapy Center	Univ. Pennsylvania, Philadelphia, PA, U.S.A.
Hampton Univ. Proton Therapy Inst.	Hampton Univ. VA, U.S.A.
The Center for Proton Therapy of Orsay	Curie Institute, Orsay, France
West German Proton Radiotherapy Center (WPE)	Essen, Germany
Wan Jie Proton Therapy Center (WPTC)	Wan Jie Hospital, Zi-Bo China
Beijing Greatwall International Cancer Center	The Soni-Japanese Friendship Hospital Beijing, China

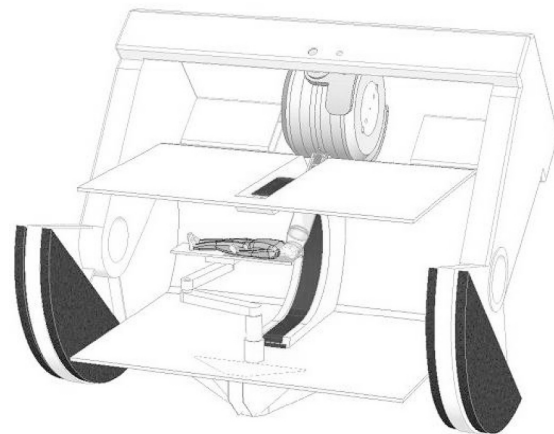


Fig. 26. The 9T superconducting synchrocyclotron for proton beam radiotherapy is shown. This compact high field cyclotron enables single room treatment at a fraction of the cost of conventional facilities, and widespread adoption is expected.

cryogen free [60]. Since the radius decreases in proportion to the field increase, this 9T synchrocyclotron is more than 50 times less massive than a conventional machine of the same final proton energy, as shown in Fig. 26, and later in Fig. 28.

Many of the beam dynamics and technical challenges solved for the introduction of the high field synchrocyclotron are shared in the design and engineering of all cyclotron types. Weak focusing cyclotrons favor low energy gain per turn (ΔT_1), and a 250 MeV proton machine requires about 15,000 turns ($\Delta T_1 \sim 15$ keV/turn), to reach the full energy. Since the turn spacing varies inversely with energy and $f(\gamma) \sim 1$,

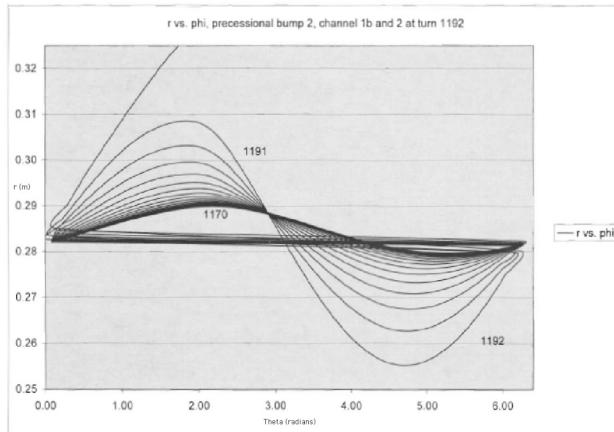


Fig. 27. An unfolded set of orbits near 250 MeV in a 9T synchrocyclotron is shown. The radial orbit separation moves exponentially from a few microns to millimeters in about 20 turns, and then is directed out of the edge of the cyclotron field as a result of a set of small field perturbations.

the turn spacing at full energy is of the order of 10 microns in this 9T synchrocyclotron. High extraction efficiency is desirable for such a patient-in-the-room accelerator, hence it was necessary to develop a new beam extraction technique, which required an exceptionally precise beam dynamics simulation, using highly accurate computed fields [62].

$$\frac{dr}{dN} = r \frac{\Delta T_1}{T} f(\gamma) \quad (4.1)$$

Fig. 27 shows a non-linear growth of a radial oscillation that results in an exponential growth in turn separation from around 6 microns to 1 cm in 20 turns, followed by passive magnetic element guided ion extraction at 250 MeV.

4.2. Compact IBT Facilities

While the number of Proton Therapy Treatment Centers is growing at a reasonable pace, they are generally placed in high population density areas because of their size and cost (approximately \$100 Million for a three treatment room facility with Gantries). To make this treatment available to larger fraction of the population, manufacturers are designing more modest and innovative one or two room facilities that would be more affordable (\$40 Million), and hence be practical for installation in smaller population centers. The development of high field superconducting cyclotrons or synchrocyclotrons is making this option a reality. Still River Systems [63] is commissioning a one room Proton Beam Radio-Therapy (PBRT) system, called the Monarch^{250TM}, based on a gantry mounted 9T

synchrocyclotron shown in Fig. 28 and discussed in Section 4.1. This 250 MeV Synchrocyclotron is much smaller than the IBA C235 and Accel 250 MeV 3T superconducting cyclotrons shown in Figs. 22 and 24, and is an excellent visual demonstration of the dimensional scaling laws with magnetic field for cyclotron magnets. This cyclotron is currently undergoing commissioning.

The Still River Systems single room PBRT system conceptual design is shown in Fig. 29. The Monarch synchrocyclotron is seen mounted on a 180° rotating gantry within the treatment room, similar to what was done with the 50 MeV Harper Grace deuteron cyclotron in 1980. Barnes Jewish Hospital in St. Louis, Missouri and M.D. Anderson Cancer Center in Orlando, Florida have made partial commitments to purchase this system, which is advertised to cost \$20 Million for the treatment equipment [64]. One of the advantages of the single room concept is that the equipment could be installed in



Fig. 28. A photo of the Still River Systems Monarch^{250TM} superconducting synchrocyclotron. The small size of this 250 MeV Proton machine is evident from the size of the man working on it.

anexisting space within a hospital or traditional photon radiation facility.

Accel has also made a tentative design, shown in Fig. 30, for a single room PBRT system based on a high field cyclotron mounted on a gantry, somewhat like the Still Rivers design [63]. Other commercial

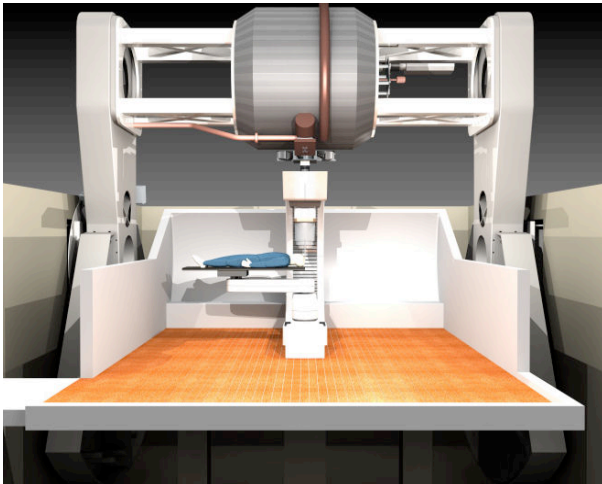


Fig. 29. The conceptual design for the Still Rivers single treatment room PBRT system showing the Monarch^{250T}™ mounted on a gantry within the treatment room.

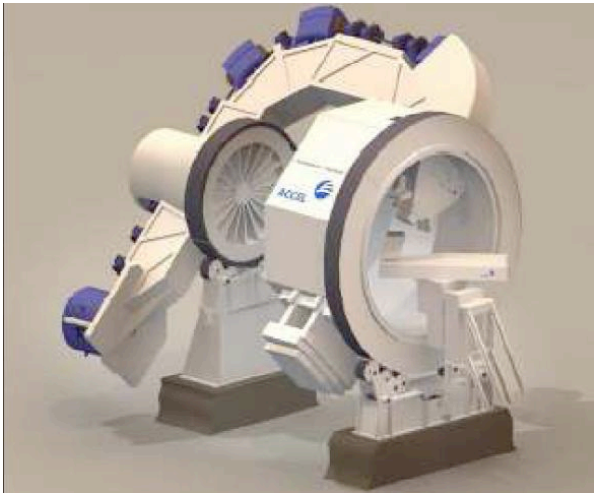


Fig. 30. The Accel Corp. conceptual design of a single room PBRT system with a gantry mounted cyclotron and beam delivery system.

manufacturers such as Procare and IBA are also studying ways to reduce the high cost of hadron facilities.

With the recent advances in cyclotron design, the cost of the cyclotron (~\$10 Million) is not the major expense for a hadron therapy facility. Larger treatment centers with 3 to 5 treatment rooms (most with Gantry) and the infrastructure to house the facility and shield public areas from stray radiation are the major cost drivers. Thus, a small single room facility has the potential to significantly reduce the overall cost of a hadron therapy treatment system.

5. Conclusions

The invention and development of the cyclotron over the last 80 years has played a major role in our ability to understand the nature of matter through scientific research and to control disease through medical applications. It is remarkable how this invention has grown from the 27 inch 3.7 MeV proton Berkeley classical cyclotron in 1932, to the massive variable energy, variable particle research machines like the 1 GeV proton synchrocyclotron at Gatchina in the 70s and 80, and today, into very powerful commercially available 250 MeV compact proton superconducting applications cyclotrons. The Still River Systems/MIT 250 MeV superconducting proton synchrocyclotron is smaller than the 27" Berkeley cyclotron used for the initial isotope production and fledgling medical studies performed by John Lawrence in 1938. The development of the cyclotron into evermore powerful and compact machines is continuing at a rapid pace to provide smaller, more powerful, more flexible, and less expensive isotope production and hadron therapy facilities for medical applications. Today, there are literally thousands of cyclotrons operating daily around the world for medical applications. More cyclotrons are developed, built and sold commercially than for scientific research, which has moved on to much higher energy synchrotron accelerators like the LHC for its studies. Who would have guessed in 1932 that the initial developments and studies of the Lawrence brothers would have such a wide spread impact on today's society?

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