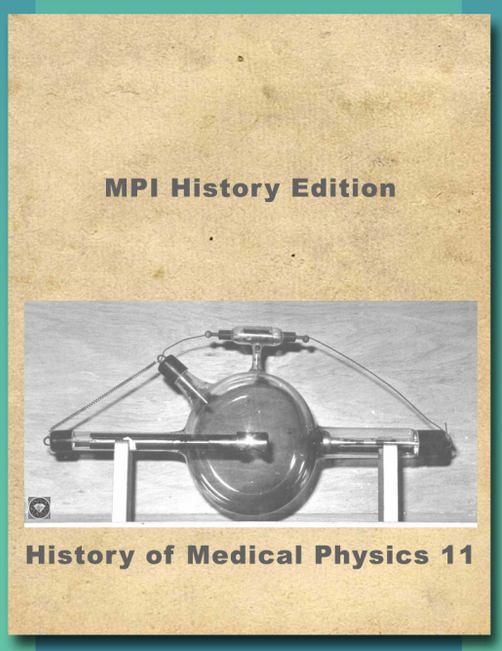
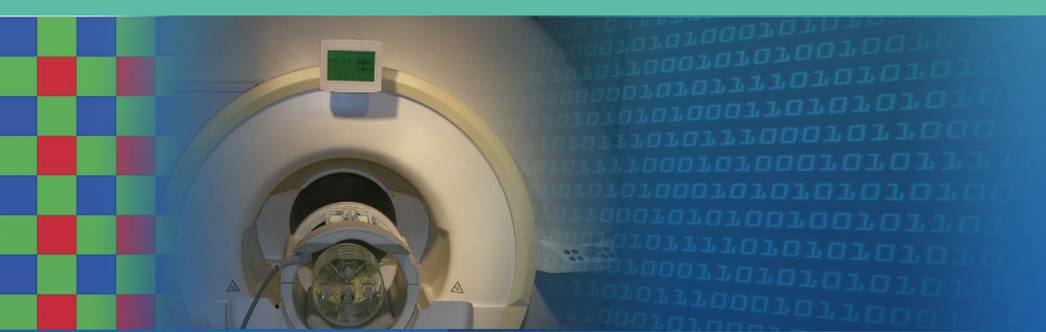
MEDICAL PHYSICS
International





The Journal of the International Organization for Medical Physics

History Edition 11, June 2025

MPI

MEDICAL PHYSICS INTERNATIONAL

THE JOURNAL OF

THE INTERNATIONAL ORGANIZATION FOR MEDICAL PHYSICS

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The Journal of the International Organization for Medical Physics

Aims and Coverage:
Medical Physics International (MPI) is the official IOMP journal. It provides a platform for medical physicists to share their experience, ideas and new information generated from their work of scientific, educational and professional nature. The e-journal is available free of charge to IOMP members. MPI- History Edition is dedicated to History of Medical Physics.

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EDITORIAL

Slavik Tabakov, Perry Sprawls and Geoffrey Ibbott - Co-Editors-in-Chief of MPI History Editions

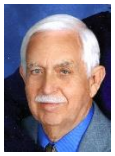
This issue of the *Medical Physics International History Edition* (MPI-HE), previously known as *MPI Special Issues* dedicated to history, marks the surpassing of 1600 pages of published materials about the history of medical physics. Starting in 2018 MPI-HE attracts thousands of readers per month at http://www.mpijournal.org/history.aspx . The articles published in this Journal MPI-HE 11, 2025 have three major foci. The first one is a sequence of 4 papers describing the history of Fast Neutron Therapy – one Introductory and 3 large consecutive papers. The papers explain that beginning almost immediately after the discovery of the neutron and continuing to the present day, fast neutron therapy has undergone several cycles of initial excitement, followed by great disappointment, and then cautious optimism. The second focus is on Nobel Prizes related to medical physics. Beginning with this Edition, such articles are being published describing the research and discoveries recognized with Nobel Awards that were contributions to the general field of medical physics. These are in the award categories of Physics, Chemistry, and Medicine and Physiology but are the discoveries that are the foundation of Medical Physics, especially the radiations and the names of radiation units. The third focus is on Pioneers/Doyens of medical physics and various contributors to our professional progress. As in several previous MPI-History issues, a number of articles here are made in collaboration with the AAPM History Committee.

The History topics extensively covered in MPI-HE so far include:

MPI-HE 1- http://www.mpijournal.org/pdf/2018-SI-01/MPI-2018-SI-01.pdf with papers on history of:
*X-ray Tubes; *Film-Screen Receptors; *Medical Physics e-Learning Introduction
MPI-HE 2 - http://www.mpijournal.org/pdf/2019-SI-02/MPI-2019-SI-02.pdf with papers on history of:
*Fluoroscopy; *Mammography; *Review of the Physics of Mammography
MPI-HE 3 - http://www.mpijournal.org/pdf/2020-SI-03/MPI-2020-SI-03.pdf with papers on history of:
*Dental Radiography ; *Contrast Media X-Ray Diagnostic Radiology; *Medical Physics in Africa
MPI-HE 4 - http://www.mpijournal.org/pdf/2020-SI-04/MPI-2020-SI-04.pdf with papers on history of:
*Cobalt-60 Radiation Therapy; *Computed Tomography; *Medical Physics in South-East Asia and in Eastern Europe
MPI-HE 5 - http://www.mpijournal.org/pdf/2021-SI-05/MPI-2021-SI-05.pdf with papers on history of:
* Ultrasound;* Acoustic Pressure Measurement;* Acoustic Power Measurement; *Thermal Ultrasound Measurement
MPI-HE 6 - http://www.mpijournal.org/pdf/2021-SI-06/MPI-2021-SI-06.pdf with papers on history of:
*Medical Ultrasound-Imaging; *Diasonograph; *HP Ultrasound Imaging; *Doppler Ultrasound; *HIFU Therapy
MPI-HE 7 - http://www.mpijournal.org/pdf/2022-SI-07/MPI-2022-SI-07.pdf with papers on history of:
*History of IOMP; *IOMP History tables with the names of all IOMP contributors in its 60 year history.
MPI-HE 8 - http://www.mpijournal.org/pdf/2022-SI-08/MPI-2022-SI-08.pdf with papers on history of:
*Medical Physics teaching; External-Beam Radiotherapy Fractionation; Medical Physics teaching in medicine, etc.
MPI-HE 9 - http://www.mpijournal.org/pdf/2023-HE-09/MPI-2022-HE-09.pdf with papers on history of:
*PET development; *Rectilinear scanner; *Women in medical physics; *IDMP History
MPI-HE 9 - http://www.mpijournal.org/pdf/2024-HE-10/MPI-2024-HE-10.pdf with papers on history of:
*Past X-ray mania; *ICMP History; * Evolution of visibility in MP; *Abstracts from ICMP 1; *Abstracts from 1994

The content of the MPI-HE (previously known as Special History Issues) of the Medical Physics International (MPI) Journal supports the objective of the History project: to research, organize, preserve, and publish on the evolution and developments of medical physics and clinical applications that are the foundations of our profession. Our young medical physicists and students will benefit from getting to know our pioneers. This can be achieved by sharing these articles and including presentations and discussions within your education and training programs. We are grateful to all authors who submitted papers and to the Technical Editor M Stoeva. We welcome contributions of colleagues from all societies, organizations and companies who would like to join the History project with articles on specific topics.


Prof. Slavik Tabakov


Prof. Perry Sprawls


Prof. Geoffrey Ibbott

A Brief History of Neutron Therapy: Introduction

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

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

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

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

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

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

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

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

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

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

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A Brief History of Neutron Therapy

Part I – The Early Years: Excitement, Disappointment, Renewed Optimism

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Abstract – **James Chadwick discovered the neutron in 1932. The potential use of neutron beams in treating cancer was almost immediately recognized. Early radiobiology studies by researchers in USA and Britain led to the first clinical trials in the USA, where Ernest Lawrence's cyclotrons were ideal for producing neutron beams. The results of these trials, between 1938 and 1942, were not encouraging. However, further radiobiology studies in the 1950s established a possible rationale for neutron therapy in the treatment of hypoxia. In 1966 treatments started at the MRC Cyclotron Unit in London and results were more encouraging. This led to a renewed interest around the world**

Keywords: Neutron, Radiobiology, Radiation Oncology, History.

I. EXCITEMENT

- *Discovery of the Neutron*

The story starts with the discovery of the neutron in 1932. This was not a spur of the moment event. Soon after Rutherford had discovered the proton in 1919, when he was professor and head of physics at Manchester University, he started speculating about the possible existence of a neutral particle composed of a proton and an electron. He argued that there needed to be such a particle to explain the existence of isotopes. One of his faculty colleagues in Manchester was his former student, James Chadwick (Fig. 1).

Fig 1. James Chadwick, discoverer of the neutron.

Rutherford had moved to the Cavendish Laboratory at Cambridge University in 1919 and Chadwick had moved with him. Together they spent over a decade discussing the existence of the neutron and during this time Chadwick tried many experimental approaches. In his *Notes on the Discovery of the Neutron* [1], Chadwick reminisces on the events leading up to his discovery. In his own words, "From time to time in the course of the next few years, sometimes together sometimes myself alone, we made experiments to find evidence of the neutron, either its formation or its emission from atomic nuclei, I shall mention some of the more respectable attempts; there were others which were so desperate, so far-fetched as to belong to the days of alchemy."

In the early 1930s the emission of gamma-rays from beryllium by alpha particle bombardment had been observed. The interesting thing was that no protons were emitted. Others were investigating this phenomenon. Chadwick was interested too; he had good electronic detectors (proportional counters) but he lacked a strong enough alpha source to obtain useful results: at this time particle accelerators were just under development. Fortunately, one of his Cavendish Laboratory colleagues, Norman Feather, had visited the Kelly Hospital in Baltimore, where they were using radon sources for brachytherapy treatments. Feather was able to obtain a number of old radon tubes, which contained a large quantity of polonium, the alpha emitter that Chadwick needed.

In 1931 Irene Curie and her husband, Pierre Joliot, were performing similar experiments with alphas and beryllium. When they placed paraffin wax in the beam emitted from their alpha-beryllium source they observed that protons were emitted from the wax. They interpreted this as photon-proton collisions from some process similar to Compton scattering [2].

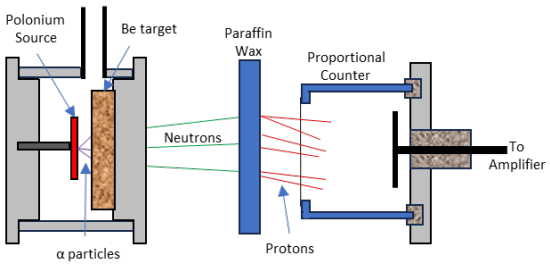

Fig 2. Schematic of Chadwick's apparatus with which he detected the neutron.

Chadwick repeated these experiments with his Po/Be source, varying the gas filling of his proportional counters. His interpretation was that the pulses in his counters resulted from recoil nuclei set in motion by neutron bombardment. From the relative size of the pulses in the different gases he was able to deduce that the mass of the neutron was very close to that of the proton [3]. His experimental arrangement and his gas detector are shown in figures 2 and 3, respectively. Figure 4 shows the paraffin wax target, metal foils and a holder for metal foils, which he stored in an old cigarette carton. James Chadwick received the 1937 Nobel prize for physics for his discovery of the neutron.

Fig. 3. The proportional counter Chadwick used to detect the recoil protons from the interaction of neutrons with the paraffin wax. The counter is on display in the Science Museum, London

Fig. 4. Paraffin wax target, metal foils and foil holder which Chadwick used in his neutron experiments. This item is also on display in the London Science Museum

- *Accelerator Development*

While Chadwick was searching for the neutron in Cambridge other important developments which would prove critical to neutron therapy were taking place in the USA. Ernest Orlando Lawrence (Fig. 5) was investigating

Fig 5. Ernest Orlando Lawrence inventor of the cyclotron

artificial methods for producing high energy particle beams: He was trying to build particle accelerators. The idea of using linear arrays of tubes with applied radio-frequency voltages was first suggested by Gustav Ising in 1924, and in 1928 Rolf Wideroe, a Norwegian engineer, built a device that accelerated sodium and potassium ions to 50 keV. After reading Wideroe's paper Lawrence adopted this line of research with his student David Sloan. Another idea, that other researchers had been working on, was that of cyclic acceleration in a magnetic field (Gabor,1924; Flegler 1926: Steenbeck, 1927, and Szilard, 1929). Most of this work was unpublished, although Szilard had filed a patent.

It is sometimes said that Lawrence combined Wideroe's linear design with the magnetic field concepts to create his cyclotron. Whatever the case, he pursued the cyclic idea with two more students, Nels Edlefsen and M Stanley Livingston. Edlefsen built two crude models which showed "slight evidence of working." Livingston continued his work and built a much more sophisticated version in 1930. This accelerator was only about 5 inches in diameter (Fig. 6) and accelerated $^{2}H^{+}$ to an energy of only 80 KeV.

Fig. 6. Lawrence's original cyclotron fit in Glenn Seaborg's hand in this photograph.

At the time there was great interest in achieving energies in excess of 1 MeV; an interest driven by the desire to have energies and beam intensities greater than those provided by alpha emitting isotopes to induce nuclear transformations. So just as his first cyclotron was operational, Livingston and Sloan were working on building the bigger 11-inch version shown in Figure 7 [4]. With this cyclotron Lawrence achieved an energy of 1.2 MeV.

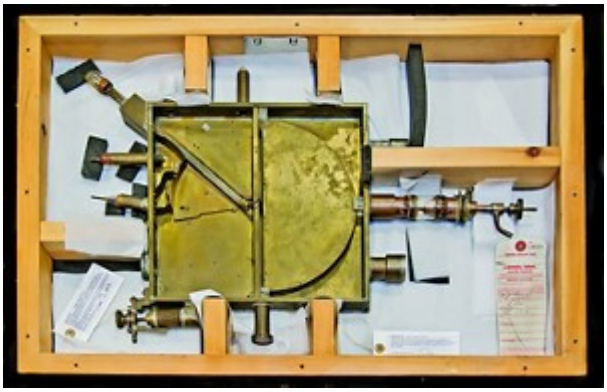

Fig. 7. Lawrence and Livingston's 11-inch cyclotron which produced an energy of 1.2 MeV.

They continued to build bigger and bigger machines; in 1933, a 27-inch deuteron cyclotron (fig. 8) which eventually operated at 6.3 Mev and 20 μA, in 1937 a 37-inch version operating at 8.5 MeV and 100 μA and in 1939 the 60 inch "Crocker" cyclotron which could produce 200 μA of 16 MeV deuterons. It was these two latter cyclotrons that played a major role in the development of neutron radiation therapy.

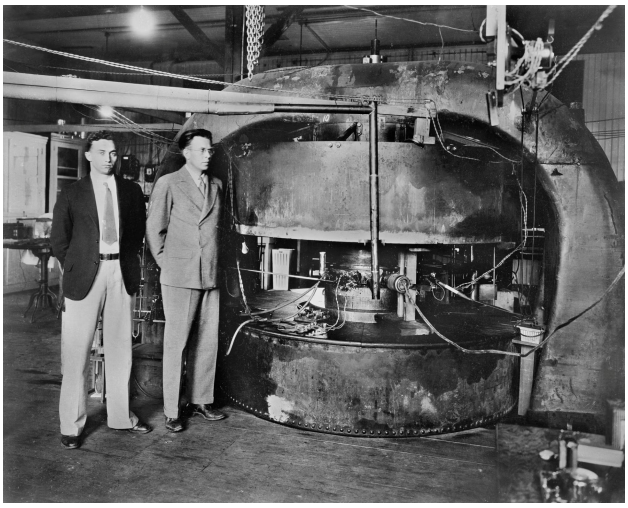

Fig 8. Livingston (left) and Lawrence with the 27-inch cyclotron.

Although Lawrence was able to achieve high energies with his cyclotrons, the current produced was quite low, typically a few nA, not sufficient to produce detectable artificial nuclear transmutation with the detection systems then available. This prize fell to the Cavendish Laboratory. Cockcroft and Walton (Fig. 9) had created a particle accelerator based on a voltage multiplying device; the device had voltage limitations but was capable of producing higher currents than Lawrence's early cyclotrons.

Fig. 9. Cockcroft on the right and Walton on the left with Lord Rutherford photographed outside the Cavendish Laboratory, Cambridge

The Cockcroft-Walton accelerator (Fig. 10) produced a current of 10 μA of protons at 700 keV. In 1932 using this machine they were able to demonstrate the first artificial transmutation of a nucleus [5]. When they bombarded a lithium target with protons, the proton was absorbed into the Li nucleus which split into two alpha particles:

$$^{1}_{1}H + ^{7}_{3}Li = ^{4}_{2}He + ^{4}_{2}He + 17.3\ Mev$$

(Incidentally, this work was the first experimental proof of Einstein's equation, $E=mc^2$.)

Fig 10. The accelerator tube of Cockcroft and Walton's accelerator on display in the Science Museum, London. The wooden observation chamber was closed by a curtain to provide a darkened space in which they could detect scintillations on a fluorescent screen.

The discovery of artificial transmutation inspired further Cavendish Laboratory work by Marcus Oliphant. In 1933 he designed and constructed a simplified Cockcroft-Walton accelerator operating at 200 keV and 100 mA, to study the interaction of deuterons with a deuterated target and discovered the isotope ^{3}He accompanied by large fluence of neutrons [6]:

$$^{2}_{1}H + ^{2}_{1}H = ^{3}_{2}He + ^{1}_{0}n + 3.26\ MeV$$

The availability of accelerator produced neutron beams, with neutron fluences orders of magnitude greater than those produced with alpha emitting isotopes, opened the possibility of producing the radiation doses necessary for radiobiology experiments. Another impetus for these experiments was the concurrent development of megavoltage x ray sources. Prior to this time therapeutic x-ray beams had been limited to 100-200 keV, and the hope in applying higher x ray energies had been that there would be some enhanced biological effect. This proved not to be the case, although dose distributions were better. The lack of any biological advantage for the high energy x rays lead to increased interest in investigating the use of neutron beams for therapeutic uses.

- *Early Radiobiology Studies*

In Berkeley, Lawrence realized as early as 1933 that neutrons produced in nuclear reactions may raise a safety concern for the staff. In 1936 Lawrence's brother John, joined the faculty of the medical school at the University of California, Berkeley. Concerned about the radiation safety aspects of neutrons, the two brothers published some of the first papers on the physiological effects of neutrons. They irradiated rats with neutrons produced by bombarding a beryllium target with several microamps of 3.5 MeV deuterons from the 27-inch cyclotron and studied blood counts as their endpoint [7]. They concluded that the biological effectiveness of neutrons was ten times that of x rays. Several months later they irradiated normal and tumor tissue [8] and this time concluded that:

"1. Per unit ionization, neutrons are much more effective than x-rays in destroying normal mice *in vivo*, and sarcoma *in vitro.*

*"*2. The preliminary results indicate that neutrons are three times as effective in destroying normal mouse tissue, and four times as effective in destroying sarcoma 180 *in vitro*."

Meanwhile, in England, Louis Harald Gray, who had been one of Rutherford's research students, had become one of Britain's first medical physicists and was working at Mount Vernon Hospital in North London. Gray was interested in radiobiology and in improving cancer treatment, and with his connections to the Cavendish Laboratory he learned of Oliphant's work. He obtained funding to build his own Cockcroft-Walton accelerator (Figs. 11 and 12), using the D-D reaction to produce a neutron beam for radiobiology research.

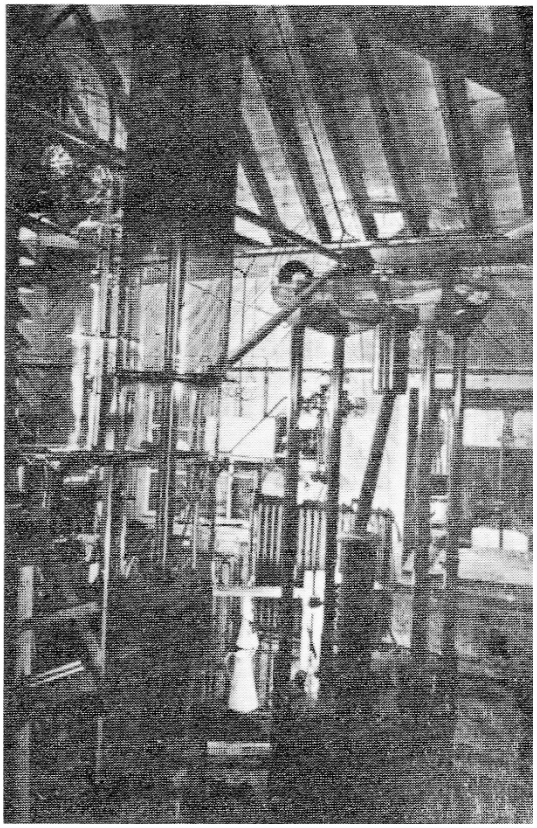

Fig 11. Gray's Cockcroft-Walton accelerator housed in a wooden hut in the grounds of Mount Vernon Hospital in North London.

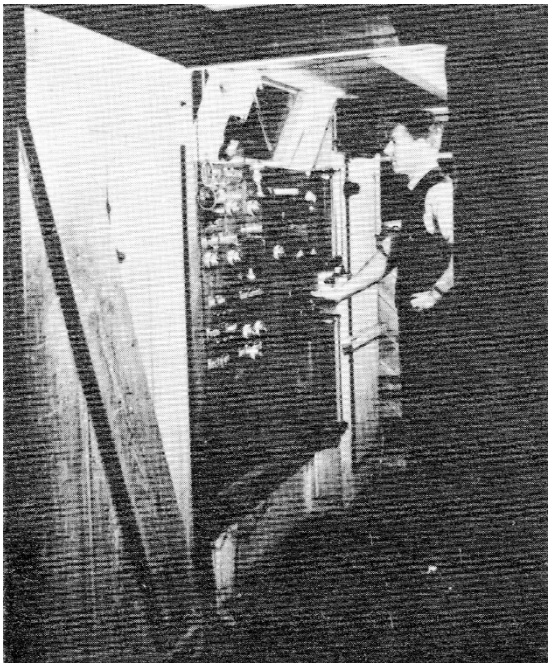

Fig. 12. Gray at the controls of his accelerator.

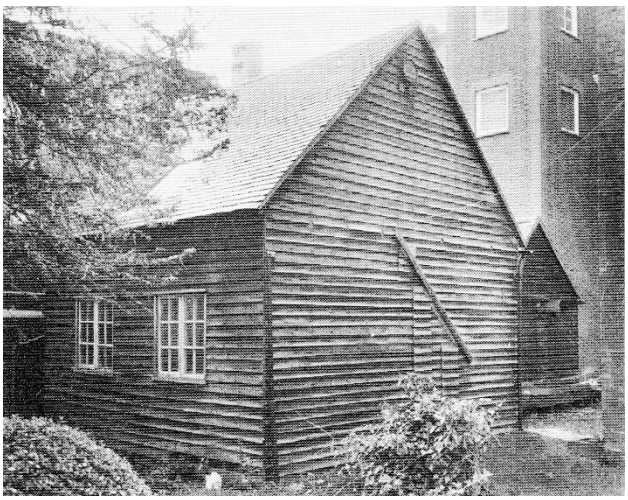

Fig. 13. The wooden hut in the grounds of Mount Vernon Hospital that housed Gray's D-D accelerator

The unit cost £600 ($2400 in 1940) to build and was housed in a wooden hut (Fig. 13) which cost an additional £!50 ($600). Maintenance costs were £80 ($320) per annum.

In 1940 he published the results of his studies on the growth delay of *Vicia Farbia* bean roots [9]. His paper also included a comprehensive review of the available biological data on neutron effectiveness, including data from researchers in the USA, the UK and Germany. The data covered a variety of endpoints: gene mutation, chromosome abnormalities, inhibition of cell mitosis or division, retardation of growth in plant roots and seedlings, and data from Berkeley on damage to mouse tumors and normal tissues.

II. DISAPPOINTMENT

- *The First Clinical Trial*

Thus, it was that in 1938, a radiologist, from UCSF, Dr. Robert Stone and John Lawrence initiated the first clinical trial of fast neutron therapy. From the limited data available at that time they concluded that "the number of neutron units that could be tried with safety on a patient was one-quarter the number of roentgens of 200 kV x-rays that would be required for a given erythema." [10] The trial was made possible by the availability of the recently commissioned 37-inch cyclotron (Fig. 14) and the neutrons were produced by an 8 MeV beam of deuterons incident on a Be target. The beam penetration defined as the depth in a water phantom at which the neutron dose is reduced to 50% of its maximum (50% PDD) was estimated to be about 6.5 cm. This was superior to the approximately 5 cm 50% PDD of the 200kV x-rays that were most widely available then.

Between September 1938 and June 1939 twenty-four patients were treated with single large doses as the cyclotron was only available one day a week.

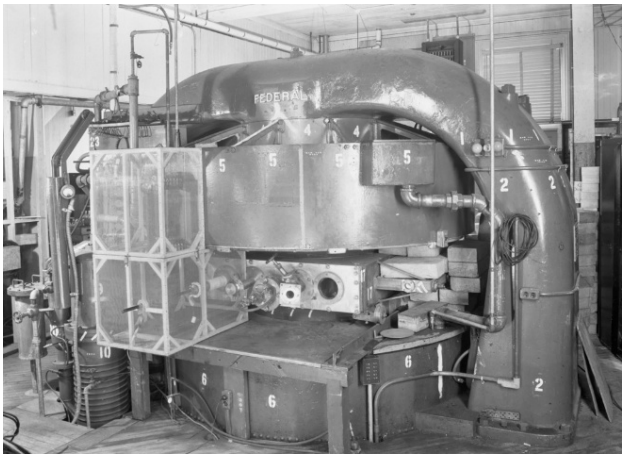

Fig 14. The 37-inch cyclotron used to treat the first patients with neutron radiation therapy. The magnet was the same one used for the 27-inch cyclotron.

Fig 15. Dr. Robert Stone (left) and Dr. John Lawrence set up a patient for treatment with the neutron beam from the 60-inch cyclotron.

Skin erythema was closely monitored and some patients received multiple treatments after the first skin effect wore off. Twenty of the patients had head and neck tumors and were treated with a single field to the side of the face, as shown in Figure 15. There was one recurrent breast case and 3 lung cases.

Their final conclusions from the preliminary trial were [10]:

"Patients have been treated with collimated fast neutron beams so as to produce tumor response without undue damage to the skin or other normal tissues. The results so far are sufficiently promising to warrant an extensive and thorough trial of this new method of treating cancer."

In the fall of 1939, the treatments were transferred to the newly installed 60-inch cyclotron (Fig. 16), which was known as the medical cyclotron.

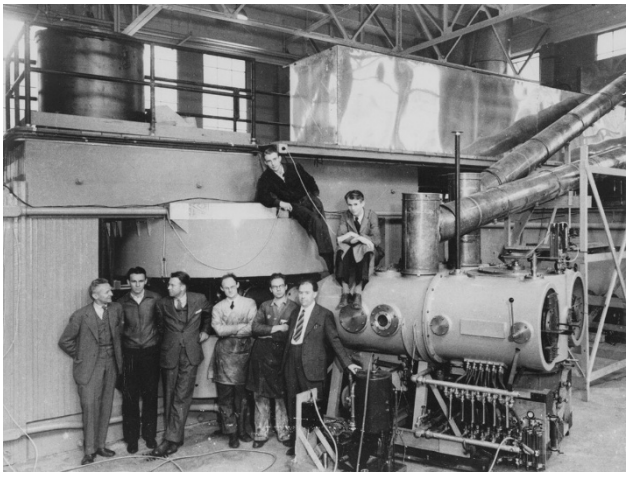

Fig. 16. Lawrence (third from left) with his colleagues and the 60-inch cyclotron.

It was intended for the primary purpose of producing new isotopes for medical use but was also available as a source of fast neutrons for external beam radiation therapy. Again, a Be target was used to produce the beam but the deuteron energy was now 16 MeV providing a neutron beam with an improved 50% PDD of 8.8 cm, providing an even greater dose distribution advantage over 200 kV x-rays.

Incidentally, funding to support the cyclotron operation for all these clinical trials was approved by The National Cancer Advisory Council, the review body of the newly created National Cancer Institute; making it one of the first NCI grants. Between the fall of 1939 and 1942 Stone treated about 225 more patients with the 60-inch cyclotron, but these trials were cut short when the cyclotron was required for work on the Manhattan Project.

The results of the treatment of the first 120 patients in this cohort, treated between December 1939 and September 1941 were reported by Stone and Larkin [12]. The patients treated were patients who, "… could not be cured by surgical or x-ray treatment. It was felt that neutron therapy must show decided effects in advanced cancer, as represented in these patients before its use for treatment of small localized lesions could be justified." Table 1 summarizes the tumor sites treated.

Again, they were mainly in the head and neck region, however, the 60-inch cyclotron, was available 3 afternoons a week and, therefore, fractionated treatments were possible. The smaller fraction size and improved beam intensity of the 60-inch vs 37-inch cyclotron reduced treatment times considerably and parallel opposed fields were used for most treatments. Considering the advanced nature of the patients' disease some encouraging results were seen [11], although overall an inconclusive assessment of the potential role of neutron therapy emerged. Stone and Larkin's clinical summary stated:

"Of the patients with presumably incurable cancer who were treated during the twenty months period, 50 percent were still alive at the time of this report (Oct. 15, 1941).

"At the end of treatment about 17 percent of the patients showed complete regression and about 48 percent showed partial regression.

"While the statistics presented appear discouraging, the effect of neutrons on tumors has been such as to encourage further study of selected cases. It was demonstrated, both clinically and pathologically, that some cancers disappeared as a result of neutron therapy."

Table 1 Anatomical distribution of legions in the data reported by Stone and Larkin.

Anatomical Site	Number of Patients
Tongue	18
Prostate	18
Skin and lip	13
Floor of mouth and alveolar ridge	18
Breast	11
Larynx and pyriform sinus	9
Stomach and intestine	9
Buccal mucosa	5
Brain	4
Nasopharynx	3
Parotid	3
Esophagus	2
Miscellaneous	12

Stone went on to treat about 120 more patients before the trial was cut short by World War II. By the time he was able to review all his patients he decided not to re-start the work after the war, because of the severe late skin and subcutaneous damage that he observed.

In his 1947 Janeway Memorial Lecture [12] at the American Radium Society, Stone's final assessment was that:

"Neutron therapy as administered by us has resulted in such bad late sequela in proportion to the few good results that it should not be continued." His concluding advice in this lecture was, "Anyone contemplating the use on patients of new radiations should study the relative biological effectiveness of them by late reactions as well as acute early ones."

III. RENEWED OPTIMISM

- *Efforts in Britain*

Stone's experience could have brought an end to neutron therapy, but it didn't. In Britain, in 1947 the Medical Research Council (MRC) decided to build a medical cyclotron, essentially a copy of Lawerence's 60-inch cyclotron, with similar aims; isotope production and neutron therapy research. Hal Gray was recruited to head up the physics effort but the overall director was a physician, Dr. Connie Wood. Although the project started in 1947, it was almost 20 years before the first neutron therapy patient was treated in September 1966. However, much happened in the intervening years to better understand the biological effects of neutrons and to establish a rationale for their clinical use. Gray in particular was interested in the role of oxygen in cancer treatments and demonstrated the importance of oxygen concentration in determining the radiosensitivity of cells. This work started at the MRC cyclotron unit where he built up a group of radiobiologists who would complete the critical pre-clinical cell and animal studies necessary before starting the clinical trials. Unfortunately, Gray would not stay at the MRC unit and in 1953 he left due to personal conflicts with Dr. Wood, who was a clinical, rather than a scientific, researcher. Gray returned to Mount Vernon Hospital where he was able to supervise the construction of the world's first dedicated radiobiology research laboratory built to his specifications. The years leading up to the MRC clinical trials were important in establishing a firm rationale for continuing clinical neutron therapy.

- *The Radiobiological Rationale for Neutron Therapy*

As we have seen, the rationale for the original neutron therapy clinical trial was simply that neutron radiation may be superior to x-ray radiation in curing human cancers. Further radiobiology research was necessary to establish the reasons for the poor results achieved in this original trial and provide a rationale for continuing. There had been very little radiobiology research in the early years, but in the years after 1945 many new techniques were developed; mammalian cell culture techniques and sophisticated normal tissue and tumor irradiation methods in animals including mice, rats and pigs.

The first definitive rationale was provided by two papers from Gray. In the first [13], Gray and his collaborators found the following: "The sensitivity of tumor cells to X rays has been shown to be about three times as great when irradiated in well-oxygenated medium as under anoxic conditions. … The sensitivity of tumors cells to fast neutron irradiation is only slightly affected by oxygen tension." In modern day terms X rays have an oxygen enhancement ratio (OER) of 3 and neutrons have an OER close to 1. This observation of itself is not a rationale for neutron therapy, but Thomlinson and Gray provided the rationale in their 1955 paper [14] which postulated the existence of hypoxic cells in tumors from a study of histological sections. The sections were from human bronchial carcinomas. They observed that these tumors developed necrotic centers as they grew larger. Furthermore, they noticed that as the tumors grew larger the necrotic centers also grew larger, and that there was a ring of viable tumor cells around the necrosis and the width of this ring was essentially constant. They concluded that the tumors needed oxygen from the surrounding stroma in order to grow. They observed the thickness of the viable tumor rings was about 150 μm. (Fig. 17).

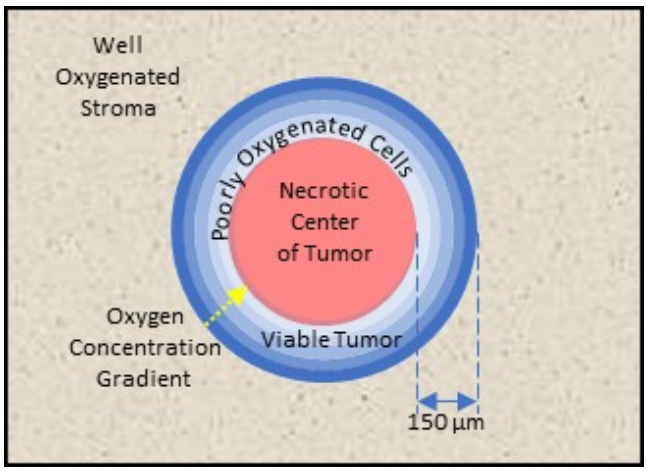

Fig. 17 Schematic representation of Thomlinson and Gray's study of bronchial carcinoma histological sections.

The necrosis was attributed to the lack of oxygen and Gray was able to calculate oxygen diffusion from the stroma through the viable tumor cells to the necrotic center. He calculated that oxygen could diffuse 150 μm. As the oxygen diffuses through the tumor there is gradual reduction of the oxygen concentration in cells as a function of their distance from the stroma. Cells close to the necrotic center are poorly oxygenated yet still viable; these cells will be radiation resistant (Fig. 8), difficult to kill, and may lead to treatment failure. With an OER of 3, X rays are three times as effective at killing well oxygenated normal tissue cells as they are at killing the poorly oxygenated tumor cells. On the other hand, neutrons, with an OER of close to 1, are equally effective at killing oxygenated and anoxic cells, hence, neutrons should offer a therapeutic advantage in tumors containing areas of hypoxia.

The first evidence for the existence of hypoxic cells in tumors was provided in 1963 by Powers and Tolmach [15], who irradiated solid lymphosarcoma tumors implanted subcutaneously in mice. They assayed the surviving fraction of cells using the dilution assay technique, (irradiation *in vivo* followed by assay *in vitro*) and

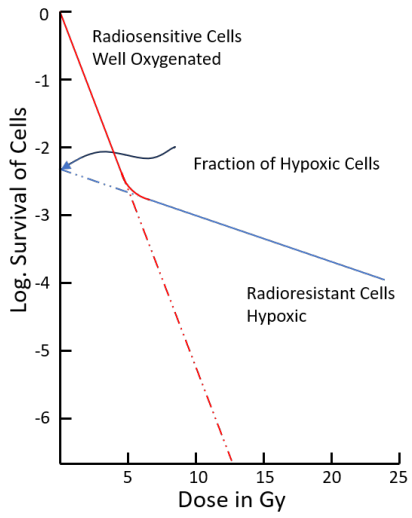

Fig. 18. Log survival curve showing how two cell populations of differing radiation sensitivity result in a breaking cell survival curve. In the Powers and Tomach experiment they were able to demonstrate the existence of hypoxic cells in a mouse tumor. The fraction of hypoxic cells in this hypothetical example is about 0.6%.

demonstrated that the survival exhibited a sharp change in slope (Fig. 18) demonstrating the existence of two separate cell components, one more radiation resistant than the other. The steep part of the curve represents well oxygenated cells and the shallow portion hypoxic cells. By extrapolating the shallow part of the curve back to the survival axis, they concluded that the tumors contained 1% of hypoxic cells.

Thus, by 1963 there was a clear rationale for neutron therapy, based on their potential effectiveness against hypoxic cells and the fact that the inability to kill hypoxic cells is often cited as a reason for treatment failure. At the time the MRC Hammersmith Hospital clinical trials started in September 1966, this was the best understood rationale for neutron therapy.

However, once the trials had started further encouragement came from a 1971 paper by Sheline *et al* [16], in which Stone and Larkin's data was reanalyzed. Work at Hammersmith Hospital had shown that in experiments on pig skin reaction the relative biological effectiveness of fast neutrons increases with the decreasing size of dose, so that the RBE for fractionated treatments is a larger than for a single fraction. It was suggested that the Berkeley trials took no account of this and that as a consequence the patients may have been overdosed. Sheline *et al* analyzed the data with this possibility in mind. They reinterpreted the effects of neutrons on skin and subcutaneous tissues. Patient treatments often varied considerable in the time, dose and fractionation, and exit doses had not been taken into account. Doses were measured in neutron-units, based on ionization chamber measurements, a unit related to roentgen units, the internationally approved exposure unit at that time. Sheline tried to "renormalize" the data taking all these factors into account and concluded that both the early and late skin reactions could be explained on the basis of the dose received.

Sheline and his collaborator's final statement was:

"With proper allowance for exit dose, fractionation scheme, and change in RBE with fraction size, both early and late skin reactions can be accounted for on the basis of dose received. … We believe that the Berkeley neutron data from 1938 to 1943 should not contraindicate a properly planned and controlled clinical investigation of neutron therapy."

The implication is that with appropriate dose criteria it may be possible to avoid the severe late skin reactions observed by Stone. This paper, combined with some encouraging preliminary results from the MRC trials, led to much greater interest in the potential benefits of neutron and many new centers were planned.

With more active centers came more radiobiology research and an important observation related to the varying sensitivity of neutrons during the cell cycle. A number of papers had been published on this effect in a variety of biological systems using photon beams. The typical result of such an experiment is shown in Fig. 19. Withers *et al* [17] performed experiments to investigate cell cycle effects with ɣ ray and neutron beams They used hydroxyurea injections to synchronize mouse jejunum crypt cell and using the dilution assay technique were able to measure the crypt cell survival at known times after synchronization. In this way they were able to measure the sensitivity of the cells as function of the cell cycle. Data were obtained for ɣ rays, and neutrons generated by both the 50 MeV $d^+ \rightarrow Be$ and the 16 Mev $d^+ \rightarrow Be$ reactions. For the ɣ rays there is 100-fold fluctuation in the cell survival across the cell cycle, while for the 50 MeV $d^+ \rightarrow Be$ reaction and the 16 Mev $d^+ \rightarrow Be$ the fluctuations are 70-fold and 60-fold, respectively. Their conclusion was:

"There is some difference between neutrons and ɣ rays in the cycle-related fluctuations of radiation response. … This difference could be important in determining a difference in the response to neutrons of different proliferative activity, and could be as important as, or more important than, hypoxia in determining such a differential."

It should be noted that the most radiation resistant part of the cell cycle is the S phase. Late G_1 is relatively radioresistant and this phase is the most variable being anywhere from 1 to 200 hours long. This led researchers to believe that the differences between cell cycle response for neutrons and x rays could be exploited for slow growing tumors, since at any time most cells will be in the G_1 phase, where there is a potential advantage over X rays.

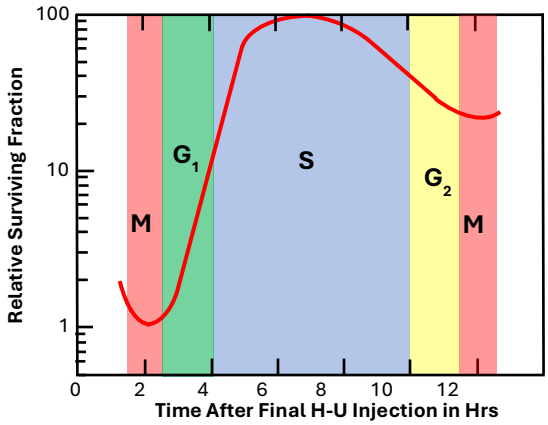

Fig. 19 Typical curve of cell survival vs phase of cell cycle. M - mitosis, G_1-first gap, S - DNA synthesis, G_2 – second gap. In this hypothetical example S-phase is 100 times more resistant than mitosis.

This resulted in some trials focused on slow growing tumors such as prostate and adenocarcinoma of the rectum. Battermann *et al* in the Netherlands studied the relationship between tumor doubling time and neutron RBE [18]. They took patients with bilateral lung metastases and irradiated tumors in one lung with ^{60}Co, and in the other with 14 MeV d-T neutrons. They measured tumor volume changes and were thus able to derive an RBE value. They also measured tumor doubling times. They recorded the primary tumor site from which the metastases had originated. They had data for about 30 patients with a wide range of different histologies. At the time there were neutron clinical trials open for treating adenocarcinoma of the rectum based on the premise that these were slow growing tumors. While Battermann's result demonstrated an approximate linear increase in RBE with tumor doubling time, no correlation was shown to exist between primary tumor type and volume doubling time. This is illustrated in Table 2 by the data for the five adenocarcinomas of the rectum that were included in the study. The tumor with the longest doubling time had the highest RBE: The implications of this are obvious, if your trial is based on the premise that all the tumors are slow growing then you cannot expect to get a definitive result in a mixed population. Of course, the rectum adenocarcinoma trials were non-conclusive.

Table 2. Battermann's data on RBE and tumor doubling times for patients with adenocarcinoma of the rectum.

Patient #	Tumor Doubling Time In days	RBE
1	39	2.3
2	107	3.0
3	130	2.9
4	153	3.1
5	550	4.8

Maybe neutron therapy trials would have been more successful if reliable predictive assays had been available, which would have predicted the tumors with long tumor doubling times (i.e. high RBE) and/or large fractions of hypoxic cells.

- *The MRC Cyclotron Clinical Trials*

At the time of the Berkeley clinical trials x ray therapy was still in its infancy; the neutron depth dose characteristics were superior to those of the 200 kV x-ray machines that were widely used. The 200 kV x rays could be better collimated using relatively thin lead cut outs. By the time the MRC trials started in 1966, the situation had changed and linacs producing megavoltage x ray beams with good penetration were available. However, X ray collimation had become a problem, X and Y jaws being used to create rectangular fields without shaping, a situation that remained largely unsolved until the introduction of Cerrobend blocks in 1973. The MRC cyclotron beam was identical in energy and PDD to Lawrence's 60-inch cyclotron producing neutrons in the 16 Mev $d^+ \rightarrow$Be reaction. However, there were more collimation options. The Be target was located in the shielding wall between the cyclotron vault and the treatment room (Fig. 20).

Treatments were delivered at a target to skin distance of 120 cm with a fixed horizontal beam and an average dose rate of about 50 cGy min^{-1}. The collimation was achieved using a set of cylindrical wooden apertures with a variety of square rectangular cuts-outs providing a field sizes of up to 20 cm x 20 cm. A schematic of the type of aperture used is shown in figure 21. These apertures were light enough for easy handling. The apertures fitted into a protective cone extending from the shielding wall which reduced the stray radiation to acceptable levels. The neutron beam penumbra was inferior to that of an x- ray linac.

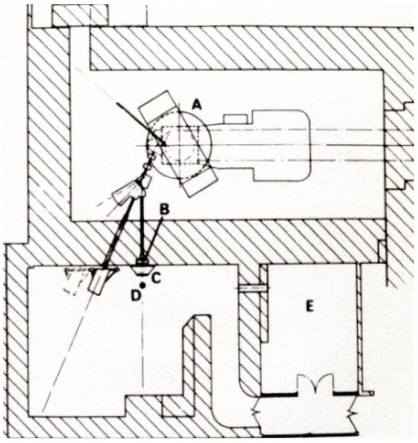

Fig. 20. The treatment room at the MRC Cyclotron Unit. A - cyclotron, B - Be target, C - protective cone and wood collimator system, D – patient skin position and E – control room.

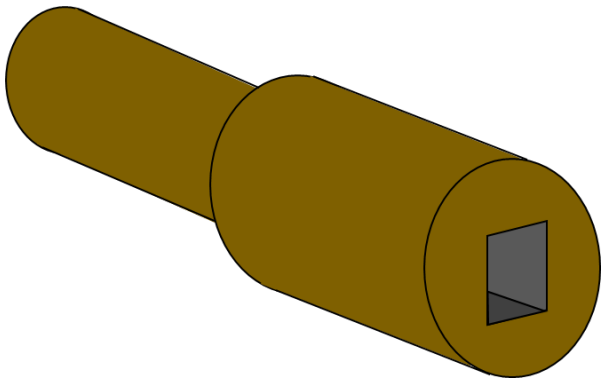

Fig 21. Schematic of the wooden aperture inserts used at Hammersmith Hospital. Similar apertures, constructed from various attenuating materials, were used in many of the early neutron therapy facilities

Figure 22 shows a head and neck patient positioned for treatment in the treatment chair at the MRC Cyclotron Unit. The aperture insert and protective cone are clearly visible. Using this arrangement Dr. Mary Catterall (Fig 23) treated many patients between 1966 and 1986, when the MRC neutron therapy program was closed. By that time there were about 25 active neutron therapy facilities, with more to come, mostly with equipment producing beams much superior to the MRC cyclotron.

In 1974 Catterall published results obtained since 1969, after which time neutron treatments were given regularly three times a week [20]. A standard treatment dose of 14.40 Gy was delivered in 12 fractions over a period of 4 weeks; a treatment regimen that was to be adopted by many other neutron therapy centers. All patients reported on had advanced, radioresistant or recurrent tumors that were not thought suitable for other forms of treatment.

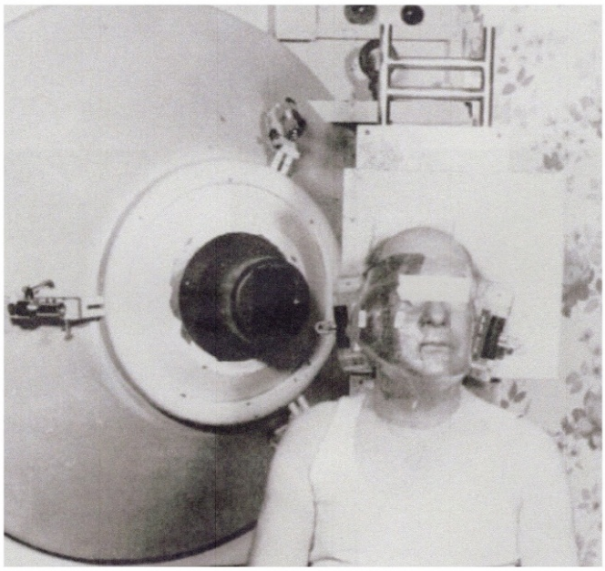

Fig. 22. A head and neck patient positioned for treatment in a seated position. The wooden collimator is seen inserted into the protective cone.

Dr. Catterall reported on 238 patients that had completed treatment and she stated that of these:

"… 58 lived with no sign of disease in the neutron treated area for more than one year. One hundred and thirty-five who survived for less than one year died of metastases but with regressing or completely regressed tumors in the neutron treated area.

"Forty-five tumors probably recurred and were all associated with doses which were lower than the standard. Necrosis appeared in 11 of 97 patients surviving more than 6 months, but in each of these cases, there was a precipitating factor and the necrosis was never unexpected or unexplained."

Fig. 23. Mary Catterall front row right with fellow Honorary Degree recipients at the University of Durham in 1982. You may recognize some of them. In the center is the Chancellor of the University, Margot Fonteyn, the famous ballerina. To her left is New Zealand operatic soprano, Kiri Te Kawana and in the back is David Attenborough, the well know broadcaster. Not so well known is the Archbishop of Canterbury at that time, Robert Runcie

She also observed that:

"Noteworthy results have been achieved in tumors of the salivary glands, buccal cavity, oropharynx, nasopharynx, stomach and in sarcoma and fixed glands invaded with adenocarcinoma, melanoma and squamous cell carcinoma."

Given the advanced nature of the tumors treated her conclusions were limited to stating that:

"The results from this application of cyclotron neutrons continue to be encouraging and are contributing to the growing interest in the world of fast neutron therapy. It is probable that with bigger cyclotrons and more penetrating beams and more flexible techniques these results will be

improved and the range of tumors accessible to treatment will be increased."

Because of the nature of the Hammersmith Hospital neutron beam, phase III style clinical trials involving this facility were difficult and somewhat limited. Dr. Catterall kept excellent records of her patients including comprehensive photographic records of disease progression. Thus, there was a large amount of anecdotal evidence of the success of neutron therapy in alleviating suffering, if not in prolonging survival. An example of Catterall's results taken from unpublished data [21] is shown in Fig. 24. Dr Catterall treated advanced cancers with neutron therapy where other options were not possible. She achieved similar results to those shown in a variety of tumor sites including, oral cavity, oropharynx and larynx, breast, sacral, bladder and bone. Many patients experienced complete or partial regression, but unfortunately many of these patients eventually died of metastases because of the advanced nature of their disease.

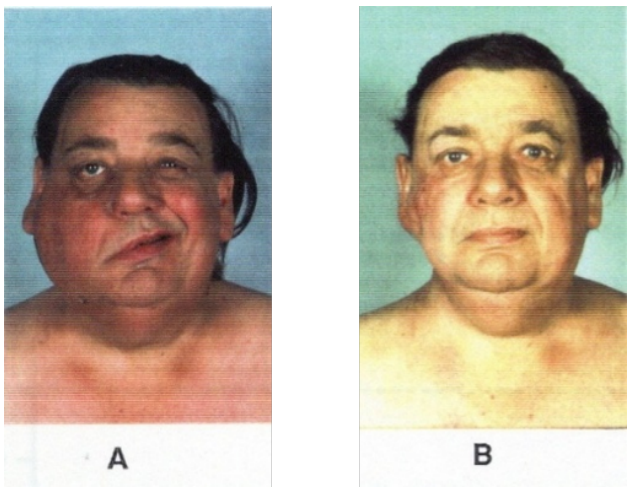

Fig. 24 A patient with neutron therapy by Dr. Catterall. A- A large parotid tumor causing paralysis of the 7th nerve. B- After treatment. Tumor regressed and facial nerve recovered fully. Patient died 3 years later of general metastases.

Table 3. A list of neutron therapy facilities with depth dose characteristics equal to or better than 4 MeV photons

Facility	Reaction	Accelerator Type	50%PDD in cm	Siting	Beam Type	Collimation
University of Washington	p(50) Be	Cyclotron	14.8	Hospital	Rotational	MLC
Wayne State University	d(48.5)Be	Superconducting Cyclotron	13.6	Hospital	Rotational	Multi-Rod MLC
Clatterbridge	p(62)Be	Cyclotron	16.2	Hospital	Rotational	Jaws
Seoul	p(50)Be	Cyclotron	14.8	Hospital	Rotational	Jaws
UCLA	p(46)Be	Cyclotron	16.2	Hospital	Rotational	Jaws
Nice	p(65)Be	Cyclotron	17.5	Hospital	Fixed Beam	MLC
MD Anderson Hospital	p(42)Be	Cyclotron	14	Hospital	Rotational	Inserts
IThemba Laboratory	p(66)Be	Cyclotron	16.2	Research Laboratory	Rotational	Jaws with MLC Trim
Louvain- la- Neuve	p(65)Be	Cyclotron	17.5	Research Laboratory	Fixed Beam	MLC
Fermi Laboratory	p(66)Be	Proton Linac	16.6	Research Laboratory	Fixed Beam	Inserts
GLANTA, Cleveland	p(42)Be	Cyclotron	13.5	Research Laboratory	Fixed Beam	Inserts
TAMVEC	d(50)Be	Cyclotron	13.1	Research Laboratory	Fixed Beam	Inserts

Number of desirable criteria satisfied: All four Three Two One

- *A Glance at the Future*

It was results like these that renewed interest in neutron therapy. It was clear that there was a need for more advanced equipment since the early facilities had many inadequacies, among them:

1. Sited in physics research laboratories remote from hospital facilities,
2. Low energy neutron beams with poor penetration
3. Fixed horizontal beams
4. Inadequate collimation.

Attempting to perform meaningful clinical trials against megavoltage x ray linac beams, with their better PDD characteristics, isocentric gantries, Cerrobend blocks, and later multileaf collimators and cone beam CT imaging, was challenging if not impossible.

The ideal neutron therapy facility specifications are:

1. Beam 50% PPD equivalent to, or better than, 4 MeV photons.
2. Sited in a hospital
3. Has a rotational gantry
4. Has an MLC

Even by the time neutron therapy was ramping down there were relatively few facilities that could satisfy all these criteria as shown in Table 3. Of the twelve centers listed in Table 3 only two could satisfy all four of these criteria, six could satisfy 3, one could satisfy 2, and the remaining three only the 50% PDD criterion. Although all these centers made significant contributions to the field of neutron therapy, those which could satisfy most criteria produced some of the best clinical results.

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A BRIEF HISTORY OF FAST NEUTRON TELETHERAPY PART II - ADOLESCENCE: EXPANSION OF TECHNOLOGY

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Abstract — **The first patient treated with fast neutron teletherapy was in 1938. Less than stellar results were achieved with the first clinical trials but re-evaluations of the trials spurred new clinical trials that began in the late 1960's. With this renewed interest, many new facilities around the world were built and began treating patients between 1970 and 1995. This article reviews and compares some of the technology used at those facilities including: sources of neutrons, gantries, radiation head components and beam shaping, beam characteristics, and treatment planning methods.**

Keywords — **fast, neutron, teletherapy, history**

I. Introduction

In 1932, James Chadwick discovered a new form of radiation, the neutron. Physicians and physicists, always looking for a better form of radiation with which to treat their patients, took interest. Eventually, three types of neutron therapy were investigated and delivered to patients. Fast neutron teletherapy (FNT) was delivered to patients with external beams of neutrons with maximum energies between 2 and 70 MeV. Neutron brachytherapy (NBT) used neutron emitting sources with energies between 1 and 10 MeV placed intracavitarily, interstitially, or on the surface of a patient. Neutron capture therapy (NCT) used external beams of thermal or epithermal energy neutrons applied to a patient after a biochemical agent with an attached neutron absorbing isotope had been injected into the patient. After the isotope absorbs a neutron, secondary radiation is emitted such as low-energy charged particles or photons. This article briefly reviews the the technology associated with the worldwide expansion of FNT between the years of approximately 1970 and 1995.

The first FNT clinical trial was performed at the University of California - Berkeley by Robert Stone; he reported unsatisfactory results [1]. A later evaluation of the trial suggested that the unknown effects of fractionation was probably the cause of the poor results and a second FNT clinical trial was thus begun at Hammersmith hospital by Mary Catterall [2]. A race to improve radiation therapy using FNT then began with at least 35 institutions around the world treating patients. Table 1 gives a list of facilities known to have treated patients, the primary neutron source reactions, the maximum neutron energies, the types of gantries, the approximate start date of the first patient treatment, and for some of the facilities, the approximate number of patients treated and the date of the last patient total. The facilities in the table are listed approximately by the first patient treatment date for each program but some programs significantly modified or obtained new equipment; in those cases, the newer facilities are listed adjacent to the original facility. Although the exact number of total patients that have been treated worldwide is difficult to obtain, a reasonable estimate from the incomplete and outdated data in table 1 suggests over 30,000 through 2024.

II. Sources, facilities, and accelerators

The four most common types of sources that have been used for FNT are given in table 2. A fission source may be supplied by a nuclear reactor that produces many thermal neutrons that can be converted to fast neutrons using a uranium-235 converter. A fusion source may be supplied by a tube where incident deuterons with energies between 100 and 500 keV are incident on a tritium target. Deuterons can be accelerated by a cyclotron or linac and impinged upon a beryllium-9 target resulting in either a stripping or breakup reaction. Lastly, protons accelerated by a cyclotron or linac can be impinged upon a beryllium-9 target resulting in an inelastic interaction.

The FNT sources given above were housed predominantly in five types of facilities:

- parasitic to a research nuclear reactor
- a dedicated fusion tube in a medical center
- parasitic to a research cyclotron
- parasitic to a research linear accelerator
- a dedicated cyclotron in a medical center

Table 1: List of known FNT facilities that treated patients. In column 4 the letters after the energy represent the type of accelerator used: c ≡ cyclotron, vdg ≡ van de Graff, L ≡ RF linear accelerator, r ≡ nuclear reactor.

Facility, City	Country	Primary Reaction	Max. Neutron Energy [MeV]	Gantry Types	First Patient	Est. # of Patients	Date of Total
UCal 1, Berkeley	USA	^{9}Be(d,n)^{10}B	8, c	H	1938	34	1939
UCal 2, Berkeley	USA	^{9}Be(d,n)^{10}B	16, c	H	1939	226	1943
Hammersmith Hospital, London	UK	^{9}Be(d,n)^{10}B	16, c	H	1965	500	1977
NIRS 1, Chiba	Japan	^{9}Be(d,n)^{10}B	2.8, vdg	V	1969	36	1975
NIRS 2, Chiba	Japan	^{9}Be(d,pn)^{9}Be	30, c	V	1975	2,129	1996
SZK Berlin-Buch, Dresden	Germany	^{9}Be(d,n)^{10}B	13.5, c	H	1972	990	1990
Texas A&M U 1	USA	^{9}Be(d,n)^{10}B	16, c	H	1972	incl. below	1973
Texas A&M U 2	USA	^{9}Be(d,pn)^{9}Be	50, c	H	1973	248	1976
MD Anderson, Houston	USA	^{9}Be(p,n)^{9}B	42, c	R, H	1983		1997
NRL (MANTA), Washington, D. C.	USA	^{9}Be(d,pn)^{9}Be	35, c	H	1973	86	1979
U Washington 1, Seattle	USA	^{9}Be(d,pn)^{9}Be	22, c	H	1973	incl. below	1984
U Washington 2, Seattle	USA	^{9}Be(p,n)^{9}B	50.5, c	R	1984	3,500	2023
Netherlands Cancer Inst., Amsterdam	Netherlands	^{3}H(d,n)^{4}He	14	R	1975	435	1981
Fermilab, Chicago	USA	^{9}Be(p,n)^{9}B	66, L	H	1976	3,348	2013
U Hospital Eppendorf, Hamburg	Germany	^{3}H(d,n)^{4}He	14	R	1976	822	1990
Inst. Medical Science, Tokyo	Japan	^{9}Be(d,n)^{10}B	14, c	H	1976	458	1991
NASA Lewis (GLANTA), Cleveland	USA	^{9}Be(d,pn)^{9}Be	25, c	H, V	1977		1982
NASA Lewis (GLANTA), Cleveland	USA	^{9}Be(p,n)^{9}B	43, c	H, V	1982	1,200	1990
U Edinburgh, Edinburgh	UK	^{9}Be(d,n)^{10}B	15, c	R, H	1977	620	1984
Christie Hospital, Manchester	UK	^{3}H(d,n)^{4}He	14	R	1977		
Belvedere Hospital, Glasgow	UK	^{3}H(d,n)^{4}He	14	R	1977		
U Heidelberg, Heidelberg	Germany	^{3}H(d,n)^{4}He	14	R	1977	441	1990
U Essen, Essen	Germany	^{9}Be(d,n)^{10}B	14	R	1978	769	2006
Catholic U, Louvain-la-Neuve	Belgium	^{9}Be(d,pn)^{9}Be	50, c	V	1978	incl. below	1981
Catholic U, Louvain-la-Neuve	Belgium	^{9}Be(p,n)^{9}B	65, c	V, H	1982	1,870	2001
INP, Krakow	Poland	^{9}Be(d,n)^{10}B	12.5, c	H	1978	202	1987
U Chicago, Chicago	USA	^{2}H(d,n)^{3}H	11	H	1979		
CHR, Orleans	France	^{9}Be(d,pn)^{9}Be	34, c	V	1981	1,729	2007
Fox Chase, Philadelphia	USA	^{3}H(d,n)^{4}He	14	R	1981	11	1990
King Faisal, Riyadh	Saudi Arabia	^{9}Be(p,n)^{9}B	26.5, c	R	1984	119	1996
NRMC, Tomsk	Russia	^{9}Be(d,n)^{10}B	13.6, c	H	1984	1,500	2022
WWU, Münster	Germany	^{3}H(d,n)^{4}He	14	R	1985	269	1995
RENT, Munich	Germany	n_{th}(^{235}U,n)	mean ˜1.9, r	H	1985	715	2000
FRM II, Munich	Germany	n_{th}(^{235}U,n)	mean ˜ 1.9, r	H	2007	124	2013
MRRC, Obninsk	Russia	n_{th}(^{235}U,n)	mean ˜ 1, r	H	1985	500	2002
UCLA, Los Angeles	USA	^{9}Be(p,n)^{9}B	46, c	R, H	1986		
Korea Cancer Center, Seoul	Korea	^{9}Be(p,n)^{9}B	50.5, c	R	1986	310	1994
MRC, Clatterbridge	UK	^{9}Be(p,n)^{9}B	62.5, c	R	1987	384	1995
iThemba Labs, Faure	South Africa	^{9}Be(p,n)^{9}B	66, c	R	1988	1,788	2015
RFNC, Chelyabinsk	Russia	n_{th}(^{235}U,n)	mean ˜ 1.9, r	H	1988	1,300	2022
IHEP, Beijing	China	^{9}Be(d,pn)^{9}Be	35.5, L	H	1991	485	2001
Wayne State U, Detroit	USA	^{9}Be(d,pn)^{9}Be	48.5, c	R	1991	2,251	2025
Centre Antoine-Lacassagne, Nice	France	^{9}Be(p,n)^{9}B	60, c	V	1993	57	2001
			Total from table			**> 29,456**	

Table 2: Most common types of FNT sources.

Type	Form	Description
fission	nuclear reactor	n_{th} with ^{235}U converter
fusion	tube	^{3}H(d,n)^{4}He incident deuterons, 100 - 500 keV
stripping or breakup of light ions	cyclotron or linac	^{9}Be(d,n)^{10}B, ^{9}Be(d,pn)^{9}Be incident deuterons, 2 - 50 MeV
inelastic reactions	cyclotron or linac	^{9}Be(p,n)^{9}B incident protons, 26 - 66 MeV

Only three of the facilities listed in table 1 are known to have used nuclear reactors for FNT. A normal light-water moderated reactor is a poor source of fast neutrons with the fluence rate of neutrons above 1 MeV being about 10^{-8} that of the thermal neutrons [3]. For FNT, a highly enriched (example 93%) U-235 conversion target can be placed near the reactor core. When a thermal neutron is captured by a U-235 nucleus, fission occurs with the emission of about two fast neutrons. A transport channel can funnel the fast neutrons out of the pool and through its shielding. Figure 1 is a conceptual diagram showing the basic components of a generic FNT facility that uses a "swimming pool" type research nuclear reactor. Many gamma rays are also emitted but a filter of lead or bismuth can be used to attenuate many of the low-energy ones. The maximum neutron energy at the RENT facility in Munich, Germany was about 10 MeV, the mean energy of the neutron spectrum was about 2 MeV, and the most probable energy was about 0.65 MeV [3]. A new research reactor (FRM) was built in Munich to replace the original facility. The treatment room at the new facility contained a motorized patient positioner and a multi-leaf collimator (MLC) to shape the irradiation field [4]. The maximum field size at the new facility was 200 mm by 300 mm.

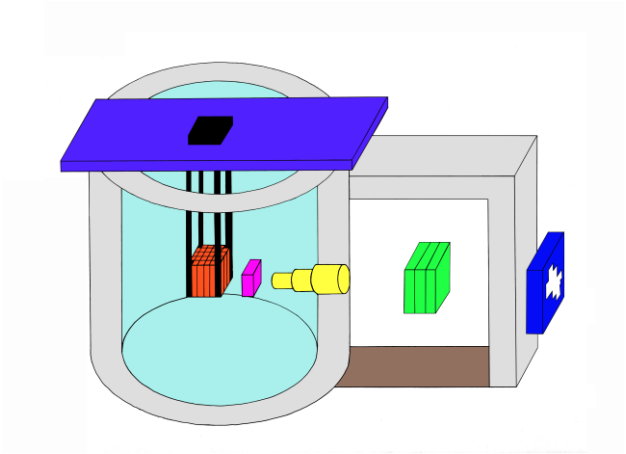

Fig. 1 Conceptual diagram of a research "swimming pool" nuclear reactor used for FNT showing the major components. Components by color: gray - shielding; red - reactor core; black - core support; aqua - water; purple - support crane platform; magenta - U-235 conversion target; yellow - fast neutron transport channel; green - beam filters; blue - MLC, brown: floor of equipment room.

The fusion-based systems typically gave a nearly monoenergetic beam of neutrons with an energy near 14 MeV with the energy depending slightly on the configurations of the ion source, the target, and collimators [5]. One method of producing fusion used a continuously pumped assembly in which a deuterium ion beam was incident upon a rotating metal hydride coated target with a heat-conducting backing. A second method used a sealed tube in which a mixed ion beam of deuterium and tritium was accelerated onto a tritium-coated target such as titanium. A third method accelerated a deuterium beam onto a vessel containing pressurized tritium gas. Fusion systems were supplied by six different companies: Haefely, Marconi-Elliott, Phillips, Radiation Dynamics, Texas Nuclear, and The Cyclotron Corporation (TCC).

Key advantages of fusion-based systems were that the accelerator and gantry were both small. Most rotating gantries for fusion-based systems used a slewing ring with a gooseneck style arm to support a radiation head somewhat larger than the head for a typical cobalt-60 unit. A few used a gantry and radiation head configuration similar to those that were used with some of the larger megavoltage betatron installations where the radiation head rotated as the patient positioner moved laterally and vertically to align the patient with the beam. Disadvantages of fusion-based systems were that they produced low dose rates (5 - 20 cGy/min), had relatively low penetrating beams (slightly less than a cobalt-60 beam), had wide lateral penumbras, and the tubes had limited lifetimes (75 to 1,000 beam hours) requiring frequent replacement. All but one of the fusion-based systems that treated patients were installed into medical facilities in Europe. Figure 2 is a picture of a TCC isocentric slewing ring gantry with the bottom part of the radiation head pulled down showing the tube inside. Figure 3(L) shows a floorplan for a facility based upon the TCC equipment. The size is comparable to a conventional megavoltage x ray room. Figure 3(R) shows a vertical cross-section through the gantry isocenter. Only a small depression in the floor was required to accommodate the radiation head while it was rotated by the gantry. The installation at Fox Chase treated very few patients as the tube needed to be replaced shortly after the system commissioning was finished but, by then, TCC had gone bankrupt and new tubes were unavailable.

Several of the early cyclotron-based facilities parasitically used research cyclotrons. When the University of Texas M. D. Anderson Cancer Center (MDA) in Houston, Texas, U.S.A. wanted to start a clinical trial of FNT, they found a cyclotron at the Texas Agriculture and Mechanical University Variable Energy Cyclotron (TAMVEC) facility, in College Station, Texas, about 100 miles away. This cyclotron had a pole tip diameter of 88 inches and could accelerate light ions with atomic numbers from 1 to 10 (protons to neon). A decision was made to use the $^{9}Be(d,n)^{10}B$ stripping reaction to generate a beam of fast neutrons. From 1972 to 1973, 16 MeV deuterons were used but during 1973 the deuteron energy was switched to 50 MeV to provide a higher energy neutron spectrum predominantly via the $^{9}Be(d,pn)^{9}Be$ breakup reaction [7-9]. Figure 4 shows the floorplan of the TAMVEC facility.

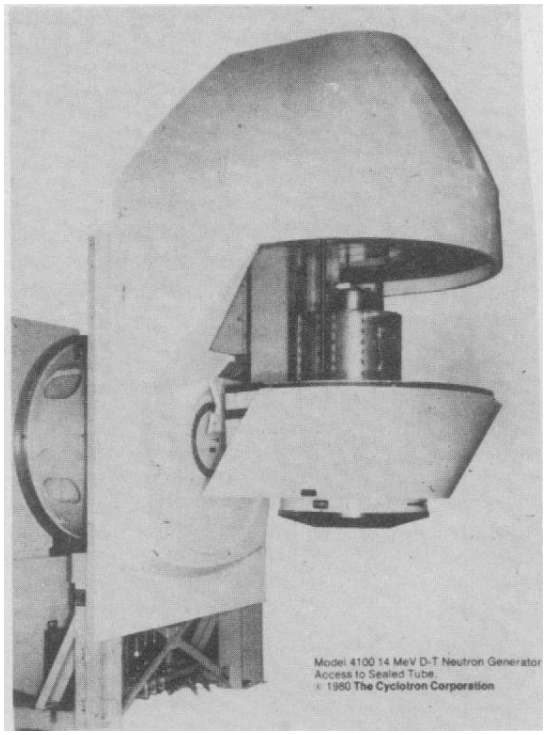

Fig. 2 Picture of gantry and opened radiation head for TCC based fusion source. Reprinted from Bloch et al. [6] with permission from IEEE.

The fixed horizontal beam configuration, low-energy neutron spectrum, lack of available beam time, and large distance from the hospital to the TAMVEC facility suggested that a dedicated medical facility be built in Houston, preferably within the hospital. During 1978 the National Cancer Institute (NCI) issued a Request for Proposal (RFP) for institutions across the USA to propose FNT facilities. In 1979, MDA received one of three 10-year contracts to design, develop, and build, hospital-based neutron therapy facilities and conduct phase III clinical trials [10]. The company chosen to provide and install the equipment at MDA was TCC [11]. This company also produced and installed equipment at several other FNT facilities around the world, both cyclotron-based and fusion-based. Figure 5 shows a floorplan of the dedicated medical facility that was housed in the basement of the MDA hospital adjacent to other radiotherapy equipment including the 32 MeV Sagittaire electron / x ray system. The extracted beam could be sent to one treatment room housing a stationary gantry to provide a horizontal neutron beam, a second treatment room housing a ± 110° rotating gantry, or a room with multiple targets for isotope production. The facility also included a "hotlab" for processing the isotopes and drugs, a cyclotron control room, and a treatment control room. Descriptions of the facility and commissioning of the treatment beams were given by Almond et al. [13] and Horton et al. [14].

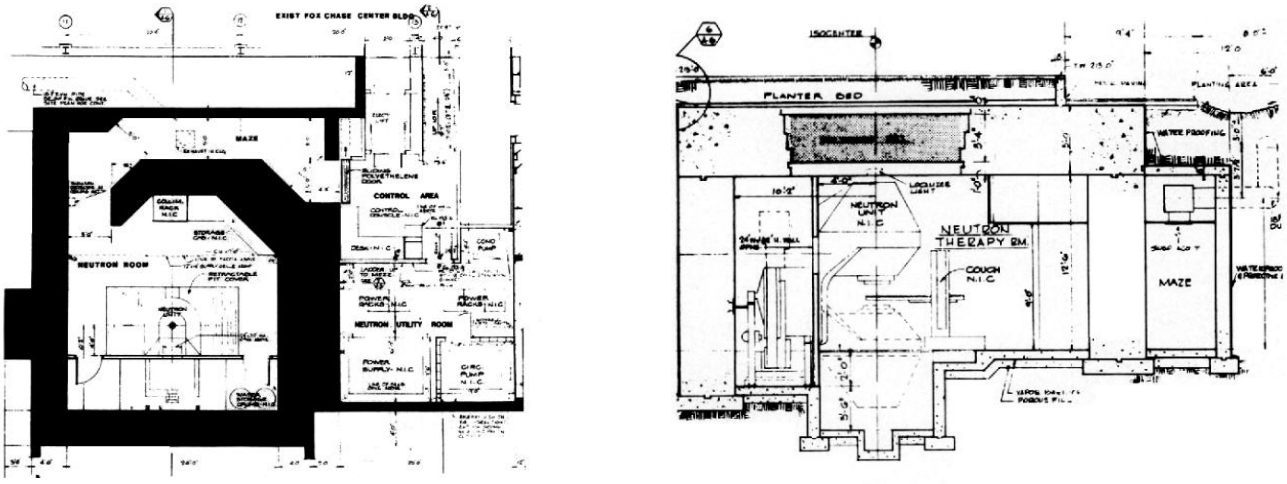

Fig. 3 (L) Floorplan for the Fox Chase facility in Philadelphia, Pennsylvania, U.S.A. based upon TCC equipment. (R) Vertical cross-section through the gantry isocenter. Reprinted from Bloch et al. [6] with permission from IEEE.

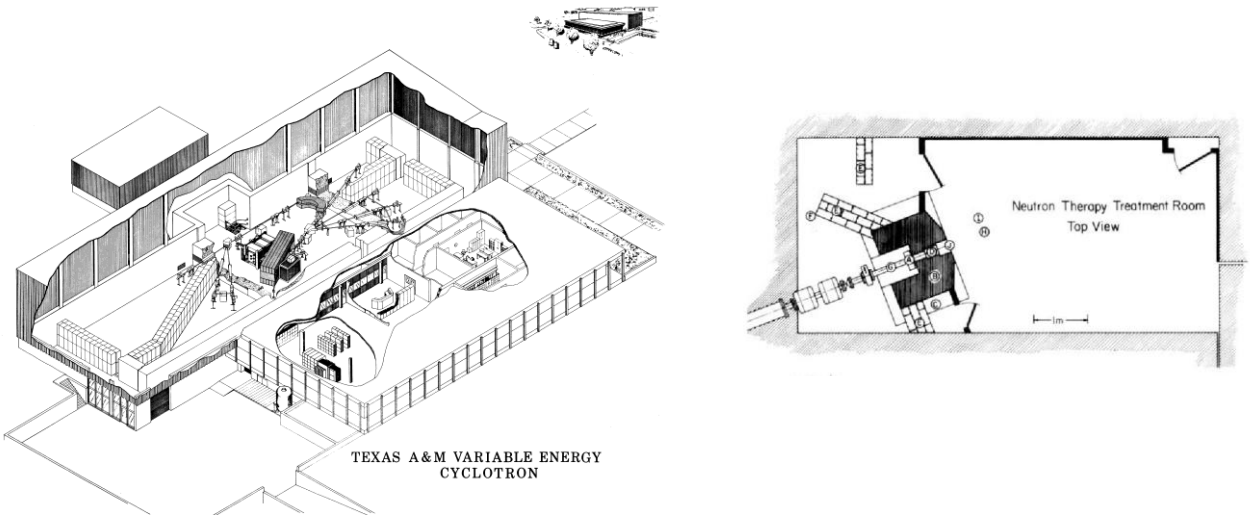

Fig. 4 Parasitic research cyclotron facility at TAMVEC. Reproduced from TAMVEC facility description document.

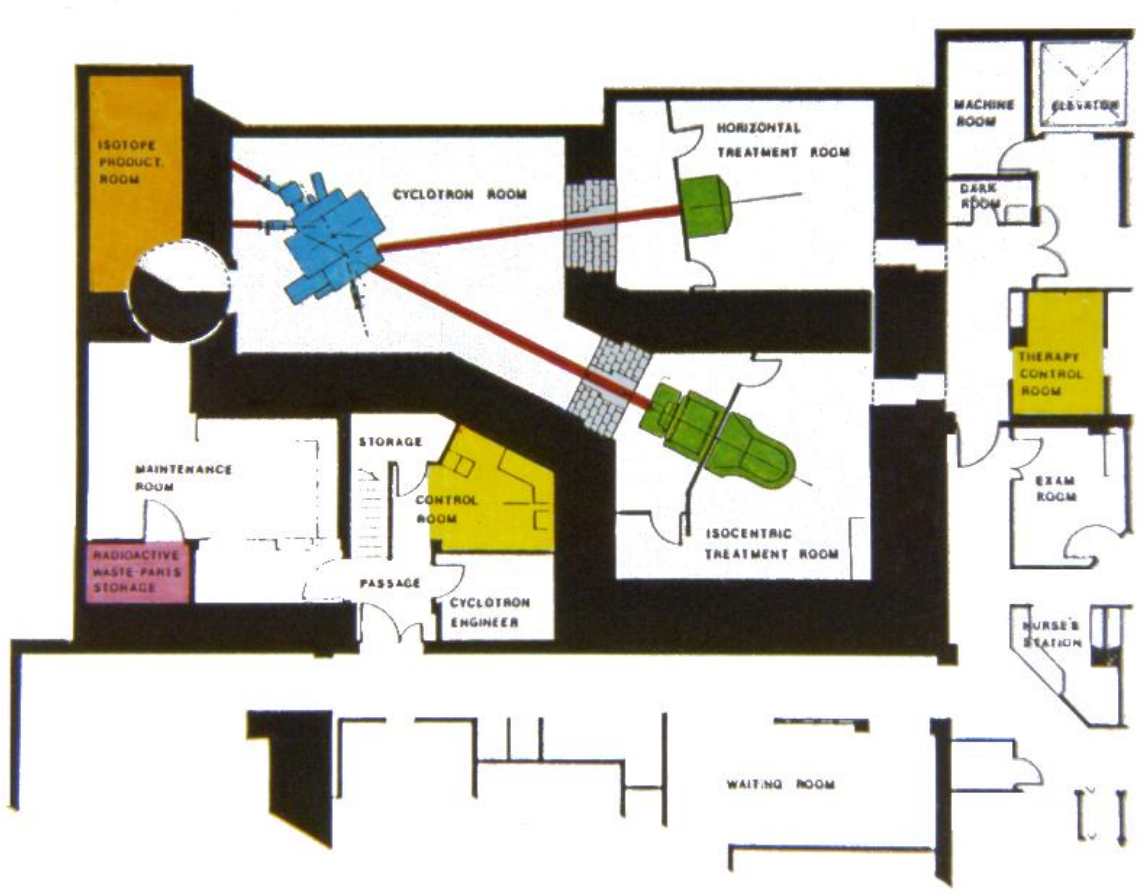

Fig. 5 Floorplan of dedicated medical cyclotron facility at MDA. One sliding shielding door was shared between the two FNT treatment rooms. One rotating shielding door allowed access from the cyclotron control room to either the cyclotron room or the isotope production room. Reproduced from Moyers [12].

Except for one parasitic linac based facility, all facilities producing neutron beams with energies higher than 16 MeV utilized cyclotron accelerators. Some cyclotrons accelerated positively charged ions while others accelerated negatively charged ions. Some cyclotrons could extract beam at multiple energies while others at only one. The system chosen for MDA was an isochronous cyclotron that accelerated negatively charged ions. Charge stripping foils were used to extract the beam from different energy orbits through one of five different extraction ports. Figure 6 shows the inside of the MDA TCC cyclotron while figure 7 shows a schematic of the inside. Figure 8 illustrates the positions of the foils on different orbits and extraction beam paths.

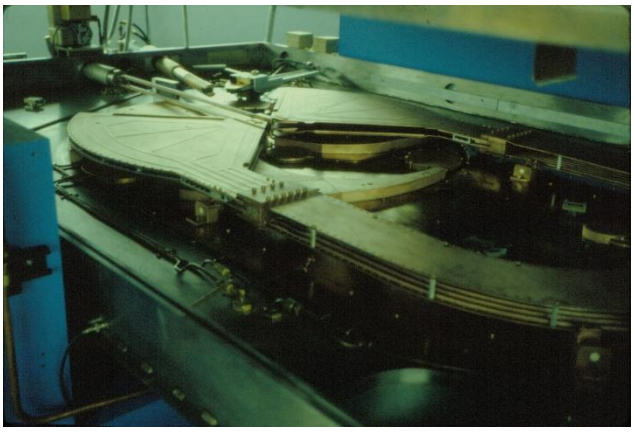

Fig. 6 Picture of inside of TCC cyclotron showing RF electrodes, pole tips, ion source, and beam diagnostics.

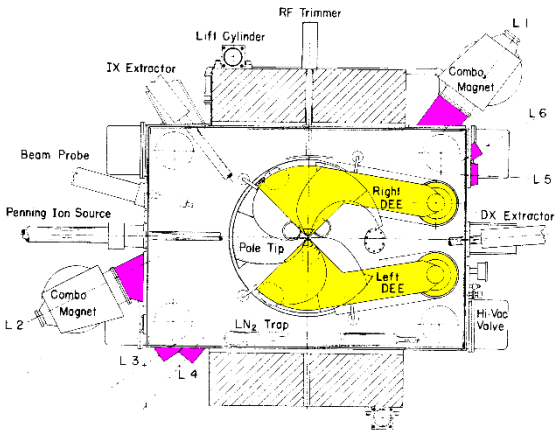

Fig. 7 Diagram of TCC cyclotron layout.

Shortly after the installation of the cyclotron and associated equipment at MDA, TCC went bankrupt and technical support decreased. This resulted in significant downtime but several upgrades improved the performance for the clinic [15]. At one point, a large breakdown occurred and the equipment was out of service for 1.5 years. After much investigation, it was discovered that internal stray radiation beam stopper strips attached to the inside of the cyclotron were approximately one quarter of the wavelength of the applied radiofrequency (RF) resulting in large power losses and strain on the equipment. During this time, the NCI arranged for some of the experiments described in section V to be performed at UCLA which had also received NCI funding to build a neutron facility using the same company. Eventually the MDA cyclotron was put back into working order. In 1998, however, the cyclotron was dismantled, transferred to Denton, Texas, and reassembled where it would only be used for radioisotope production [16].

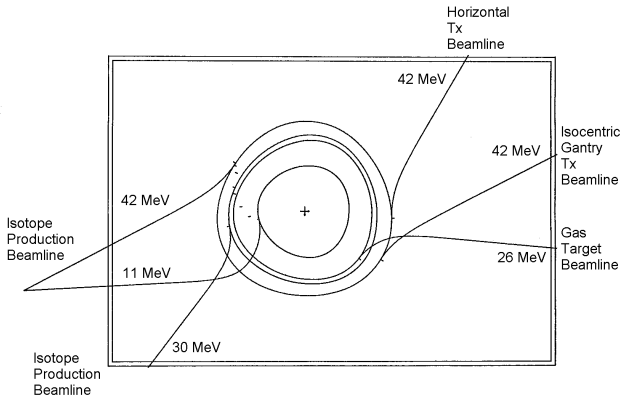

Fig. 8 Diagram showing stripping foils paced at different locations around the cyclotron to intercept different energy orbits and extract beam through one of five different extraction ports.

Another commercial cyclotron used for FNT was produced by Scanditronix and installed in Seattle, Washington in the U. S. A. and in Clatterbridge in the U. K. This cyclotron accelerated positive ions and extracted beam through a magnetically shielded channel. A diagram of the cyclotron is shown in figure 9.

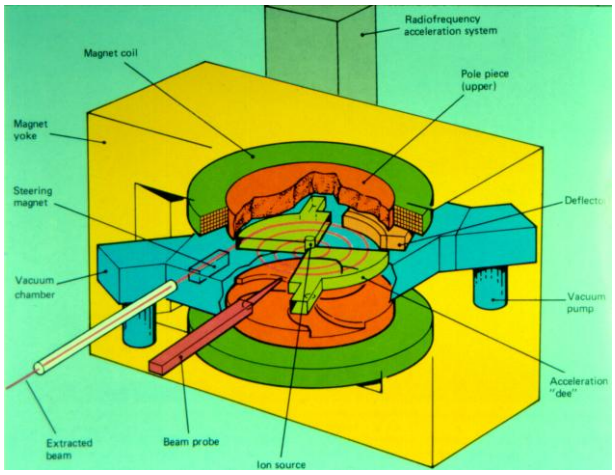

Fig. 9 Diagram of positive ion cyclotron produced by Scanditronix. Reproduced from Scanditronix MC series cyclotrons brochure.

An interesting cyclotron that was used parasitically for FNT was the separated-sector cyclotron at the iThemba labs in South Africa seen in figure 10. This cyclotron accelerated protons for FNT to 66 MeV, for proton therapy to 200 MeV, and for isotope production to several other energies. For this positive ion cyclotron, the energy changes were achieved by changing the magnetic field of the main magnets. For the switch from 200 MeV to 66 MeV, the change required about two hours before becoming stable enough for treatment.

Fig. 10 Separated-sector cyclotron at iThemba Labs near Faure, South Africa. Yellow objects are the C-shaped bending magnets.

III. Gantries for cyclotron-based facilities

To produce high energy neutron beams with a cyclotron, the ion beam is first accelerated and then transported to a radiation head attached to a gantry where it is converted to neutrons. Many of the early cyclotron facilities used a stationary gantry with either horizontal, vertical, or both beam directions. During the trial at TAMVEC, patients could only be treated two days a week, Tuesday and Thursday, and therefore most neutron treatments were combined with megavoltage x ray beams. Due to the beamline having a stationary horizontal direction, pelvic patients were treated standing. The average anterior-posterior diameter for these patients when treated supine or prone with 25 MV photons was 20.2 cm but, when the same patients were treated in a standing position with FNT, the diameter was 25.6 cm resulting in inferior dose distributions [17]. Another consequence of this positioning is that when a patient was lying, the intestine tended to move into the upper abdomen whereas, when standing, the intestine tended to shift into the lower abdomen and pelvis. These issues confounded having a "clean" clinical trial of neutrons versus photons.

Figures 11(L) and 11(R) show a configurable rotating patient positioner for seated and standing patients respectively in the Fermilab treatment room which had a horizontal gantry. To improve dose calculations for seated or standing patients, Fermilab installed an XCT scanner with a vertical axis to reproduce the position of the patients when treated. Figures 12(L) and 12(C) show the scanner in the raised and lowered positions respectively. Figure 12(R) shows the computer hardware for the scanner.

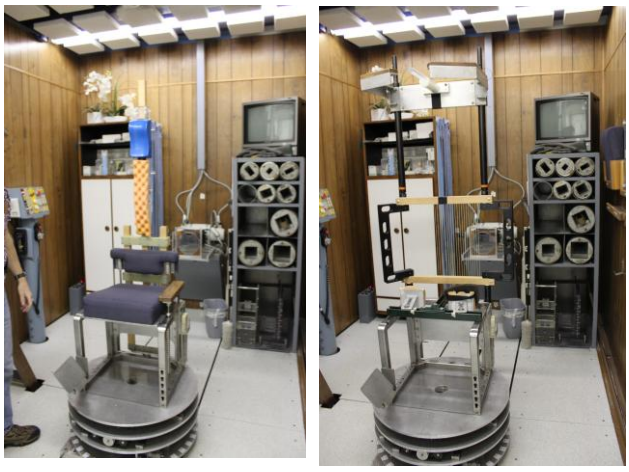

Fig. 11 Fermilab configurable patient positioner used in combination with horizontal beamline. (L) Configured for seated patients. (R) Configured for standing patients.

Fig. 12 Vertical axis XCT scanner installed at Fermilab. (L) Scanner in raised position. (C) Scanner in lowered position. (R) Scanner computer hardware.

Improvements in FNT dose distributions came with the introduction of rotating gantries. The first generation of rotating gantries for high energy neutrons typically rotated only about ± 100° from the vertical to avoid the need for a large pit in the floor that would make patient set-ups difficult. Figure 13 shows three of these rotating gantries. The target-to-isocenter distance for the MDA gantry was 125 cm. For posterior beams, the patient had to be placed in either prone or decubitus orientations causing some uncertainty in the dose distributions for multiple beam direction plans. A second generation of rotating gantries was built by Scanditronix that rotated a full 360°. Two of these are shown in figure 14. All of the above-mentioned rotating gantries used a slewing ring near the axis of rotation and a goose-neck configured beamline to deliver beam to the radiation head [18].

One of the last FNT installations was at Wayne State University in Detroit, Michigan, U. S. A. This facility had a superconducting cyclotron mounted directly to a 360° rotating gantry without the need for an ion transport beamline [19]. This cyclotron accelerated deuterons onto a beryllium target. Figure 15(L) is a conceptual diagram of the double ring gantry showing the basic components while figure 15(R) shows the patient enclosure during preparation for treatment.

Fig. 13 Rotating gantries with approximately ± 100° rotation from the vertical. (L) Essen, Germany. (C) MDA. (R) UCLA.

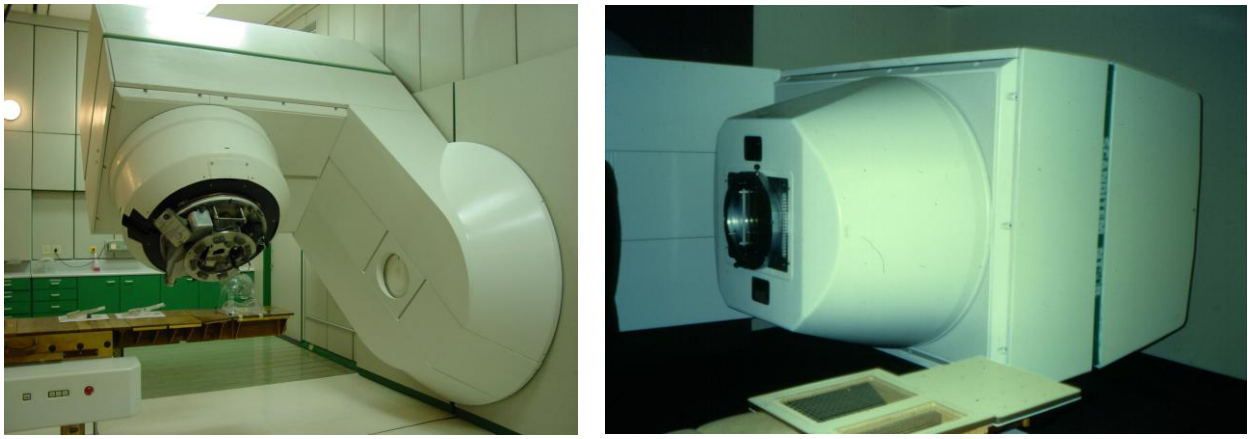

Fig. 14 Examples of fully rotating slewing ring gantries. (L) iThemba Labs. (R) University of Washington. For beams pointing upwards, floor panels would shift to the side allowing the radiation head to be rotated into a pit below the level of the false floor. The major difference between the two gantries is the shape of the collimator housing.

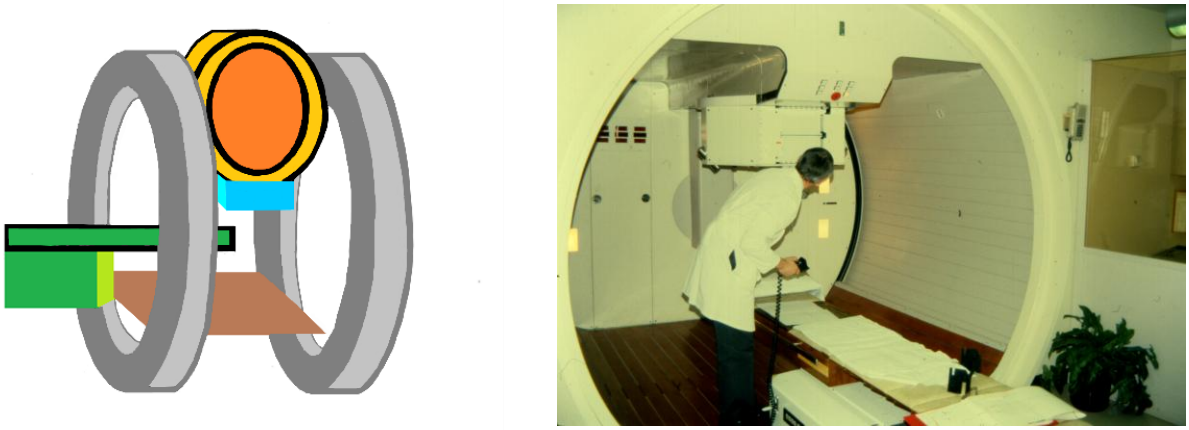

Fig. 15 Fully rotating double ring gantry for a superconducting cyclotron. (L) Conceptual diagram showing major components: gray - front and back rotating rings; orange and yellow - superconducting cyclotron mounted between front and back rings; blue - collimator assembly; green - patient positioner; brown - false floor. (R) Picture of patient enclosure.

IV. Radiation Head Components and Beam Shaping

The arrangement and composition of parts within the radiation head from each manufacturer is different but typically contain some similar basic components. Figure 16 is a diagram of the inside of the MDA radiation head mounted on the rotating gantry. It will be used as an example to illustrate the different components.

An important part of the radiation head is the neutron conversion target assembly. Figures 17(L) and 17(R) show pictures of the MDA target assembly and a diagram of its components respectively. The upper section contains four steering slits that intercept the edges of the light ion beam before it impinges upon the neutron conversion target. If the light ion beam is delivered off-center, feedback signals are sent to steer the beam back to center. The intense light ion beam carries a lot of power and thus water cooling is provided for the slits. The lower part of the assembly houses the beryllium slab target for converting the light ions to neutrons. The beryllium slab is also equipped with cooling water. When the light ion beam strikes the beryllium, different energy neutrons are produced in different directions. Moyers [12] reviewed various studies of thin target data for incident protons and developed a model for a thin target neutron spectrum in the forward direction. Figure 18 shows several thin target spectrums calculated for different incident energies.

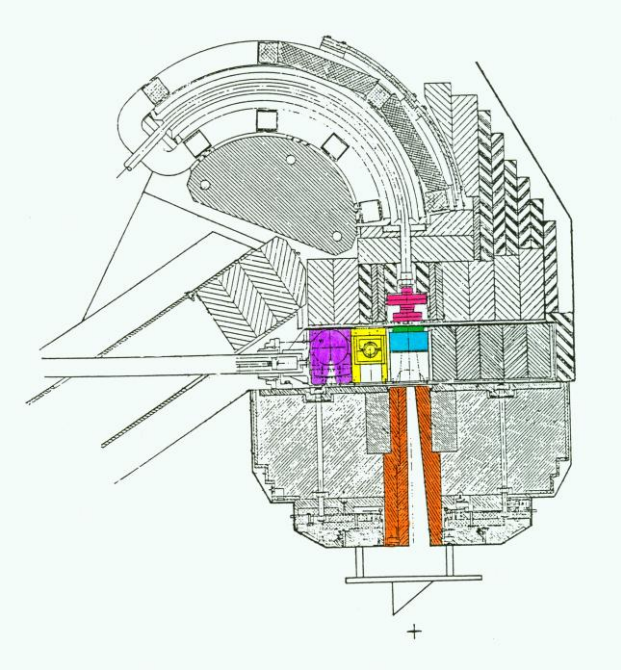

Fig. 16 Diagram showing the components of the MDA radiation head. The different styles of cross-hatched regions represent different kinds of shielding. The target assembly that includes steering slits is colored magenta. A 33 mm thick polyethylene hardening filter is colored green. The monitor ionization chamber assembly is colored blue. The exchangeable Benelex collimator is colored orange. A light source assembly is colored yellow. An in-line x ray tube is colored purple. Beneath the radiation head is a tray to which a wedge filter may be mounted. Reproduced from Moyers [12].

Obviously, the number of neutrons produced from a thin target is small so thick beryllium targets are used to increase the dose rate delivered to patients. Figure 19 shows the bottom half of the target assembly shown in figure 17 but taken apart to reveal the beryllium target slab, copper heat conductor, and inlet and outlet water channels. To reduce the number of low-energy neutrons produced, the thickness of the beryllium target is less than the range of the protons in beryllium, a so-called intermediate thickness target. After passing through the beryllium, the protons stop in the copper which has a smaller neutron production cross-section than does beryllium. Nevertheless, some low-energy neutrons are still produced. The UCLA target assembly, seen as a diagram in figure 20, is similar to the MDA assembly but slightly different. After protons pass through the intermediate thickness target, they enter a slab of graphite that has a much lower cross-section for neutron production than does copper. Copper is still used in the assembly, however, to conduct heat from the beryllium and graphite to the circulating cooling water.

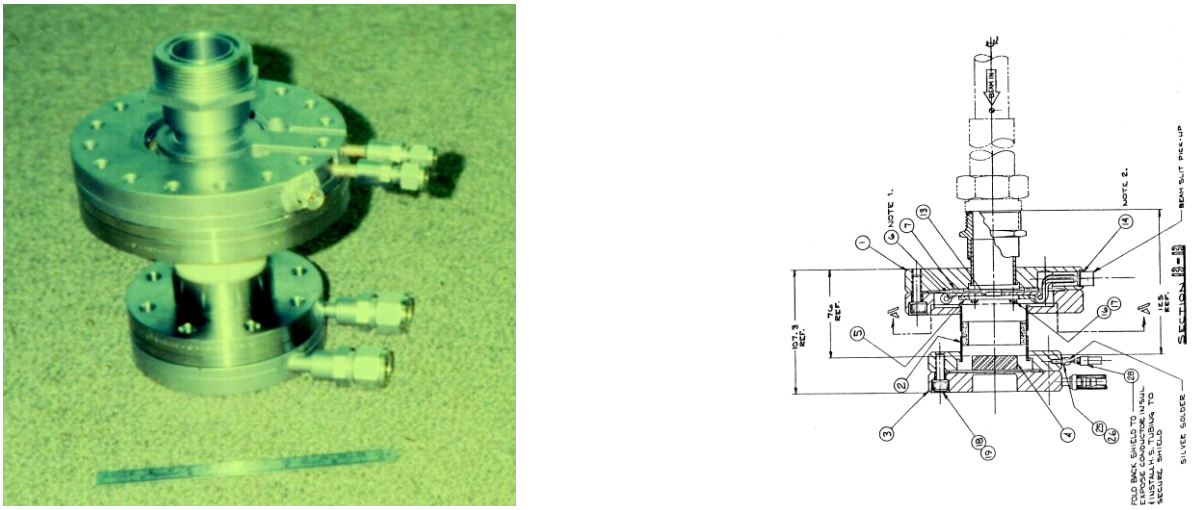

Fig. 17 MDA target assembly. (L) Picture of assembly showing water cooling pipes. (R) Diagram showing assembly components.

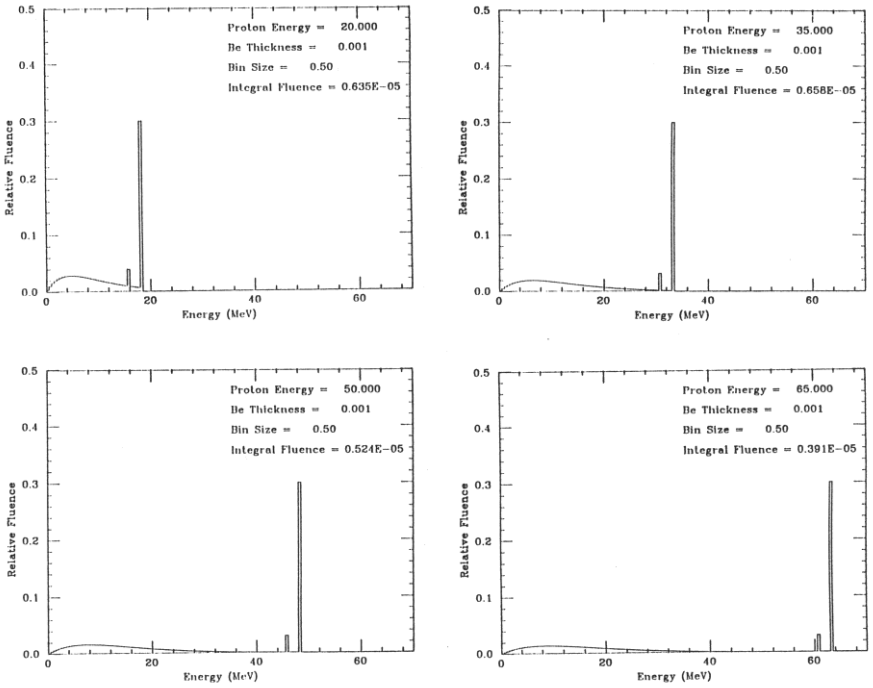

Fig. 18 Neutron production spectrum in the forward direction for different energy proton beams incident on a thin beryllium target. Reproduced from Moyers [12].

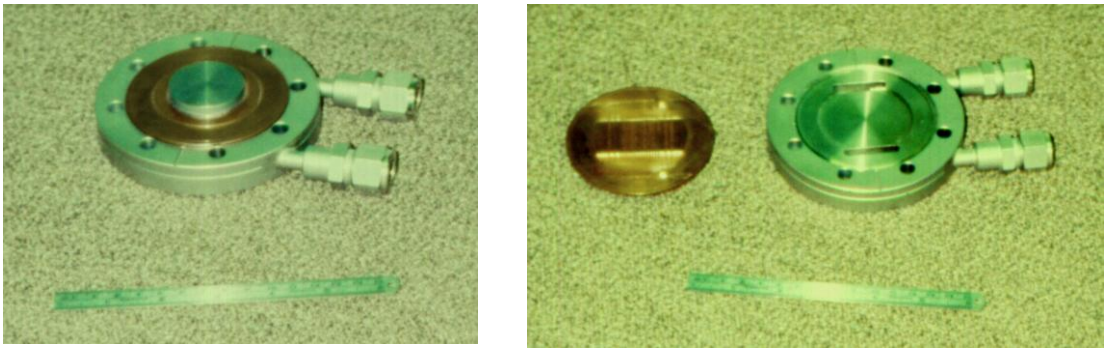

Fig. 19 Beryllium slab target and heat dissipation mechanism. (L) Surface at which the proton beam impinges on the beryllium. (R) Beryllium and copper slabs removed and turned upside down revealing narrow slits in the copper to increase the surface area over which water may flow for cooling.

Just distal to the target assembly is an assembly that houses a hardening filter, neutron beam monitor chambers, and a pre-collimator. Figure 21 is a diagram of this assembly. This assembly is only in place during beam delivery for treatment. At other times, such as during patient set-up, either a light field or x ray tube assembly would be in place. As can be seen in figure 16, this would also place the pre-collimator, that had been exposed to intense radiation, inside a shielded volume of the radiation head thereby reducing exposure of the staff and patient to residual radioactivation.

Table 3 lists the radiation head components for the high-energy neutron facilities that were treating patients during the late 1980s. It is apparent that no two facilities were the same. Figure 22 compares calculated neutron spectrums in the forward direction for four of these facilities. These spectrums were calculated by summing many thin target neutron spectrums that were generated at multiple depths as the proton beam traversed each component of the target assembly and then attenuating the neutrons in each energy bin by the thickness of the hardening filter. The effects of other components of the radiation head such as the collimators and monitor detectors were not included.

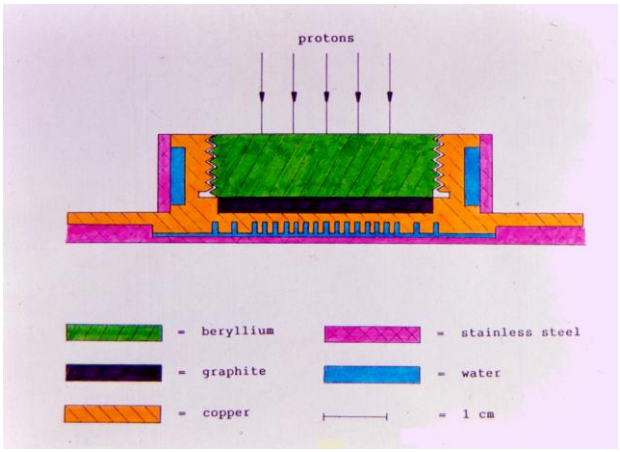

Fig. 20 UCLA neutron conversion target design. Reproduced from Moyers [12] that was modified from an original drawing by Miller (personal communication).

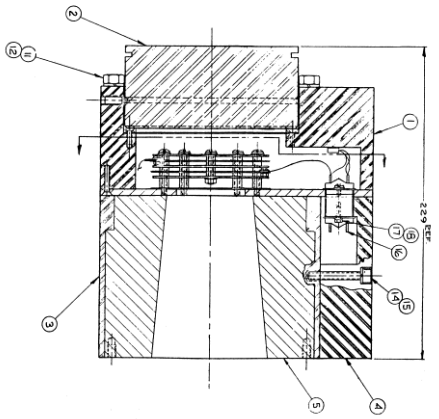

Fig. 21 MDA assembly for holding polyethylene hardening filter (2), monitor ionization chambers, and tungsten pre-collimator (5).

Table 3: Comparison of radiation head components for various high-energy facilities. Reproduced from Moyers [12].

Institution	UT-MDACC Houston Texas	CC Cleveland Ohio	UCLA Los Angeles California	UW Seattle Washington	MRC Merseyside UK	UCL Louvain Belgium	MINTF Batavia Illinois	NAC Faure S. Africa
Proton Energy	41.9 MeV	43 Mev	46 MeV	49.6 MeV	62 MeV	65 MeV	66 MeV	66 MeV
Beryllium	0.6 cm (15 MeV)	0.79 cm (22 MeV)	1.00 cm (26 MeV)	0.9 cm (24.6 MeV)	1.78 cm (36 MeV)	1.7 cm (35 MeV)	2.21 cm (49 MeV)	1.96 cm (40 MeV)
Backstop 1	copper	water	graphite 0.23 cm	copper 0.055 cm	copper 0.6 cm	carbon 0.85 cm	gold 0.05 cm	
Backstop 2	water		copper	water 0.1 cm	water	brass 0.4 cm		
Backstop 3			water	graphite 0.25 cm				
Hardening Filter	C_2H_4 3.3 cm	none	none	none	none	C_2H_4 2.0 cm		C_2H_4 2.5 cm
Flattening Filter	Teflon	none	none	Fe 2.3 cm CAX	Fe			steel
Collimator	Benelex inserts 92.0 cm	WEP inserts	Fe roman square 108.0 cm	Fe / C_2H_4(B) multi-leaf 111.0 cm	Fe / C_2H_4(B) book ends	Fe / epoxy(B) inserts	cement / C_2H_4 inserts 109 cm	Fe / C_2H_4(B) book ends 115 cm
Wedge	Teflon		iron		tungsten		tungsten	
Isocenter	125.0 cm $_{+}^{100°}$	125.0 cm	150.0 cm $_{+}^{95°}$	150.0 cm $_{+}^{185°}$	150 cm $_{+}^{185°}$	162.5 fixed vert.	153.2 cm fixed horiz.	150 cm $_{+}^{185°}$

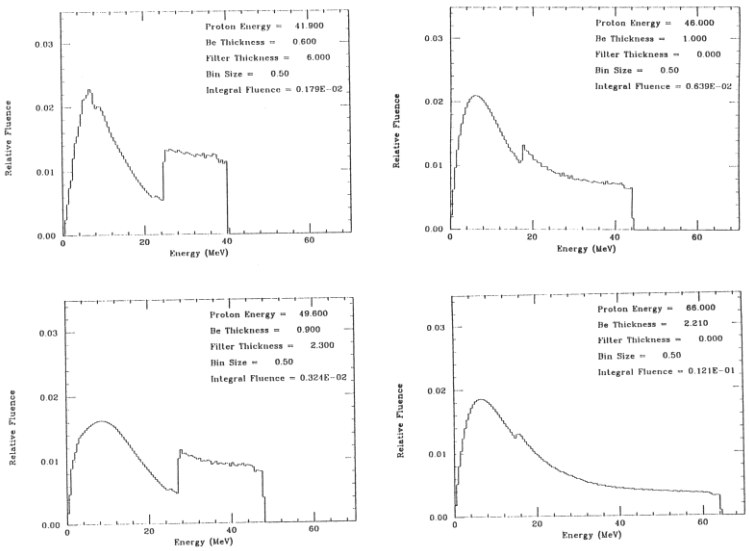

Fig. 22 Calculated thick target neutron spectrums for various high-energy FNT facilities. (TL) MDA. (TR) UCLA. (c) LL. (LR) Fermilab. Reproduced from Moyers [12].

One drawback of early FNT facilities that possibly impacted treatment results was the type of collimation. Unlike for x rays, lead and tungsten are not good attenuators for neutrons. Collimators thus need to be made from a lower atomic number material but generally these materials are less dense requiring them to be quite long. The material chosen for the collimators at MDA and several other facilities was a pressed wood called Benelex®. An inventory of fixed cone collimators was provided to make rectangular field sizes. Occasionally a tungsten block could be added to provide corner blocking. Figure 23(L) shows a single collimator cone while figure 23(R) shows a cabinet with an inventory of collimator cones. The field uniformity of the raw beam was generally good except near the field edge. Each cone was thus provided with a Teflon flattening filter to reduce the neutron fluence in the center of the field to compensate for out-scattered neutrons near the edges of the field. Figure 24 shows three flattening filters that were inserted into the distal ends of the different cones. Some other facilities used shaped steel flattening filters upstream of the collimators.

Fig. 23 (L) Single Benelex collimator cone at MDA. Length of collimator was 92 cm. (R) Cabinet with inventory of collimator cones for different field sizes.

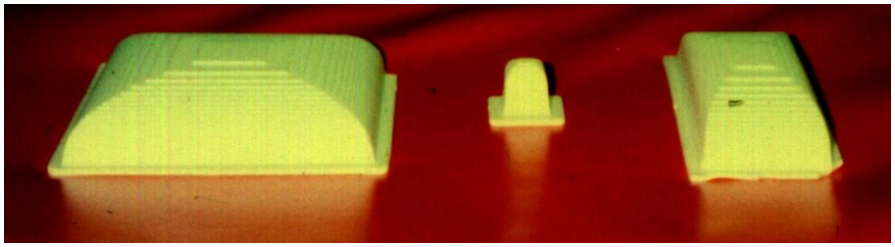

Fig. 24 Teflon flattening filters for different field sizes. The filters were inserted into the patient end of the collimator cones.

A different composition of fixed cones was used at Fermilab. The cones at that facility were composed of a mix of concrete and polyethylene as seen in figure 25. Another material that was used for fix cones was water extended polyester (WEP). Cones of WEP were used at the NASA Lewis Lab in Cleveland in which staff from the Great Lakes Neutron Therapy Association (GLANTA) treated patients.

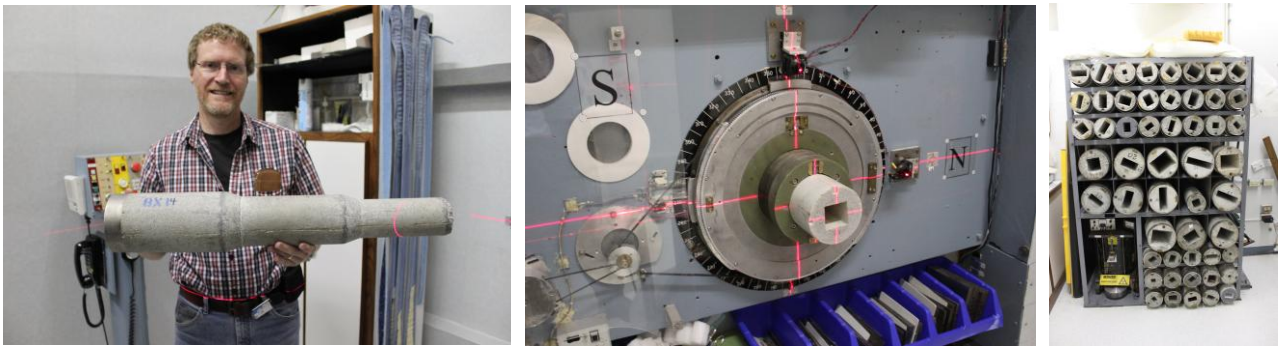

Fig. 25 Fixed cones used at Fermilab constructed of a mix of concrete and polyethylene. (L) Single cone held by Thomas Kroc. (C) Cone installed in radiation head. (R) Inventory of cones for different field sizes.

A significant advance in collimation occurred with the opening of the UCLA facility. This facility had a roman jaw style of collimator that could provide continuously adjustable rectangular field sizes. A high-density material was chosen to reduce the overall length and iron was chosen over other materials due to its reduced radioactivation cross-section. Figure 26 shows the jaws in the open and closed configurations.

Another collimation advance was able to provide irregular field shapes. At Wayne State University (WSU), a multi-rod collimator was devised [20]. This device consisted of 12,000 tungsten rods. The shape of the field was made by first cutting Styrofoam blocks to the desired shape, inserting the blocks against the rods and pushing them into place in the beam path, and then locking the rods so they would not move while rotating the gantry. Figure 27 shows insertion of the Styrofoam rod array shaper and a field shape that can be produced.

At the iThemba Labs, an irregular field shape was made by placing an array of collimation slabs thick enough to significantly attenuate the beam into the beam path. These slabs, called blades, were used similarly to the rods at WSU; the blocks were first moved manually and then locked into place. The blades were backed up by conventional block jaws. Figure 28(L) shows the multi-blade array. Figure 28(R) shows a reverse Beam's Eye View of an MLC similar to the one installed at the University of Washington (UW). The shape of the opening of the MLC was programmed and moved into place electronically. For better neutron attenuation, the MLC leaves at some facilities had disks of borated polyethylene strategically placed into multiple holes of each leaf [21].

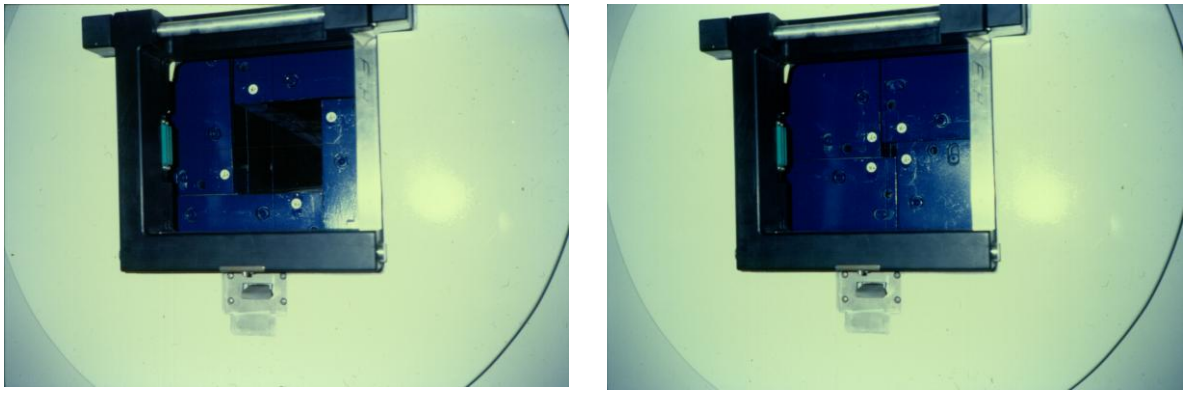

Fig. 26 Pictures of distal end of roman jaws type collimator installed at UCLA. (L) Opened to fullest extent that projects a neutron field with a size of 200 mm by 200 mm at the isocenter. (R) Closed to fullest extent that projects a neutron field with a size of 40 mm by 40 mm at the isocenter.

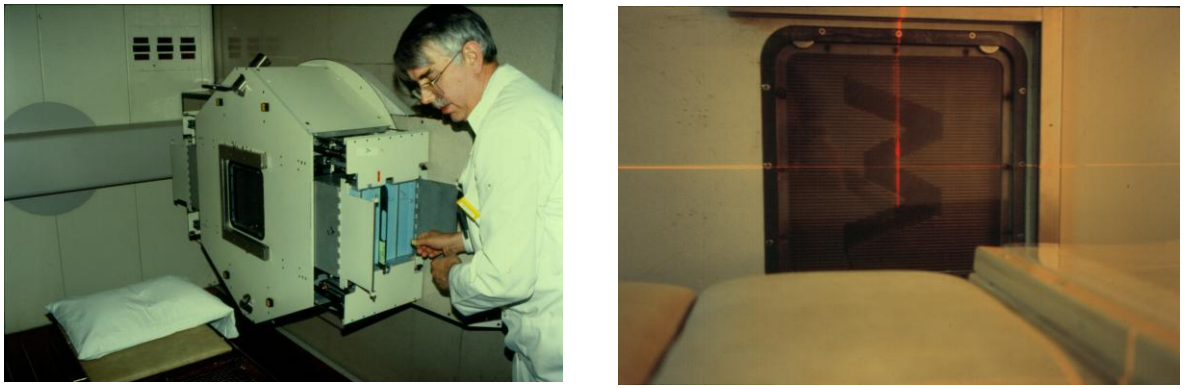

Fig. 27 Tungsten rod array for patient-specific collimation at WSU. (L) Richard Maughan inserting cut Styrofoam blocks used to move the rods into place. (R) A reverse beam's eye view of the tungsten rods after having been moved into place.

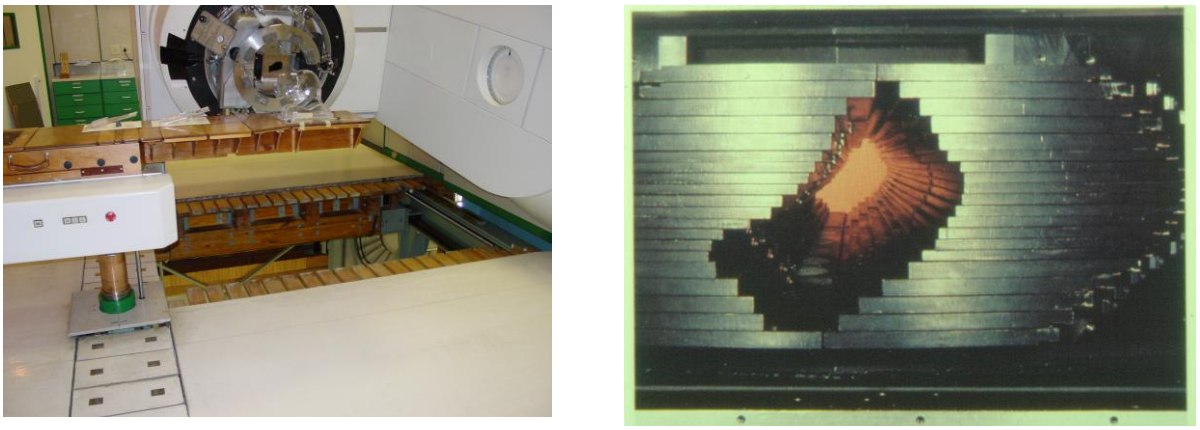

Fig. 28 (L) Multi-blade collimator at iThemba Labs. Note the retractable false floor to allow gantry rotation. The floor and patient positioner top were made of wood to reduce radioactivation. (R) Programmable multi-leaf collimator at UW. Reproduced from Scanditronix MC series cyclotrons brochure.

V. 3D DOSE CALCULATIONS FOR TREATMENT PLANNING

During the 1970's and 1980's, computerized calculation methods for FNT relied on traditional megavoltage x ray (MVX) methods such as: matrix methods (cartesian, polar, fan-line / depth-line, decrement lines for rectangular fields; parameterized generating functions; sector integration (TAR0 + SAR); and pencil beams (that were then just starting to be used). Unfortunately, these methods did not account well for the neutron spectrum, neutron scatter, and contaminating photons. Furthermore, computed tomography scans using x rays (XCT) did not provide sufficient data to accurately calculate neutron interactions, especially for determining the effects of heterogeneous tissue. Monte Carlo methods were known but impractical for routine clinical use at that time.

To overcome these inaccuracies, a new calculation method was developed that utilized multiple fast Fourier transform (FFT) convolutions of multiple three-dimensional (3D) Monte Carlo generated kernels [22-23]. This method utilized a three-source model consisting of primary neutrons, scattered neutrons, and photons. Heterogeneities within the patient were considered by ray tracing through the anatomy and performing linear attenuation on the three source spectrums. Two convolution paths were used for each of the three sources as seen in figure 29. One path convolved a water kernel at each voxel while the other path convolved a difference kernel that was the difference between lung and water kernels. The contribution from each was determined by a weighting factor based upon the material at the voxel.

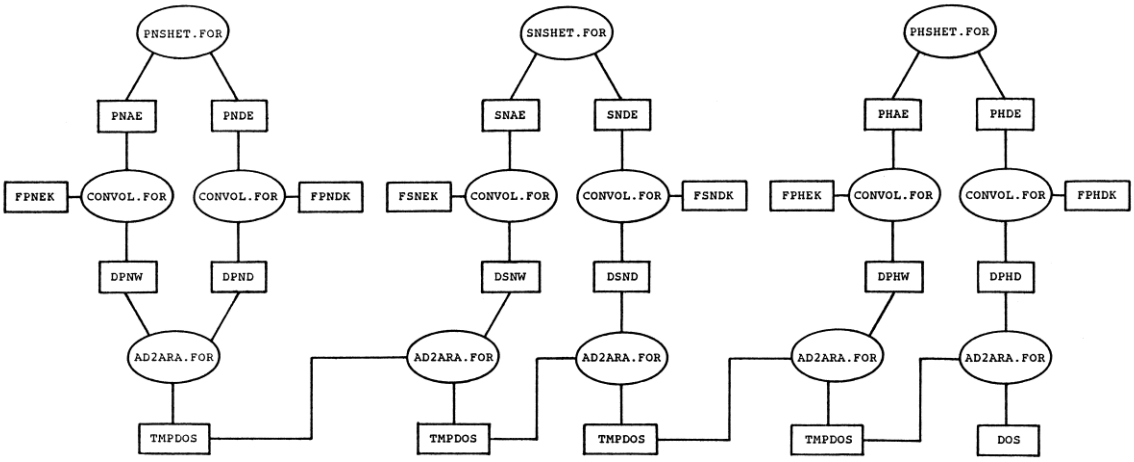

Fig. 29 Program flow for model that considered heterogeneous tissue and three radiation sources. Reproduced from Moyers [12].

The calculated spectrums shown in figure 22 were not sufficiently accurate for the three-source model shown in figure 29 because the flattening filter, hardening filter, and collimation system were not included. Measurements were thus made to refine the spectrums for the three sources. Both narrow and broad field measurements were made with neutron sensitive and neutron insensitive detectors. For these measurements, ionization chambers with walls made of A-150 muscle equivalent plastic and magnesium were used and filled with tissue-equivalent and argon flowing gas respectively. Due to a long breakdown of the cyclotron, the final measurements were made at UCLA that had similar neutron beam delivery equipment to MDA. Figure 30 shows the setup. Three differences between the MDA and UCLA facilities were that UCLA used a roman jaw style of collimator made of iron instead of Benelex cones, the target-to-isocenter distance was 150 cm instead of 125 cm, and the proton energy from the cyclotron was 46 MeV instead of 42 MeV. Figure 31(L) shows the primary and scattered neutron spectrums while figure 31(R) shows the photon spectrum for the UCLA equipment. The contaminating photon spectrum was the world's first published measurement for a high-energy FNT facility.

The off-axis neutron fluence profile was also required for accurate calculations. This was obtained by placing flat copper strips perpendicular to the beam at different distances from the isocenter. The radioactivated strips and a piece of film were then inserted into a film cassette with a scintillation screen to produce a latent image. The film was then developed and scanned to get fluence profiles at different distances from the isocenter. The diameter of a circular pillbox source was then iteratively fit to achieve profiles similar to the activated copper profiles. Figure 32 shows the fluence profile measurement technique, source model, and a fitted profile.

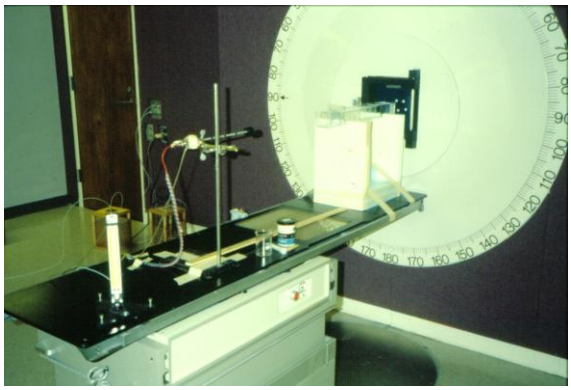

Fig. 30 Setup for measuring attenuation data used in deriving the neutron and photon spectrums. A variable but discrete thickness water column was used to provide narrow beam attenuation. Attenuation measurements were repeated with one chamber being sensitive to both neutrons and photons while a second chamber was sensitive primarily to photons.

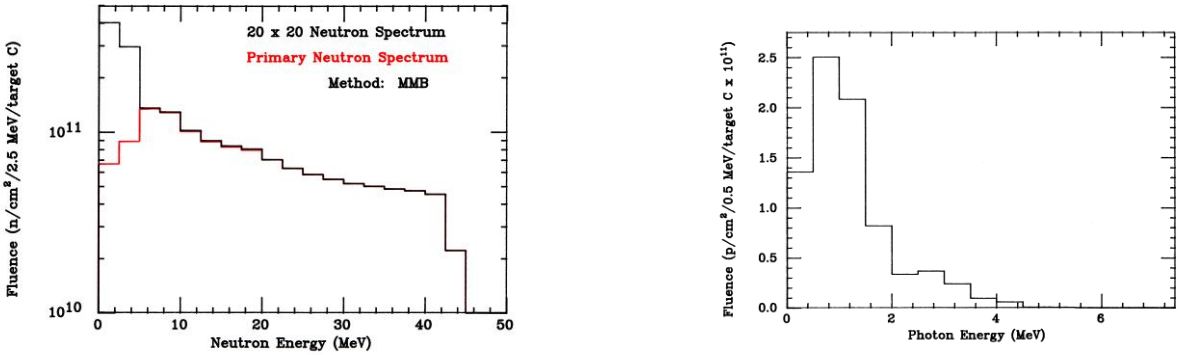

Fig. 31 (L) Primary and scattered neutron spectrums. Figure from Moyers [12]. (R) Photon spectrum. Figure reproduced from Moyers et al. [24] and used with permission of Wiley.

Fig. 32 Measurement and determination of primary neutron source size. (L) Diagram of source model. (C) Copper strips inside film cassette after irradiation of film. (R) Comparison of measured and fit profiles in the lateral penumbra region. Figures (L) and (R) from Moyers [13].

The calculation algorithms were developed using FORTRAN and DEC command language (DCL) on a VAX 750 computer. Initially the FFT codes were taken from Art Boyer and Ed Mok. A grant from Cray Research, however, allowed the calculations to be performed on a Cray X-MP supercomputer with a vector processor located in Austin, Texas (see figure 33). The 3D FFTs sub-routines were then changed to assembly code obtained from the Boeing aircraft company resulting in one of the most efficient programs running on the Austin computer. As seen in table 4, the calculation times for a fully 3D distribution using the Cray computer for irregularly shaped fields and heterogeneous anatomy was, in 1990, between three and four minutes for field sizes ranging from 50 mm to 200 mm on a side.

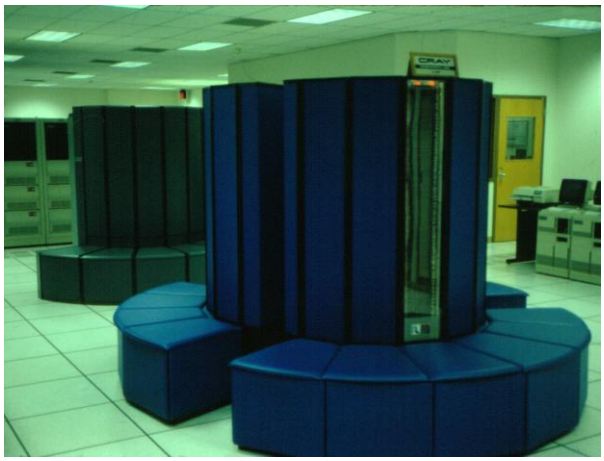

Fig. 33 Cray X-MP supercomputer located at the University of Texas - Austin campus, circa 1988.

Table 4 Calculation times for 3D dose calculations using three source model. Reproduced from Moyers [12].

Estimated Times in Seconds for Various Calculations on Cray X-MP/24

Type of Calculation	GENFAN	PNSHET	GENPEN	CONVOL (twice)	AD2ARA (twice)	Component Total	Beam Total
64x32x128 rectangular rectangular 1 cpu	0	1.6*	0	2.6*	0.06*	4.3*	12.9*
		15.4*				18.1	54.3*
64x32x128 irregular rectangular 1 cpu	0	2.6	4	2.6*	0.06*	9.3	27.8
		16.4				23.1	69.2
128x64x32 irregular fan 1 cpu	4	0.9	4	1.0	0.04	10.0	29.9
		2.6				11.7	35.0
256x128x64 irregular fan 1 cpu	32	7.2	64	16.0	0.5	119.7	359.1
		20.8				133.3	399.9
256x128x64 irregular fan 2 cpu	18	4.0	36	8.9	0.3	67.2	201.6
		11.6				74.8	224.4

Note: top numbers for 5 cm by 5 cm field, bottom numbers for 20 cm by 20 cm field.

* = actual times based upon CPU time charges on one processor

VI. Summary

Sources of neutrons for FNT have included fission, fusion, stripping or breakup of light ions, or inelastic reactions. Fission sources have a high relative biological effect (RBE), a low oxygen enhancement ratio (OER), are very low penetrating, and pose a security risk in a public hospital. Fusion sources had small gantries, required only small treatment rooms, had low beam penetrations, had low dose rates, and required frequent tube changes. High energy beams made by protons or deuterons on beryllium targets have a high dose rate, are highly penetrating, but may undesirably have increased OER values.

Between 1970 and 1995 FNT facilities evolved from parasitic facilities to dedicated medical facilities; from low-energy (< 16 MeV) to high-energy (40 - 66 MeV) beams; from stationary gantries to fully rotating gantries; and from manually exchangeable rectangular collimators to automated MLCs. These advances served to reduce side-effects for treated patients but by the time these advances were realized, a sour taste for FNT had already been acquired by many radiation therapy practitioners. Near the end of this period, many people were discussing the possibilities of carbon ion treatments that could presumably offer the high-LET advantage of neutrons but the physical precision of protons. By the late 1990s, most FNT facilities around the world had shut down with only a few facilities further advancing the technology and continuing to treat patients. FNT could, however, serve as a lower-cost alternative to carbon ion treatments in some situations.

Acknowledgements

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Unless otherwise specified, all photographs were taken by the author.

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A Brief History of Neutron Therapy Part III – Maturity: Technological Advancements, Appraising the Past, Considering the Future

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Abstract — **The history of neutron radiotherapy is characterized by cycles of great enthusiasm followed most often by discouraging outcomes. The ability of neutrons to eliminate even radioresistant tumors has been apparent since shortly after their discovery. The ability to accomplish this without unacceptable normal tissue toxicity has been the impediment to widespread implementation in radiation oncology. This article is the third in a series about the history of neutron radiotherapy. While the first two elucidate the early incarnation of neutron therapy, its biological rationale, and the expansion of technology, this article will examine the latest chapter in the history of neutron therapy. It will discuss the development of hospital-based facilities for the delivery of fast neutron therapy along with numerous technological advancements designed to improve our ability to capitalize on the advantages of neutron therapy. Finally, it will review some of the clinical successes and failures of fast neutron therapy, its role in providing data for other high-LET therapies, and its potential for future contributions to radiation oncology.**

Keywords — **Fast Neutron Therapy, Neutrons, Radiation Therapy, FNT, IMNRT**

I. Introduction

The history of fast neutron radiation therapy (FNT) has included periods of great excitement and great disappointment. The initial treatments at Berkeley represent the first example of this cycle. Indeed, Ernest Lawrence stated in 1938, "I personally believe, and this belief is shared by my medical colleagues, that this will be the beginning of a new method of cancer therapy which in a few years will be as widespread as that of x rays and radium." Within a decade, this sentiment stood in stark contrast to that of Robert Stone, the physician who delivered these treatments, who advised that "neutron therapy as administered by us has resulted in such bad late sequelae in proportion to the few good results that it should not be continued." This cycle has been repeated over the history of FNT, and while it currently appears to be at its nadir in terms of worldwide use, one may question whether we might expect another cycle. Regardless, we have learned many lessons from the history of FNT and can take a tremendous amount of associated data with us into the future of radiation therapy. This article is the third in a three-part series on the history of FNT in which we'll review the most recent phase of the development of FNT, including numerous technological advancements developed to better harness the biological advantages of FNT, along with a discussion of its current state and potential future directions.

II. Discussion

The potential biological advantages of FNT were well established in the early years of FNT. The ability to safely harness and capitalize on these advantages represented the impediment to the successful broad implementation of FNT as a standard component of our radiotherapy arsenal. The second phase of clinical implementation of FNT, ushered in by the Hammersmith experience, led to renewed excitement about the future of FNT. In general, however, the use of FNT facilities that developed from research accelerators led to shortcomings in our technical capabilities. As succinctly summarized by Catterall, "results were achieved using beams from primitive machines with serious disadvantages." [1] This fact was recognized by the National Cancer Institute who began a tremendous investment in FNT in 1971. The 20 year, $70 million project represented the largest investment in radiation therapy in the history of the NCI, involving the construction or modification of 10 neutron facilities.

Early experience in the US was led by the Neutron Therapy Facility (NTF) at Fermi National Laboratory (FNAL) which began treatment in 1976. Unlike other FNT facilities which were based on equipment designed for research, the NTF had a very high energy beam produced by 66 MeV protons on a beryllium target (p(66)+Be). It was recognized by this time that high energy beams would be necessary to exploit the biological benefits of FNT. The high energy protons for the NTF were extracted from the FNAL linac which provided 200 MeV protons for injection into the other accelerators. Since proton beam injection was required for only 0.8 seconds out of every 6 second cycle of the accelerator operation, the remaining beam was available for other use. The NTF was built along this beamline between the pre-accelerator and the booster ring and the proton beam was directed to an adjacent room where it struck a lithium target for neutron beam production. Patient treatment was delivered within an elevator shaft which would bring the patient to the level of the beamline. Since the biological effectiveness of FNT is strongly energy dependent, several other FNT facilities would later be built with accelerators designed to bombard a lithium target with proton energies at or near 66 MeV. The NTF beam was

shaped using a set of interchangeable regularly shaped polyethylene-concrete collimators placed in a steel and Benelex collimator assembly. The NTF treated over 3300 patients before its closure in 2013 and contributed tremendously to our understanding of FNT. The top panel in figure 1 provides an aerial view of the FNAL while the other panels depict the beamline and treatment room. The NTF was located just below and to the left of the high-rise Wilson Hall structure visible in the aerial image. Figure 2 shows a patient preparing for treatment at the NTF. An additional contribution of the NTF was the development of the first vertical CT scanner to allow 3D treatment planning for patients in the seated position necessitated by the nature of the treatment facility. This served as a precursor for the significant current research and interest in upright radiotherapy.

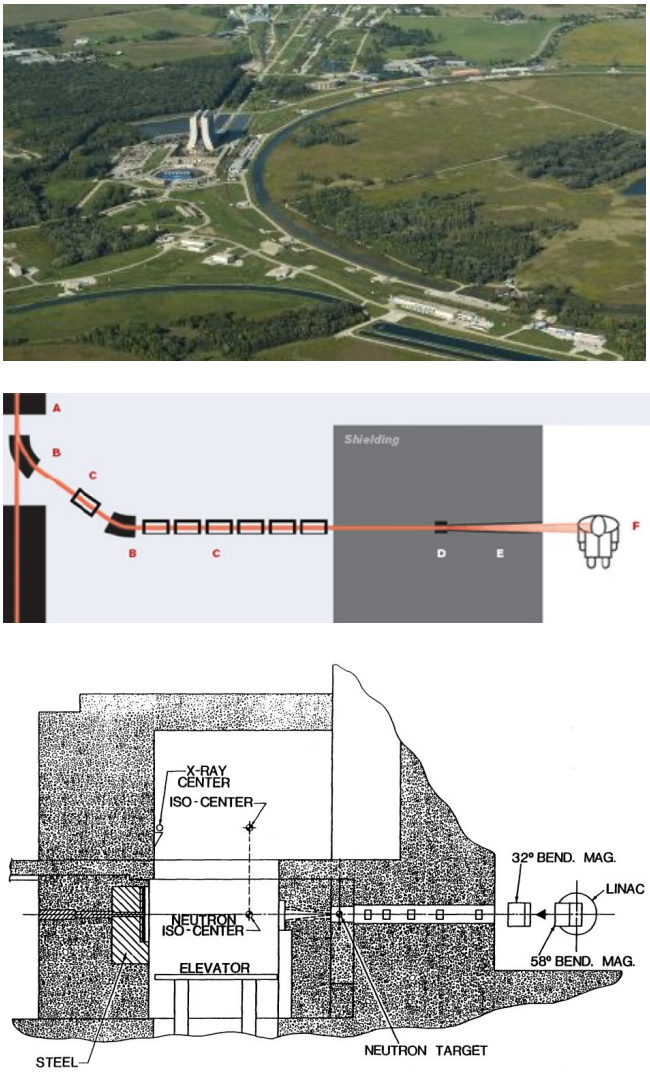


Fig. 1 Aerial view of Fermi National Accelerator Laboratory (top). The NTF was located just below and to the left of high-rise Wilson Hall. Top view of the proton beamline (middle) and cutaway view of the beamline and treatment room (bottom). (Reproduced from FNAL archives.)

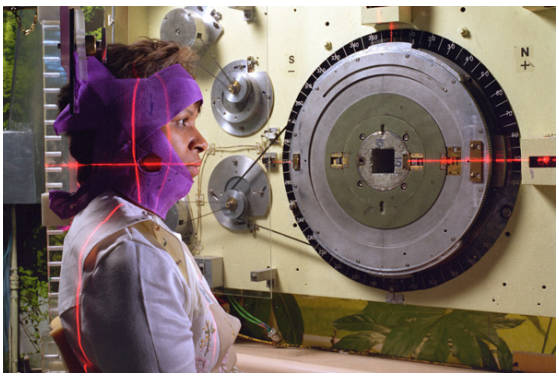


Fig. 2 Patient preparing for treatment at the FNAL NTF. (Reproduced from FNAL archives.)

As the investment from the NCI began to bear fruit, FNT moved from substandard laboratory-based delivery facilities in the 1970s to specially designed hospital-based facilities in the 1980s. This era saw the clinical implementation of the University of Washington FNT facility called the Clinical Neutron Therapy System (CNTS) in 1984. This p(50.5)+Be beam was shaped using a 40 leaf multi-leaf collimator (MLC) projecting a 1cm leaf width at isocenter. Figure 3 shows the treatment room and gantry. Figure 4 depicts the characteristics of the treatment head.

Fig. 3 Gantry and treatment couch for the University of Washington Clinical Neutron Therapy System (CNTS). (Reproduced from Wikipedia.)

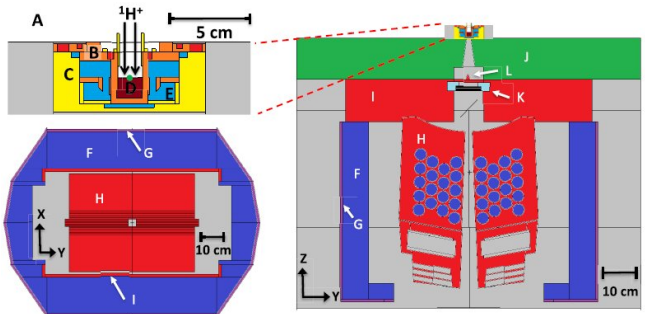


Fig. 4 Diagram of the UW CNTS target and MLC showing protons incident on the target (upper left), beam's-eye-view of the MLC (bottom left), and cross-sectional view of the beamline from target to MLC (right). (Reproduced from ref. 25.)

Figure 5 shows the UW CNTS MLC and a sample target with corresponding MLC shape. The CNTS is still operational and has now treated more than 3500 patients.

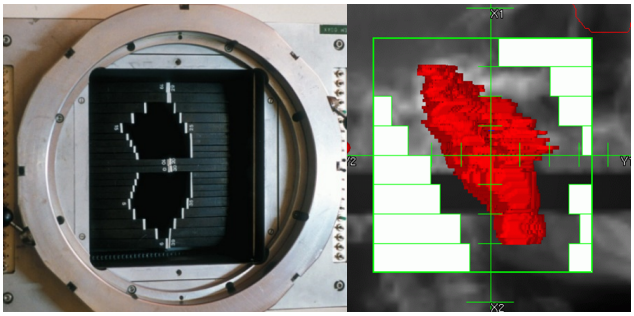


Fig. 5 UW CNTS MLC (left) along with MLC shape for representative radiotherapy target (right). (Reproduced from Wikipedia.)

Following in 1988 was the first treatment at the National Accelerator Center in South Africa, later to be renamed iThemba Laboratory. This p(66)+Be beam was shaped using variable jaws and a multi-blade trimmer. The gantry is shown in figure 6 while figure 7 shows a patient preparing for treatment next to the multiblade trimmer. The facility treated approximately 1800 patients before its closure in 2017.

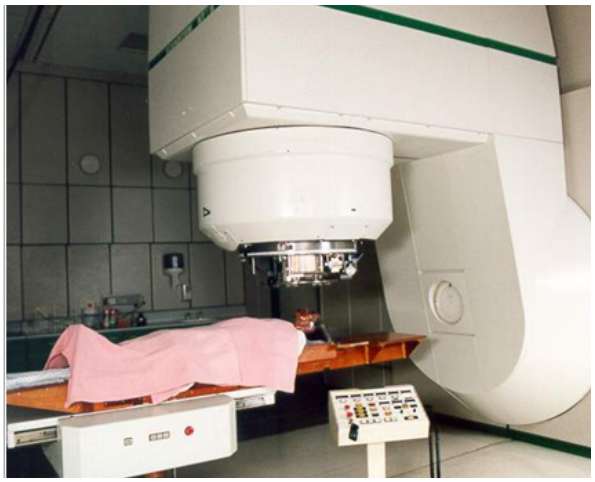


Fig. 6 Gantry and treatment couch for the iThemba fast neutron therapy facility. (Photo courtesy of Dan Jones.)

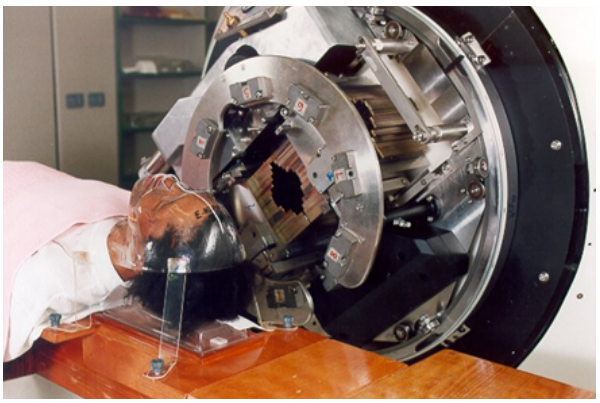
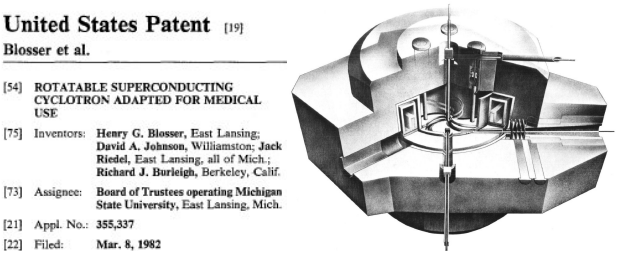


Fig. 7 Multi-blade trimmer for the iThemba fast neutron therapy facility. (Photo courtesy of Dan Jones.)

In 1991, the world's first gantry-mounted superconducting cyclotron was implemented for FNT at Harper Hospital, later to be named the Karmanos Cancer Center (KCC), affiliated with Wayne State University (WSU) in Detroit [2,3]. Michigan State University (MSU) had recruited Dr. Henry Blosser in 1958 to head a new cyclotron laboratory funded by the National Science Foundation. Dr. Blosser would create the world's first superconducting cyclotron and lead the development of the National Superconducting Cyclotron Laboratory (NSCL) at MSU. At the request of Dr. William Powers, radiation oncologist and chair of the Department of Radiation Oncology at Harper Hospital, MSU and Harper Hospital would begin a collaboration to create a neutron therapy facility. Blosser designed a gantry-mounted rotatable superconducting cyclotron for this facility. Figure 8 shows the patent for this device along with a cutaway view, while figure 9 shows the plan view of the accelerator.



United States Patent [19]

Blosser et al.

[54] ROTATABLE SUPERCONDUCTING CYCLOTRON ADAPTED FOR MEDICAL USE

[75] Inventors: Henry G. Blosser, East Lansing; David A. Johnson, Williamston; Jack Riedel, East Lansing, all of Mich.; Richard J. Burleigh, Berkeley, Calif.

[73] Assignee: Board of Trustees operating Michigan State University, East Lansing, Mich.

[21] Appl. No.: 355,337

[22] Filed: Mar. 8, 1982

Fig. 8 Patent and cutaway view of the superconducting cyclotron for FNT at WSU/KCC. (Images courtesy of the author.)

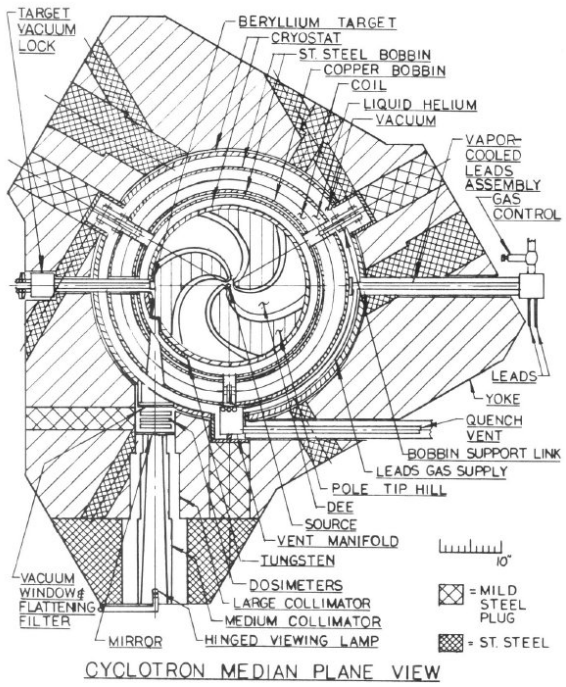


Fig. 9 Plan view of the superconducting cyclotron for FNT at WSU/KCC. (Image courtesy of the author.)

Figure 10 shows Drs. William Powers and Henry Blosser in front of a model of the treatment bore while figure 11 shows the two on the gantry structure during testing at the MSU NSCL where the unit was constructed and tested. Figures 12 and 13 show Dr. Richard Maughan next to the multi-rod collimator and Dr. Mark Yudelev in the treatment bore after clinical implementation.

Fig. 10 Drs. William Powers and Henry Blosser in front of a model of the WSU/KCC gantry and treatment couch. (Image courtesy of the author.)

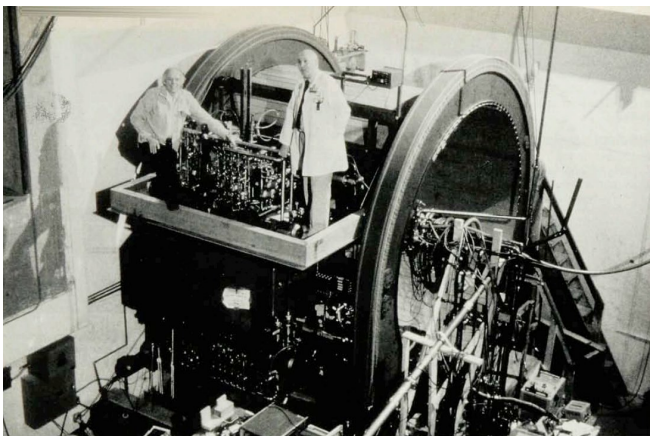


Fig. 11 Drs. Henry Blosser and William Powers on the gantry structure of the WSU/KCC FNT cyclotron during testing. (Photo courtesy of the author.)

While most accelerators developed for FNT used the p+Be reaction, the WSU/KCC cyclotron used a d(48.5)+Be beam since the d+Be reaction generates a neutron fluence rate roughly six times higher than the p+Be reaction. A novel multi-rod collimator was designed for this unit which allowed more detailed dose shaping characteristics than other facilities at that time [4]. Another unique feature of this treatment unit was the implementation of two gantry mounted x-ray tubes which facilitated pre-treatment image guidance.

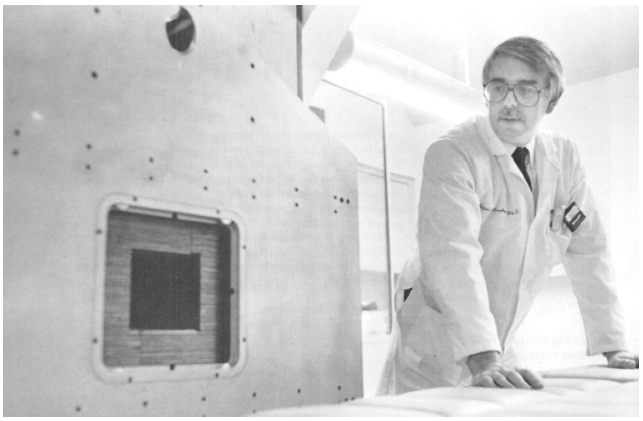


Fig. 12 Dr. Richard Maughan beside the tungsten multi-rod collimator for the WSU/KCC FNT unit. (Photo courtesy of the author.)

The WSU/KCC FNT facility was developed before CT simulation and 3D treatment planning were commonly available. The department had a wide bore CT and developed a novel laser marking device to facilitate CT-based simulation [5]. The CT data was then transferred to an in-house treatment planning system called VRSPlan which was originally developed from the GRATIS (trademark Sherouse Systems, Inc.) system [6]. This

allowed the unique opportunity to perform 3D conformal treatment planning for FNT using modern CT simulation processes, something that was extremely uncommon even for photon therapy at that time. The WSU/KCC facility treated over 2250 patients before its closure in 2011.

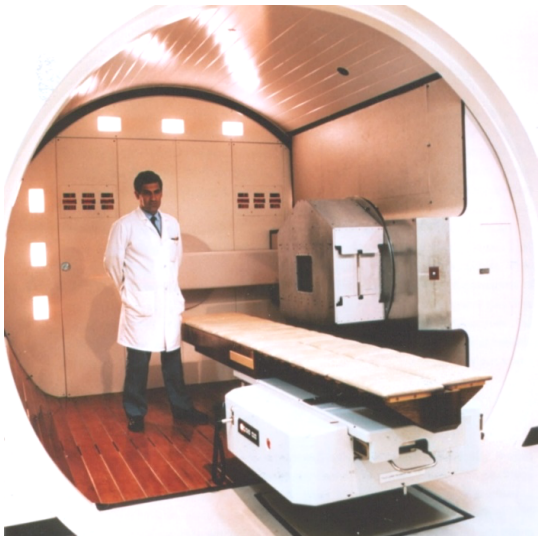


Fig. 13 Dr. Mark Yudelev in the treatment bore of the WSU/KCC unit. (Photo courtesy of the author.)

The development of these facilities ushered in a new phase in the history of FNT, the beginning of clinical trials using high energy, hospital-based neutron facilities. The majority of worldwide FNT treatments from the 1990s to the present day have been delivered by the four previously described facilities, with nearly 11,000 patients treated between them and counting.

Even before the development of advanced hospital-based facilities, a number of successes were observed from FNT treatments in the 1970s and 80s. Griffin summarized a number of studies showing favorable outcome for neutrons, most notably successes for unresectable salivary gland tumors and prostate cancer [7]. The RTOG-MRC study of FNT vs photon therapy for inoperable, recurrent or unresectable malignant salivary gland tumors was closed early due to the far superior local control provided by the neutron arm [8]. Two prostate cancer trials, RTOG 77-04 and NTCWG 85-23, both showed a statistically significant improvement in local control and RTOG 77-04 demonstrated a significant improvement in overall survival at 10 years [9,10]. It was anticipated that deployment of these new, more advanced, facilities would result in additional clinical success. Unfortunately, many subsequent studies yielded disappointing results.

While FNT has always enjoyed radiobiological advantages over low-LET photon and electron radiotherapy, the technological aspects of FNT have had difficulty keeping pace with those of conventional radiotherapy, thus sacrificing some of its potential advantage. The NTCWG 85-23 study provides an excellent example of the value of such technological advancements in radiotherapy delivery. While the neutron arm resulted in an overall increase in severe (Grade 3 and above) complications, all of these complications occurred at the two facilities without an MLC [10]. The CNTS treated 51 patients on this trial without a single Grade 3 complication. The WSU/KCC facility would later treat over 800 prostate cancer patients with a Grade 3 toxicity incidence of < 2% [11]. Even with a radiobiological advantage, accurate and precise delivery is of paramount importance.

While a number of favorable clinical outcomes for FNT have been observed, one may argue whether the results from these trials contain any true clinical "home runs." Positive clinical results have been obtained for salivary gland, advanced prostate cancer, soft tissue sarcoma, osteosarcoma, paranasal sinus, breast, and melanoma. However, many of these tumors are rare, and while local control has been demonstrated statistically in many trials, few trials have shown a survival benefit. Indeed, despite significant differences in local control, there was no statistically significant long term survival benefit for patients in the neutron arm of either the RTOG-MRC salivary gland trial or the NTCWG 85-23 prostate study. The mixed neutron and photon results presented by Forman for high-risk prostate cancer patients are exceptional [11] but there are many successful options available for patients with this disease. As of the turn of the millennium, FNT was still in search of something more to solidify its niche in radiotherapy.

Most clinical publications in the 2000s were based on results from studies performed in the 1980s and 90s as few trials have been initiated since then. Not only did these pre-2000s treatments suffer from relatively poor delivery capabilities in comparison to current technology, many were delivered without the aid of robust treatment planning systems which would allow visualization of the quality of the delivered dose distributions. The dawn of the new millennium saw a number of technological advancements including, but not limited to, improved beam shaping facilitated by advanced MLCs, improved treatment planning and dose calculations facilitated by advanced treatment planning systems, improved dosimetry and prediction of biological effects facilitated by advanced dosimetry techniques, and advances in radiobiological modeling methods and available data.

Advanced microdosimetry techniques were developed for high flux, high LET applications which would provide comprehensive mixed field dosimetry and facilitate accurate prediction of RBE for these beams [12]. An example from the WSU/KCC facility is shown in figure 14. These techniques would also provide the ability to evaluate

contributions from neutron capture reactions and were used not only to evaluate the characteristics of FNT and Cf-252 neutron brachytherapy, but also the potential of boron neutron capture enhancement of these two neutron treatment modalities. In addition, they were used to evaluate the dosimetric characteristics of the two BNCT facilities in the US, the reactor facilities at the Massachusetts Institute of Technology and Brookhaven National Laboratory [13-15].

Cf-252, discovered in 1950 at Berkeley, using the same cyclotron used to deliver most of the early FNT treatments, spontaneously emits neutrons with a mean energy of 2.1 MeV and half-life of 2.65 years. The first human treatments with Cf-252 were carried out in 1968 and since then, a number of treatment sites have been studied for which neutron brachytherapy may be potentially advantageous, including cervical, esophageal, and rectal cancer. Figure 15 depicts the lineal energy (microdosimetry) spectrum from Cf-252 at 5 cm in water for several simulated site diameters. The main impediment has been the availability and cost of developing Cf-252 sources and this has resulted in a relatively limited amount of clinical data for fast neutron brachytherapy.

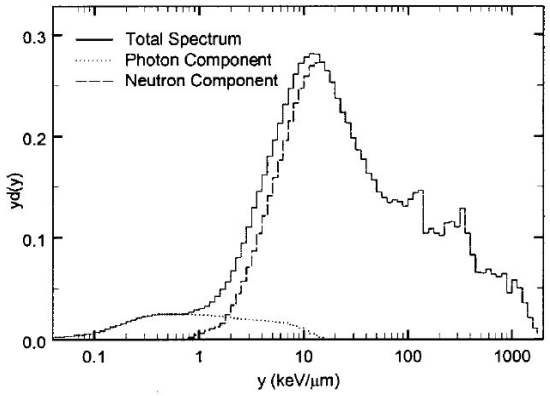


Fig. 14 Lineal energy spectrum for a 1μm site measured in the WSU/KCC FNT beam along with individual neutron and photon components. (Reproduced from ref. 12.)

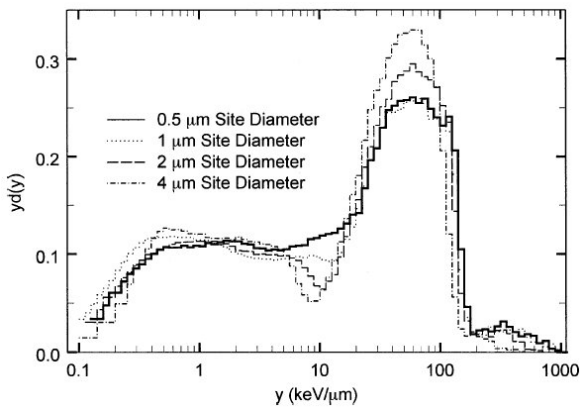


Fig. 15 Cf-252 lineal energy spectrums measured at 5 cm in water for multiple site diameters. (Reproduced from ref. 13.)

In 2004, a state of the art MLC was designed and implemented at the KCC/WSU FNT, enhancing treatment field resolution and facilitating rapid, automated treatment beam shaping [16]. This new MLC used 30 cm thick steel leaves projecting a 5 mm leaf width at isocenter and featured a robust computer control system which included both a primary motor drive mechanism and secondary automated visual leaf position validation system. The singly focused leaves had a blocking step to reduce interleaf transmission and an end-leaf step to allow opposing leaves to close within the primary beam. Figures 16 and 17 illustrate the design of this device while figure 18 shows the control system interface. The development of this beam shaping device would pave the way for the delivery of intensity modulated neutron radiotherapy (IMNRT).

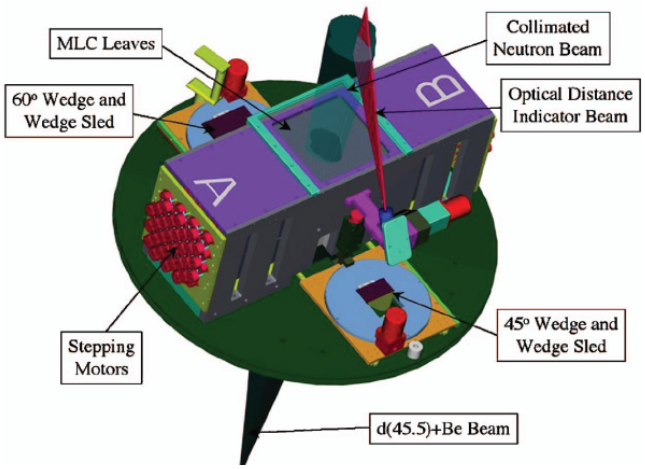


Fig. 16 Rendering of the high-resolution, computer-controlled MLC developed for the WSU/KCC FNT facility. (Reproduced from ref. 16.)

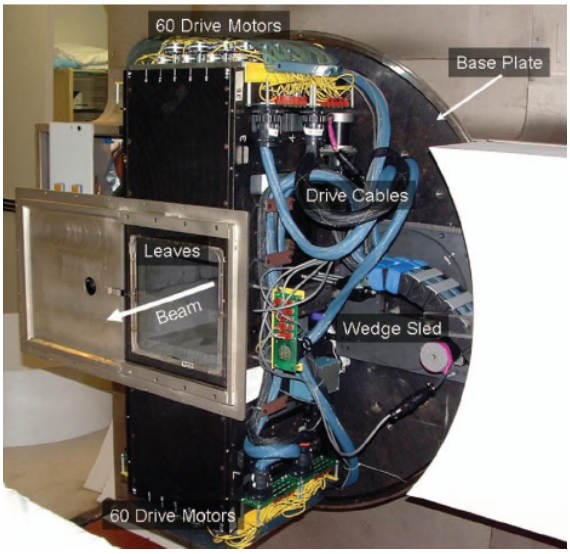


Fig. 17 The WSU/KCC MLC mounted on the gantry, shown here without the cover. (Reproduced from ref. 16.)

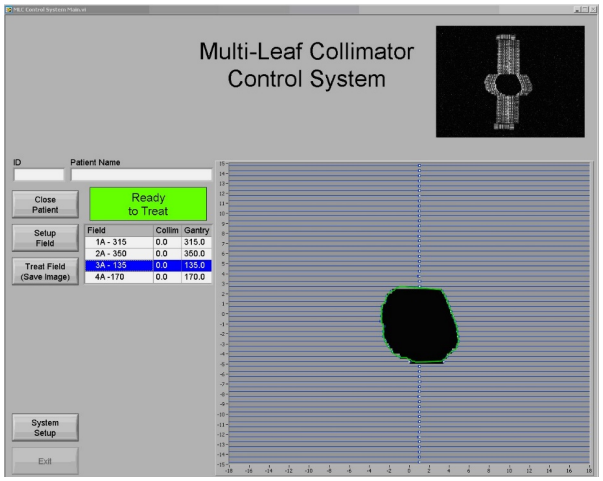
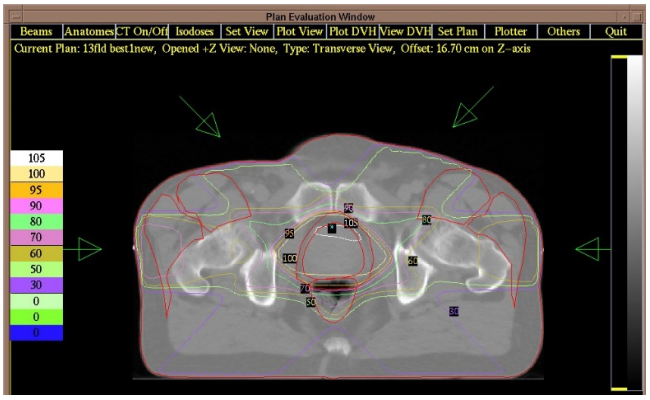


Fig. 18 WSU/KCC computer-controlled MLC system interface. (Image courtesy of the author.)

Concurrent development of advanced treatment planning capabilities at WSU/KCC allowed the creation of IMNRT plans and the first such plans were developed in 2004 [17,18]. An example IMNRT plan is shown in figure 19.



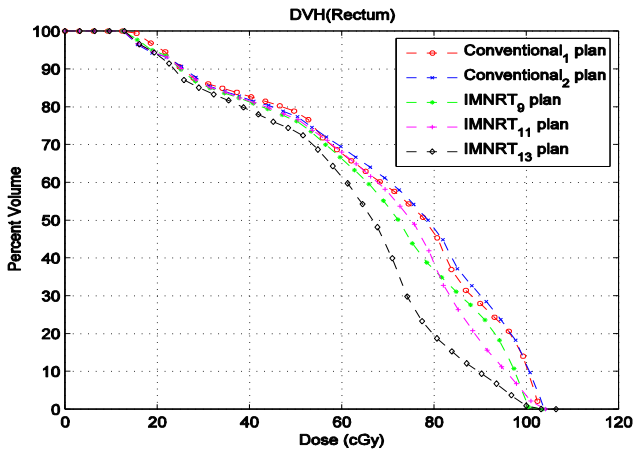


Fig. 19 Calculated dose distribution for an IMNRT plan created for a prostate cancer case (top) along with a comparison of rectal DVHs between conventional and IMNRT plans (bottom). (Reproduced from ref. 18.)

An associated set of biologically effective dose calculations and radiobiological dose escalation evaluations were performed for prostate cancer treatment as the first target site [19]. An example is illustrated in figure 20. Delivery accuracy was further improved with the implementation of modern image guidance techniques using the gantry-mounted x-ray tubes. An automated six degree of freedom correction method using implanted fiducial markers was developed for the treatment of prostate cancer [20,21]. The development of IMNRT capabilities greatly improved the dose distribution characteristics of FNT while the concurrent development of image guided FNT allowed the reduction of treatment margins. Both of these enhancements would provide the capability to significantly reduce out of target doses which had long been an area of difficulty for FNT given its proclivity for significant normal tissue complications.

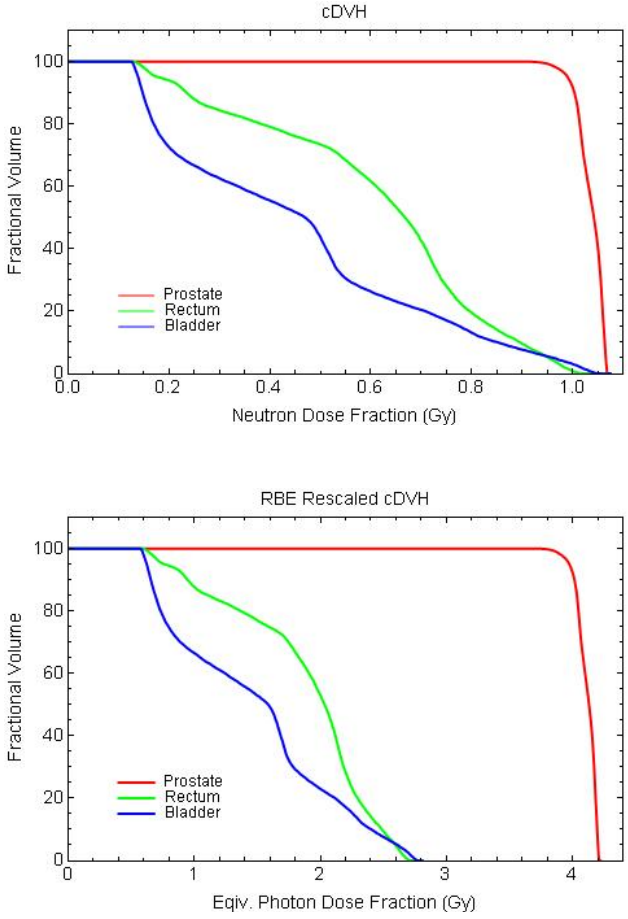


Fig. 20 Cumulative neutron DVHs for prostate, rectum and bladder for a representative prostate cancer case (top) along with corresponding equivalent photon DVHs scaled by RBEs for each organ modeled as a function of dose per fraction (bottom). (Images courtesy of the author.)

Unfortunately, the world would have to wait for the clinical implementation of IMNRT as the KCC/WSU facility was closed in 2007. The cost of operation of such a facility far exceeds that of conventional radiotherapy treatment units and no specific reimbursement codes were available for FNT. However, the unique nature and technological capabilities of this facility made it exceptionally well positioned to deliver state of the art image guided IMNRT treatment. And due to the belief that the clinical potential of FNT had yet to be fully unlocked and that it still had an important role to play in radiotherapy, the KCC/WSU facility was re-opened in 2010 and work commenced on IMNRT.

A new method was developed for IMNRT planning using a commercial TPS for inverse plan optimization and leaf sequencing and an in-house TPS for dose calculation [22]. New techniques were developed for dosimetry, evaluation of biologically effective dose, and delivery quality assurance. Commissioning culminated in 2011 with the planning, delivery, and evaluation of the AAPM TG-119 test suite for IMNRT [23]. Figure 21 shows calculated dose distributions for the TG-119 mock prostate and head and neck cases and figure 22 shows the first use of an ion chamber array filled with tissue-equivalent gas for planar dosimetry for IMNRT QA.

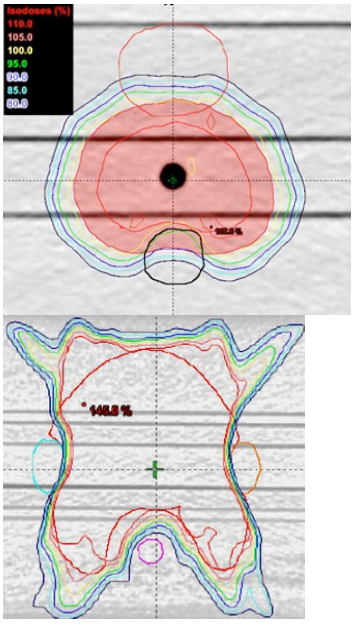


Fig. 21 Calculated dose distributions for the TG-119 mock prostate and head and neck cases during IMNRT commissioning at the WSU/KCC FNT facility. (Images courtesy of the author.)

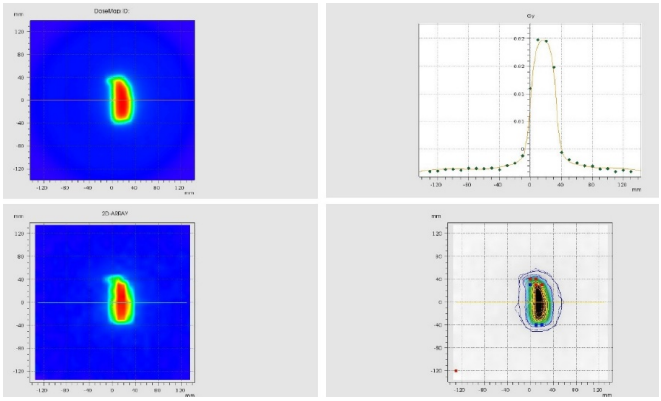


Fig. 22 Representative MLC shape from segmental IMNRT delivery evaluated using a tissue-equivalent gas filled ion chamber array for IMNRT quality assurance at WSU/KCC. (Reproduced from ref. 23.)

Despite the relatively poor penetration of the WSU/KCC FNT beam and practical limitations in the number of segments, these IMNRT plans were similar to those generated for photon IMRT, with the exception of very complex cases. Delivery accuracy was similar to photon IMRT at the time, as measured and calculated doses for > 90% of measurement points were within TG-119 derived confidence intervals. Unfortunately, during pre-treatment QA measurements for the first IMNRT patient, failure of the superconducting magnet caused another shut down of the facility, this time permanently. While WSU/KCC would be the first to commission IMNRT, it would never deliver it to a patient and the world would have to wait again for IMNRT.

Meanwhile, the University of Washington CNTS also developed numerous advances in technical capability, first showing that the MLC dramatically reduced treatment toxicity to local normal tissue structures [24]. Figure 23 illustrates the improved dose distributions achievable using the MLC to deliver 3DCNT for a prostate treatment. Improvements in the accuracy of neutron dosimetry and beam characterization [25] and development of a custom built commercial TPS with neutron-specific scattering kernels allowed more accurate dose calculations and the ability to perform inverse planning for the creation of IMNRT plans [26].

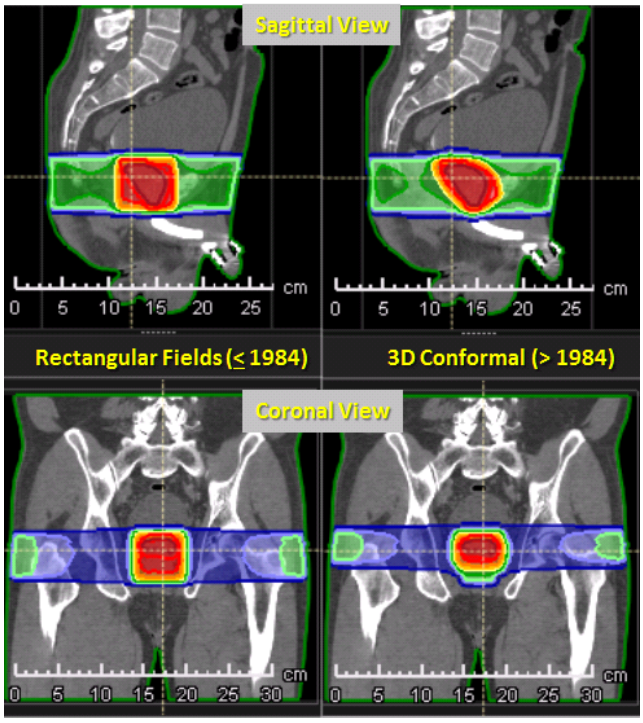


Fig. 23 Comparison of pre-MLC neutron dose distributions (left panels) with 3DCNT plans shaped with the UW CNTS MLC (right panels). (Images courtesy of Landon Wootton and Robert Stewart.)

In 2022, the CNTS ultimately became the first (and thus far only) facility to deliver IMNRT [27]. Figure 24 illustrates an example of the improved dose distributions achievable with IMNRT for a head and neck cancer treatment. For the initial cohort of plans created for comparative dosimetry for head and neck cancer treatment, IMNRT improved the therapeutic ratio by an average of >50% compared to 3DCNT. To date, over 100 patients have been treated with this improved delivery technique and a new imaging system has been developed to facilitate efficient patient specific QA for IMNRT [28]. Figure 25 provides an illustrative example of this technique which compares Monte Carlo calculated ^{11}C decay maps with induced ^{11}C activity measured using neutron positron emission portal imaging. The CNTS is also currently investigating flattening filter free delivery for IMNRT and exploring additional ways to capitalize on the biological advantages of FNT, including expanded use of hypofractionation, and more advanced RBE modeling techniques [29,30]. Figure 26 illustrates the distribution of various particle types in the CNTS beam while figure 27 presents RBE for DNA double strand breaks as a function of energy for recoil protons and other ions.

A substantial portion of our published clinical data from FNT trials has come from the UW CNTS group and developments at this facility continue to push the field of FNT forward. It is, to the author's knowledge, the only remaining clinical FNT facility still in operation.

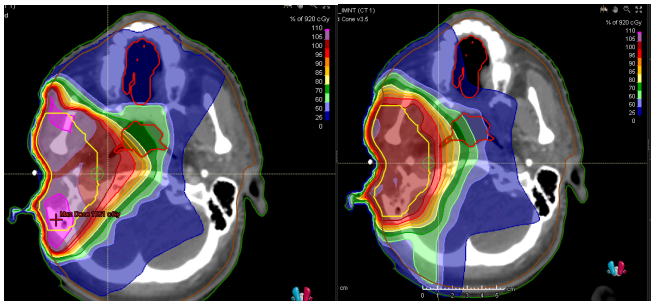


Fig. 24 Comparison of dose distributions created for head and neck cancer treatment using 3DCNT (left panel) and 5 field IMNRT (right panel) at the UW CNTS. (Images courtesy of Landon Wootton and Robert Stewart.)

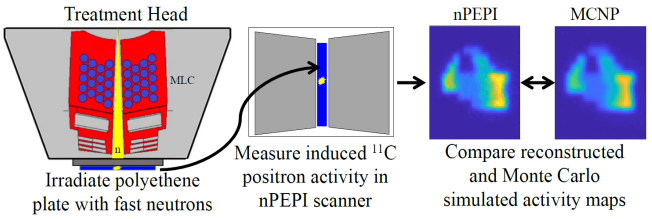


Fig. 25 Patient specific QA tool comparing MC calculated ^{11}C decay maps with measured induced ^{11}C activity using neutron positron emission portal imaging. (Image courtesy of Robert Stewart.)

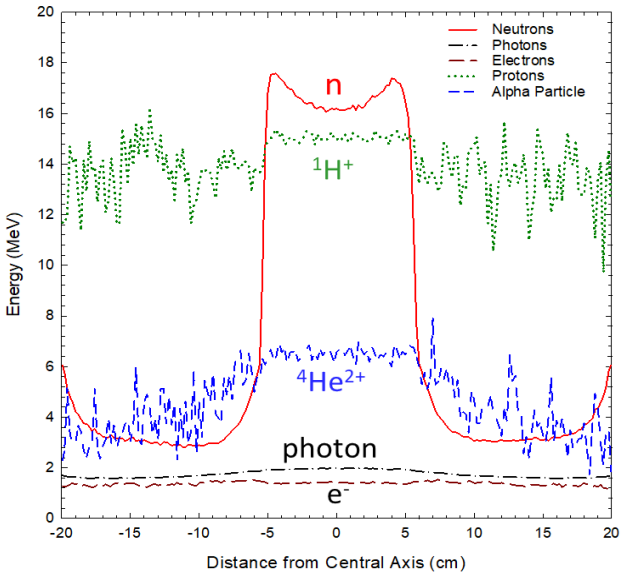


Fig. 26 Distribution of neutrons and secondary particles in the UW CNTS beam. (Reproduced from ref. 30.)

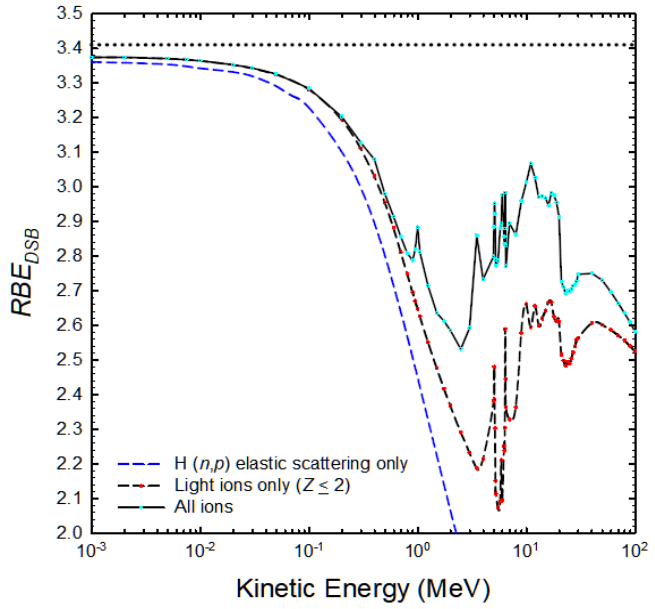


Fig. 27 RBE for DNA double strand break induction in normoxic cells as a function of kinetic energy for recoil protons, light ions and all ions. (Reproduced from ref. 29.)

One elusive target that would certainly represent a clinical "home run" for FNT is Glioblastoma Multiforme (GBM). FNT is currently the only treatment modality which has demonstrated the capability to consistently sterilize a GBM [31,32]. Unfortunately, no therapeutic window was observed in the early FNT trials for GBM as normal brain tolerance doses are substantially lower than doses required for local control. In 2007, a modern PET-guided conformal FNT study for GBM patients also unfortunately yielded disappointing results [33]. A mechanism for providing a tumor-specific boost to FNT for GBM could potentially yield a solution to this problem and such a treatment, referred to as Boron Neutron Capture Enhanced Fast Neutron Therapy (BNCEFNT), was originally proposed in 1978 [34]. Estimates of its radiobiological effects and clinical potential were further explored in 1994 [35], and a clinical feasibility investigation was performed for the WSU/KCC facility in the late 1990s [14,36]. Figure 28 shows lineal energy spectrums measured in the WSU/KCC FNT beam (unmoderated beam) and a beam moderated with 25 cm of steel (moderated beam) to increase the thermal neutron fluence in order to facilitate the boron neutron capture (BNC) boost. Also shown is a biological weighting function correlating LET with RBE which demonstrates a small predicted increase in RBE in the moderated beam. Figure 29 shows microdosimetry results using paired dosimeters, one of which contains ^{10}B and thus illustrates the enhancement from the BNC reaction. This relative dose enhancement is shown in both the moderated FNT beam and at 5 cm from a ^{252}Cf neutron brachytherapy source.

Figure 30 illustrates the relative shapes of the FNT dose distribution in the WSU/KCC moderated FNT beam and the associated thermal neutron distribution which is representative of the potential BNC dose given an appropriate ^{10}B distribution. This illustrates that the FNT beam can be accurately collimated around the gross disease while the BNC boost can potentially eliminate microscopic disease even at significant distances from the collimated field edge. Figure 31 shows the thermal neutron fluence as a function of depth suggesting that peak BNC enhancements are achievable at depths appropriate to treat a GBM.

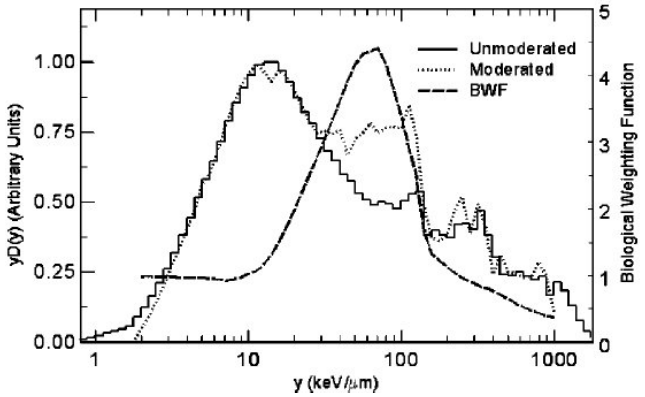
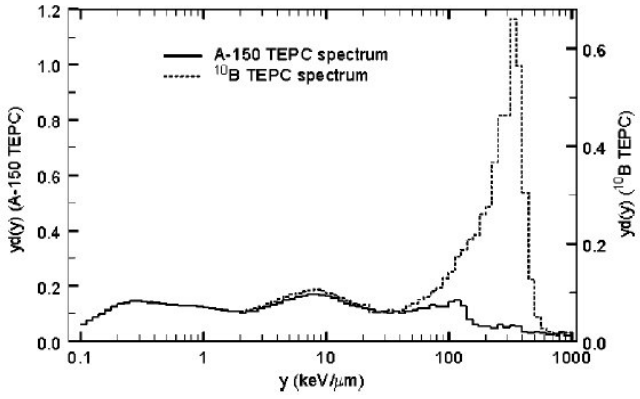


Fig. 28 Neutron lineal energy spectrums for a 1μm site diameter in moderated and unmoderated WSU/KCC FNT beams along with a biological weighting function. (Reproduced from ref. 14.)



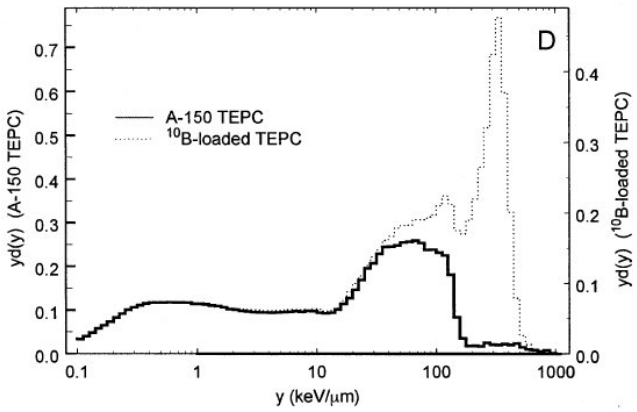


Fig. 29 Lineal energy spectrums measured for a 1μm site diameter in the moderated WSU/KCC FNT beam (top panel) and at 5 cm from a ^{252}Cf neutron brachytherapy source (bottom panel) with and without BNC enhancement. (Reproduced from ref. 14 (top) and 13 (bottom).)

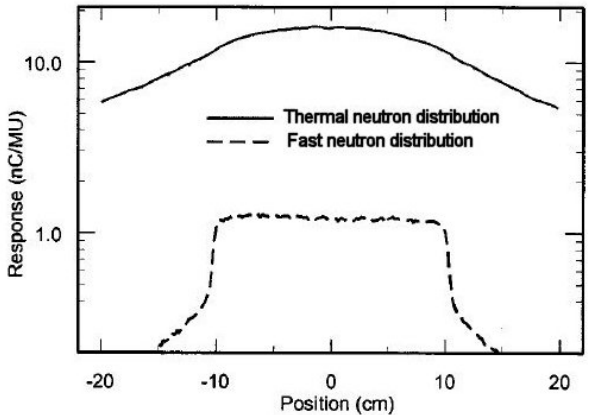


Fig. 30 Measured thermal neutron and fast neutron profiles in the WSU/KCC BNCEFNT beam measured using ionization chambers with (thermal neutron) and without (fast neutron) ^{10}B loading. (Image courtesy of the author.)

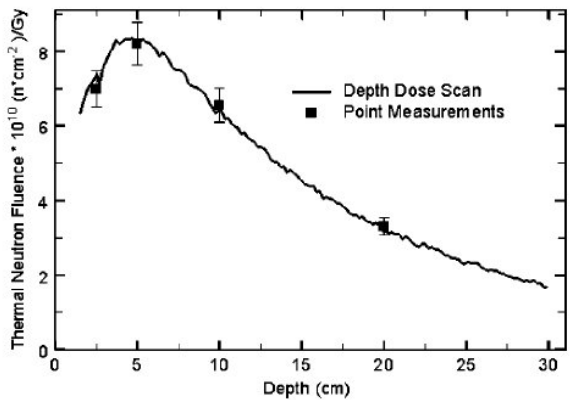


Fig. 31 Thermal neutron fluence as a function of depth in water measured in the WSU/KCC BNCEFNT beam. (Reproduced from ref. 14.)

In the BNCEFNT feasibility study using the WSU/KCC moderated FNT beam, an estimated therapeutic gain of nearly 60% was achieved using this BNCEFNT beam and boron concentrations already achievable in boron neutron capture therapy patients at that time [14]. This gain appears sufficient to open a substantial therapeutic window for the treatment of GBM but requires a significant investment of resources for dosimetric characterization, plan creation and evaluation, and drug delivery and evaluation, and a variety of other aspects necessary for the development of a clinical program. Such applications represent the kinds of opportunities that may still be available with FNT and remain largely unexplored.

III. Summary

While FNT is no longer a major weapon in our radiotherapy arsenal, its story remains an important chapter in the history of radiation oncology. The history of FNT includes many important lessons about the biological effectiveness of different particle types, energies, beam delivery capabilities, mixed treatment regimens, and fractionation schemes, to name a few. These lessons should reinforce our efforts to understand fundamental radiobiological characteristics of radiation therapy and should continue to be taught to future practitioners of radiotherapy including radiation oncologists, medical physicists, and radiobiologists. FNT has provided conclusive evidence for improved local control compared to photon treatment in a variety of disease sites, specifically those that are known to be resistant to conventional radiotherapy. It remains an important potential option in the treatment of rare radioresistant tumors, particularly given new advances in our delivery and treatment planning capabilities. Better control of the dose delivery and better understanding of its radiobiological effects could further enhance the ability of FNT to eliminate radioresistant tumors for which there are limited therapeutic options. FNT still thrives at the CNTS who "continue to find fast neutron therapy clinically more useful and effective in the treatment of patients at high risk for local recurrences in both curative and palliative settings." [25]

And what of the future? Interest in FNT has diminished greatly since the excitement of previous decades but one may question whether there remains a reimagined role in precision oncology. While neutrons earned a poor early reputation from significant normal tissue toxicities, its advantages have often been underestimated. Ideally, FNT should remain a primary option for rare, radioresistant cancers. Along with its utility for the treatment of radioresistant tumors, it also has the potential to provide significant financial and logistical advantages in shortening treatment courses. Neutrons have comparable clinical RBE and similar clinical results for some tumor types in comparison to heavy ions such as ^{12}C. Heavy ion therapy is

prohibitively expensive in many countries, thus supporting the potential development of new neutron therapy installations, particularly in developing countries where patients often present with large, advanced tumors. Shorter treatment time is also advantageous in these circumstances for clinical, logistical, and financial reasons. Compared to heavy ion facilities, FNT offers a cost-effective high-LET option for low- and middle-income countries. The future of FNT may thus lie partly in its potential for wider availability.

Regardless of whether new FNT facilities are created, clinical data from FNT will continue to guide other high LET therapy techniques. As noted by Suit in his review of heavy particle therapy, "fast neutron therapy was the first high LET radiation therapy." [37] It is difficult to overstate the contributions of FNT to our understanding of the radiobiology of radiation therapy. This experience has proven invaluable for the development of contemporary particle therapy protocols. The development of RBE modeling frameworks, many of which were first validated using clinical data from FNT trials, have informed the development of treatment protocols and the prediction of the biological effectiveness of proton and carbon ion therapy [38-41]. Results from FNT treatment of hypoxic tumors laid the groundwork for many trials in carbon ion therapy. Indeed, FNT trials helped delineate the therapeutic window for high-LET radiation, balancing increased tumor control probability against the risk of severe normal tissue complications.

We have learned much from our experience with FNT, however, as it continues to seek clinical "home runs" which would solidify its role in radiotherapy, we must ask whether it might strike out first. Our lack of understanding of the radiobiology of FNT and the subsequent profound normal tissue toxicities of the first phase of its history could be considered strike one. The failure of the majority of clinical trials in the second phase of FNT to demonstrate a survival advantage over conventional treatments could be considered strike two. Could strike three become the closure of the final remaining FNT facility, or will FNT make a dramatic comeback? Consider the trajectories of major areas of current clinical radiation oncology research as well as the current comprehensiveness of our understanding of radiation biology. Most studies of proton therapy thus far have demonstrated little or no difference in outcomes from photon therapy [42-44]. Most current photon therapy efforts are based on the "belief that optimal doses to the tumor and normal tissue have already been determined with near complete accuracy, and the only challenge remaining is to ensure that these idealized doses are reproduced in the clinic with the utmost rigor." [45] "Such approaches treat our wildly inadequate understanding of cancer biology and radiation effects in tissue as settled science." [45] Indeed, how much have we yet to learn about radiobiology? Maybe FNT still has more to teach us and more to offer to our patients.

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Wilhelm Conrad Roentgen

The First *NOBEL PRIZE in Physics, 1901*

“"in recognition of the extraordinary services he has rendered by the discovery of the remarkable rays subsequently named after him"

P. Sprawls[1]

[1] Emory University Radiology and Imaging Sciences, Atlanta, USA
Sprawls Educational Foundation, www.srawls.org

I. INTRODUCTION

Wilhelm Conrad Roentgen was a German physicist recognized and honored for his discovery of a “new kind of radiation”. His contribution was not just the discovery, but the extensive research determining and documenting the characteristics of the radiation and demonstrating its value for medical applications.

A comprehensive biography describing his education and academic activities has been published and can be read here.
wilhelm conrad röntgen – biographical - nobelprize.org.

Our interest here is his research following the discovery and his publications and presentations.

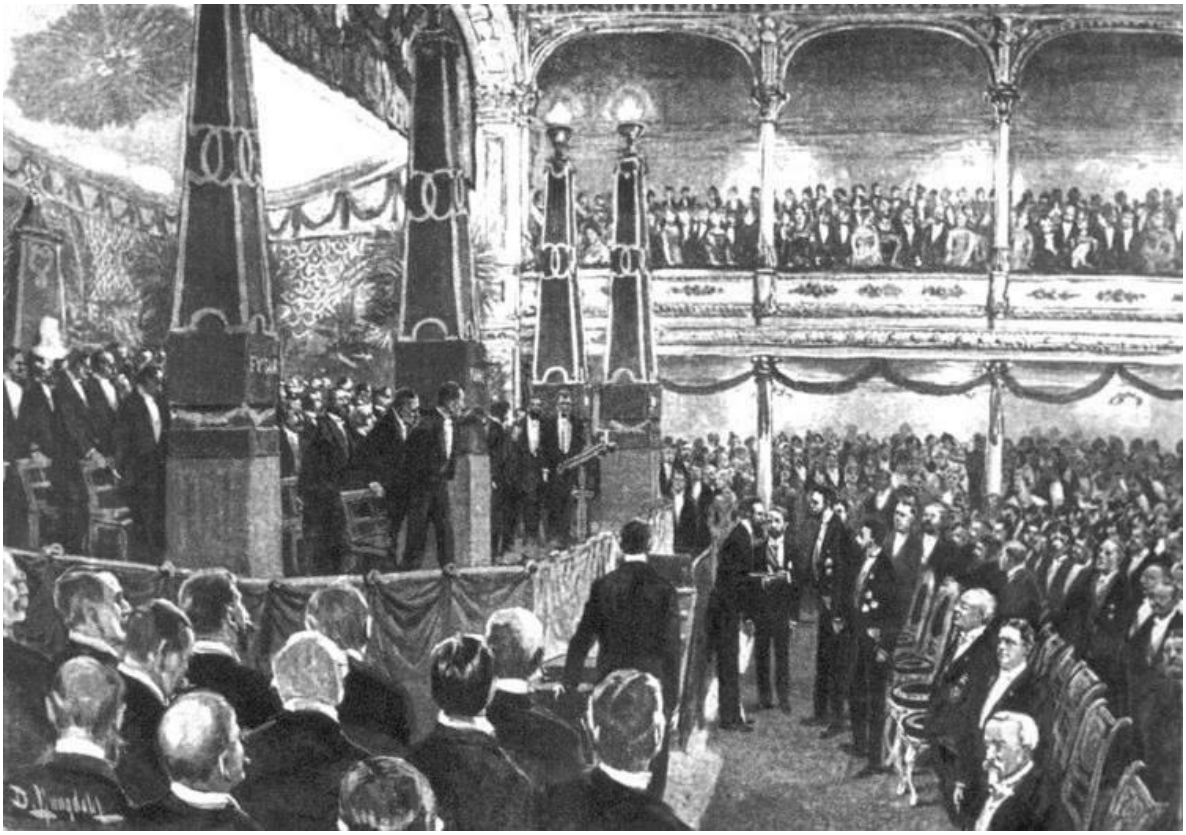
II. THE NOBEL AWARD CEREMONY

The Nobel Award ceremony on 1901 was the first for physics and is especially significant for the field of medical physics. It was for the discovery of radiation that was to become a major medical procedure and establish the profession of medical physics as we know it now.

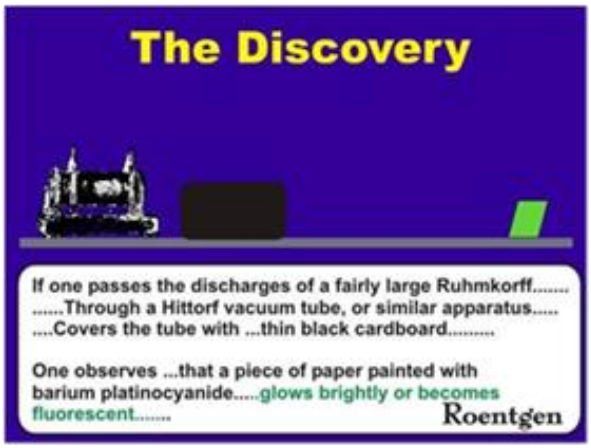
Roentgen did not provide a lecture, and the presentation was by the-former Rector of the National Archives C. T. Odhncr, President of the Royal Swedish Academy of Sciences:

Your Royal Highnesses, Ladies and Gentlemen. The Royal Swedish Academy of Sciences received from Alfred Nobel the privilege of awarding two of the great Prizes which he founded in his will- the Prizes in those branches of Science which lay nearest his heart - those in Physics and Chemistry. Now that the Royal Academy of Sciences has received from its Committees their expert opinion on the suggestions sent in, as well as their own suggestions, it has made its decision, and as current President I am here to make it known. The Academy awarded the Nobel Prize in Physics to Wilhelm Conrad Röntgen, Professor in the University of Munich, for the discovery with which his name is linked for all time : the discovery of the so-called Röntgen rays or, as he himself called them, X-rays. These are, as we know, a new form of energy and have received the name <<rays>> on account of their property of propagating themselves in straight lines as light does. The actual constitution of this radiation of energy is still unknown. Several of its characteristic properties have, however, been discovered first by Röntgen himself and then by other physicists who have directed their researches into this field. And there is no doubt that much success will be gained in physical science when this strange energy form is sufficiently investigated and its wide field thoroughly explored. Let us remind ourselves of but one of the properties which have been found in Röntgen rays; that which is the basis of the extensive use of X-rays in medical practice. Many bodies, just as they allow light to pass through them in varying degrees, behave likewise with X-rays, but with the difference that some which are totally impenetrable to light can easily be penetrated by X-rays, while other bodies stop them completely. Thus, for example, metals are impenetrable to them; wood, leather, cardboard and other materials are penetrable and this is also the case with the

muscular tissues of animal organisms. Now, when a foreign body impenetrable to X-rays, e.g. a bullet or a needle, has entered these tissues its location can be determined by illuminating the appropriate part of the body with X-rays and taking a shadowgraph of it on a photographic plate, whereupon the impenetrable body is immediately detected. The importance of this for practical surgery, and how many operations have been made possible and facilitated by it is well known to all. If we add that in many cases severe skin diseases, e.g. lupus, have been successfully treated with Röntgen rays, we can say at once that Röntgen's discovery has already brought so much benefit to mankind that to reward it with the Nobel Prize fulfils the intention of the testator to a very high degree.



III. THE DICOVERY



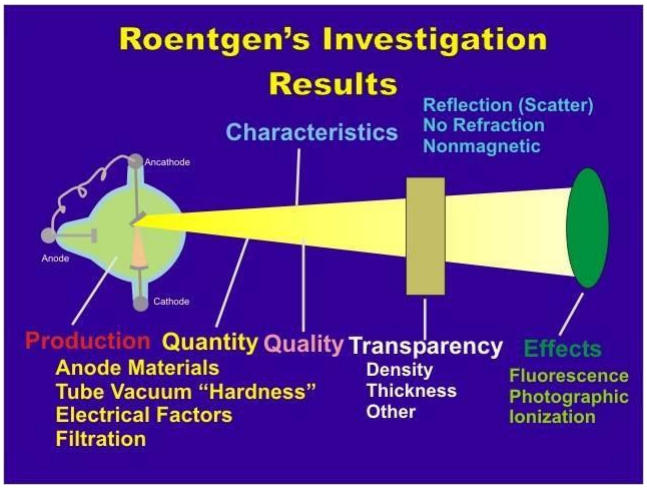
Before the time of the discovery physicists in various institutions were experimenting with partially evacuated glass tubes connected to high-voltage sources of electricity. It had been determined that streams of accelerated electrons, or cathode rays, were produced within the tubes. If a tube had a sufficiently thin window, some of the cathode rays penetrated the surrounding air. Roentgen was experimenting with cathode rays coming from a tube when he made the discovery. Typically, the tubes would glow because of the ionization of the air that remained in the tube. This light interfered with Dr. Roentgen's experiment of observing fluorescence produced by the cathode rays close to the tube. To produce a dark environment, he enclosed his glowing tube with an opaque cover. It was in this darkness that he noticed light being emitted from a fluorescent material at some distance from the tube-a distance much greater than the range of cathode rays in air.

IV. THE INVESTIGATIONS

Following the discovery, Roentgen realized he had a new kind of radiation and began an intense investigation to determine Their characteristics and especially compare it to other known radiations, visible light and cathode rays.

The series of experiments described by Roentgen and illustrated by Sprawls are published here:

ROENTGEN'S INVESTIGATION DETERMINING THE CHARACTERISTICS OF X-RADIATION
P. Sprawls. MEDICAL PHYSICS INTERNATIONAL Journal, vol.2, No.2, 2014
http://www.mpijournal.org/pdf/2014-02/MPI-2014-02-p435.pdf .



The experiments are summarized in this illustration.

His investigations included experiments with tubes designed for X-ray production with different anode materials operated at different electrical voltages and the effects of filtration on the characteristics of the radiation. It is significant that he discovered the effects of the radiation, fluoresence and photographic, because this was to become the basics of the two X-ray imaging modalities, radiography and fluoroscopy.

Roentgen published the results of the investigations in a scientific journal as a series of three (3) articles:
1.W. C. Roentgen: On a New Kind of Rays, December 28, 1895. (Preliminary Communication)

2.W.C. Roentgen: On a New Kind of Rays. March 9, 1896 (Continued)

3.W. C. Roentgen: Further Observations on the Properties of X-rays. March 10, 1897.

It appears that these did not attract attension beyond the physics community that did not recognize the significants for imaging the human body.

V. THE PRESENTATION

In 1896 he gave a presentation at the University of Wurzburg in which he described the physics of the new radiation and demonstrated its medical potential by producing an image of the anatomy professor's hand on a photographic plate. When it was developed and shown to the audience it was greeted with excitement and with cheers for Dr. Roentgen.

VI. THE NEWS SPREADS TO OTHER COUNTRIES

The story of the new kind of radiation and its medical applications was picked up by the news media and published in other countries. This is when physicists and engineers in various institutions realized that the partially evacuated tubes and high-voltage electrical sources they were experimenting with and used in demonstrations were actually X-ray machines and began to use it make images of the human body in collaboration with medical doctors.

VII. THE FOUNDATION OF MEDICAL IMAGING AND THE MEDICAL PHYSICS PROFESSION

Now that the principle and process of medical imaging has been demonstrated by Dr. Roentgen, physicists and engineers began the development of more appropriate x-ray tubes, high-voltage and controllable electrical sources, fluorescent screens and photographic film receptors. This area of research and development continues with the general objective of increasing visibility of anatomical structures and signs of pathological conditions…especially in the breast and brain, both challenging anatomical regions to image. With improvements in X-ray projection imaging and the development of X-ray computed tomography (CT), other modalities using radionuclides, ultrasound, and radio frequency (RF) signals were developed.

The role of physicists expanded beyond research and development to include direct involvement in clinical imaging procedures, with special attention to image quality and the radiation exposure to patients. These became recognized as radiological or medical physicists, often with certificating boards examining and providing recognition of their qualifications to practice the profession.

With the development of radiation oncology or therapy, physicists were required for calibrations of equipment and creating treatment plans for maximum effectiveness. This became the largest specialization within the field of medical physics.

With the expanding scope of medical physics, graduate level academic courses have generally become recognized as a requirement for entering the profession.

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Antoine Henri Becquerel

NOBEL PRIZE in Physics, 1903

shared with Marie Curie and Pierre Curie

"in recognition of the extraordinary services he has rendered by his discovery of spontaneous radioactivity"

P. Sprawls[1]

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Sprawls Educational Foundation, www.sprawls.org

I. INTRODUCTION

Antoine Henri Becquerel was born into a family with a rich legacy in science, on December 15, 1852, in Paris, France.

His father Alexandre-Edmond Becquerel, was an esteemed physicist. And his grandfather, Antoine César Becquerel, had been a pioneering researcher in the field of electrochemistry. Growing up in such an intellectually stimulating environment, Henri was naturally drawn to the sciences from a young age. His family's influence and access to a wealth of scientific knowledge and resources played a crucial role in shaping his early interest in physics.

Henri's formal education in physics began at Lycée Louis-le-Grand, a prestigious secondary school in Paris. During his time here, Henri demonstrated exceptional aptitude in mathematics and physics, which were bolstered by his family's encouragement and academic background. His experiences at this school solidified his foundation in scientific principles and prepared him for advanced studies.

In 1872, Henri Becquerel enrolled at the École Polytechnique, one of France's leading engineering schools. His education here was marked by rigorous training in the sciences and engineering, which honed his analytical skills and deepened his knowledge of physical phenomena. The school's emphasis on practical and theoretical aspects of science greatly influenced his approach to research.

After completing his studies at the École Polytechnique. Henri advanced to the École des Ponts et Chaussées, where he focused on civil engineering. This phase of his education introduced him to a more applied aspect of science. He integrated his knowledge of physics with engineering challenges. It was during his time here that he began to develop a keen interest in the properties of natural elements, which would later lead to his experiments with uranium salts and the discovery of radioactivity.

II. HENRI BECQUEREL EXPERIMENTS

<u>The Discovery, as reported by Ernie Tretkoff in the APS News, Feb. 25, 2008:</u>

In one of the most well-known accidental discoveries in the history of physics, on an overcast day in March 1896, French physicist Henri Becquerel opened a drawer and discovered spontaneous radioactivity.

Henri Becquerel was well positioned to make the exciting discovery, which came just a few months after the discovery of x-rays. Becquerel was born in Paris in 1852 into a line of distinguished physicists. Following in his father's and

grandfather's footsteps, he held the chair of applied physics at the National Museum of Natural History in Paris. In 1883 Becquerel began studying fluorescence and phosphorescence, a subject his father Edmond Becquerel had been an expert in. Like his father, Henri was especially interested in uranium and its compounds. He was also skilled in photography.

In early 1896 the scientific community was fascinated with the recent discovery of a new type of radiation. Wilhelm Conrad Roentgen had found that the Crookes tubes he had been using to study cathode rays emitted a new kind of invisible ray that was capable of penetrating through black paper. The newly discovered x-rays also penetrated the body's soft tissue, and the medical community immediately recognized their usefulness for imaging.

Becquerel first heard about Roentgen's discovery in January 1896 at a meeting of the French Academy of Sciences. After learning about Roentgen's findings, Becquerel began looking for a connection between the phosphorescence he had already been investigating and the newly discovered x-rays. Becquerel thought that the phosphorescent uranium salts he had been studying might absorb sunlight and remit it as x-rays.

To test this idea (which turned out to be wrong), Becquerel wrapped photographic plates in black paper so that sunlight could not reach them. He then placed the crystals of uranium salt on top of the wrapped plates and put the whole setup outside in the sun. When he developed the plates, he saw an outline of the crystals. He also placed objects such as coins or cut out metal shapes between the crystals and the photographic plate and found that he could produce outlines of those shapes on the photographic plates.

Becquerel took this as evidence that his idea was correct, that the phosphorescent uranium salts absorbed sunlight and emitted a penetrating radiation like x-rays. He reported this result at the French Academy of Science meeting on February 24, 1896.

Seeking further confirmation of what he had found, he planned to continue his experiments. But the weather in Paris did not cooperate; it became overcast for the next several days in late February. Thinking he couldn't do any research without bright sunlight, Becquerel put his uranium crystals and photographic plates away in a drawer.

On March 1, he opened the drawer and developed the plates, expecting to see only a very weak image. Instead, the image was amazingly clear.

The next day, March 2, Becquerel reported at the Academy of Sciences that the uranium salts emitted radiation without any stimulation from sunlight.

Many people have wondered why Becquerel developed the plates at all on that cloudy March 1, since he didn't expect to see anything. Possibly he was motivated by simple scientific curiosity. Perhaps he was under pressure to have something to report at the next day's meeting. Or maybe he was simply impatient.

Whatever his reason for developing the plates, Becquerel realized he had observed something significant. He did further tests to confirm that sunlight was indeed unnecessary, that the uranium salts emitted the radiation on their own.

At first, he thought the effect was due to particularly long-lasting phosphorescence, but he soon discovered that non-phosphorescent uranium compounds exhibited the same effect. In May he announced that the element uranium was indeed what was emitting the radiation.

Becquerel initially believed his rays were similar to x-rays, but his further experiments showed that unlike x-rays, which are neutral, his rays could be deflected by electric or magnetic fields.

Many in the scientific community were still absorbed in following up on the recent discovery of x-rays, but in 1898 Marie and Pierre Curie in Paris began to study the strange uranium rays. They figured out how to measure the intensity of the radioactivity, and soon found other radioactive elements: polonium, thorium, and radium. Marie Curie coined the term "radioactivity" to describe the new phenomenon.

The story of Becquerel's discovery is a well-known example of an accidental discovery. Somewhat less well known is the fact that 40 years earlier, someone else had made the same accidental discovery. Abel Niepce de Saint Victor, a photographer, was experimenting with various chemicals, including uranium compounds. Like Becquerel would later do, he exposed them to sunlight and placed them, along with pieces of photographic paper, in a dark drawer. Upon opening the

drawer, he found that some of the chemicals, including uranium, exposed photographic paper. Niepce thought he had found some new sort of invisible radiation and reported his findings to the French Academy of Science. No one investigated the effect any further until decades later when Becquerel repeated essentially the same experiment on that gray day in March 1896.

III. ON RADIOACTIVITY, A NEW PROPERTY OF MATTER THE NOBEL LECTURE, 1903

The most comprehensive description of the research and discovery, with illustrations, was presented in Becquerel's lecture that can be read here.
https://www.nobelprize.org/uploads/2018/06/becquerel-lecture.pdf .

IV. THE BECQUEREL UNIT

The becquerel (symbol: Bq) is the unit of radioactivity in the International System of Units (SI). One becquerel is defined as an activity of one per second, on average, for aperiodic activity events referred to a radionuclide. For applications relating to human health this is a small quantity, and SI multiples of the unit are commonly used.

The becquerel is named after Henri Becquerel, who shared a Nobel Prize in Physics with Pierre and Marie Curie in 1903 for their work in discovering radioactivity.

The becquerel succeeded the curie (Ci), an older, non-SI unit of radioactivity based on the activity of 1 gram of radium-226. The curie is defined as 3.7×1010 s−1, or 37 GBq..

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ROSALYN YALOW

NOBEL PRIZE in Physiology or Medicine 1977

"for the development of radioimmunoassays of peptide hormones"

L. Rothenberg

Dept of Medical Physics. Memorial Sloan Kettering Cancer Center
1275 YORK AVE, NEW YORK , NY 10065 UNITED STATES

I. INTRODUCTION

Rosalyn Yalow was born on July 19, 1921, and grew up in and lived almost her entire life in New York City, except for 3 and ½ years when she was a graduate student at the University of Illinois. Her mother, Clara Zipper came to the U. S. from Germany at the age of four and her father, Simon Sussman, was born on the Lower East Side of New York, a Melting Pot for immigrants from Eastern Europe. The fact that her parents came from humble backgrounds did not stop Rosalyn and her brother, Alexander, from striving for something greater. Rosalyn began to read before she began preschool. By 7th-grade Rosalyn was committed to mathematics, and then her chemistry teacher at Walton High School, a public secondary school, aroused her interest in chemistry and science in general. When she went to Hunter College, the college for women in New York City's free college system, her interest was diverted to physics, and particularly to nuclear physics, which many considered the world's most exciting field in the late 1930's, because it seemed that every major experiment brought a Nobel Prize. Rosalyn was very excited to read the biography of Madame Marie Curie which had just been published by Eve Curie, Marie's daughter.

Rosalyn also remembered being greatly excited by having attended a lecture by Enrico Fermi in a packed lecture hall at Columbia University. Although her family thought that the best career for her would be as an elementary school teacher, she persisted in achieving a career in physics. Although she initially agreed to business school with the intent of becoming a stenographer, she was eventually offered a teaching assistantship at the University of Illinois in Champaign-Urbana. There, Rosalyn not only pursued her physics career, receiving a Ph. D. in nuclear physics under her thesis director, Maurice Goldhaber, who later became the Director of Brookhaven National Laboratories, but she also met her husband, Aaron Yalow. Eventually they both received their doctorates and settled in New York City, initially in Manhattan, but later in a house in the Riverdale section of the Bronx.

Rosalyn obtained a full-time teaching position at Hunter College but also volunteered in the laboratory of Dr. Edith Quimby at Columbia and was then introduced to the "The Chief "of medical physics at Columbia, Dr. Gino Failla. (Failla and Quimby had previously established the distinguished Department of Medical Physics at Memorial Hospital, now Memorial Sloan Kettering Cancer Center, which was to be Chaired by Dr. Yalow's fellow graduate student at Illinois, Dr. John Laughlin.)
Failla recommended and insisted that Dr. Bernard Roswit, Chief of Radiotherapy at the Bronx Veterans Administration Hospital, hire Rosalyn Yalow and that began her long career at the V. A. Hospital.

Upon transitioning from her teaching position at Hunter to a full-time role with the VA staff, Rosalyn embarked on a highly productive collaboration with Dr. Solomon Berson, who had recently completed his residency in internal medicine at the Bronx VA. Their collaborations continued from around 1950 until 1968, when Dr. Berson left their laboratory to assume the Chairmanship of the Department of Medicine at Mt. Sinai School of Medicine. Unfortunately, Dr. Berson suffered a premature death four years later. Because Dr. Yalow's work on Radioimmunoassay, described in detail below, was done with Dr. Berson, many assumed that she would never be awarded a Nobel Prize for their work – they were to be proven wrong in 1977. In addition to the Nobel Prize, Rosalyn Yalow also received many other prestigious awards: she was Distinguished Service Professor at Mt. Sinai School of Medicine, membership in the National Academy of Sciences, Albert Lasker Basic Medical Research Award, and many others.

Rosalyn and Aaron Yalow had two children, Benjamin and Elanna, Benjamin became a systems programmer at the City University of New York and Elanna pursued a Doctoral degree in Educational Psychology at Stanford University. Aaron Yalow was a well-known medical physicist as well as a popular physics professor at Cooper Union university in New York City.

II. HER RESEARCH AND CONTRIBUTIONS

Radioimmunoassay: Fallout from a seemingly unrelated study

Dr. Arthur Mirsky had hypothesized that maturity-onset diabetes might not be due to a deficiency of insulin secretion but to abnormally rapid degradation of insulin by hepatic insulinase.

To test this hypothesis, Drs Berson and Yalow studied the metabolism of ^{131}I-insulin in diabetic patients on insulin and in non-diabetic subjects. Their hypothesis was that the retarded rate of insulin disappearance was due to the binding of labelled insulin to antibodies, produced in response to the administration of exogenous insulin.

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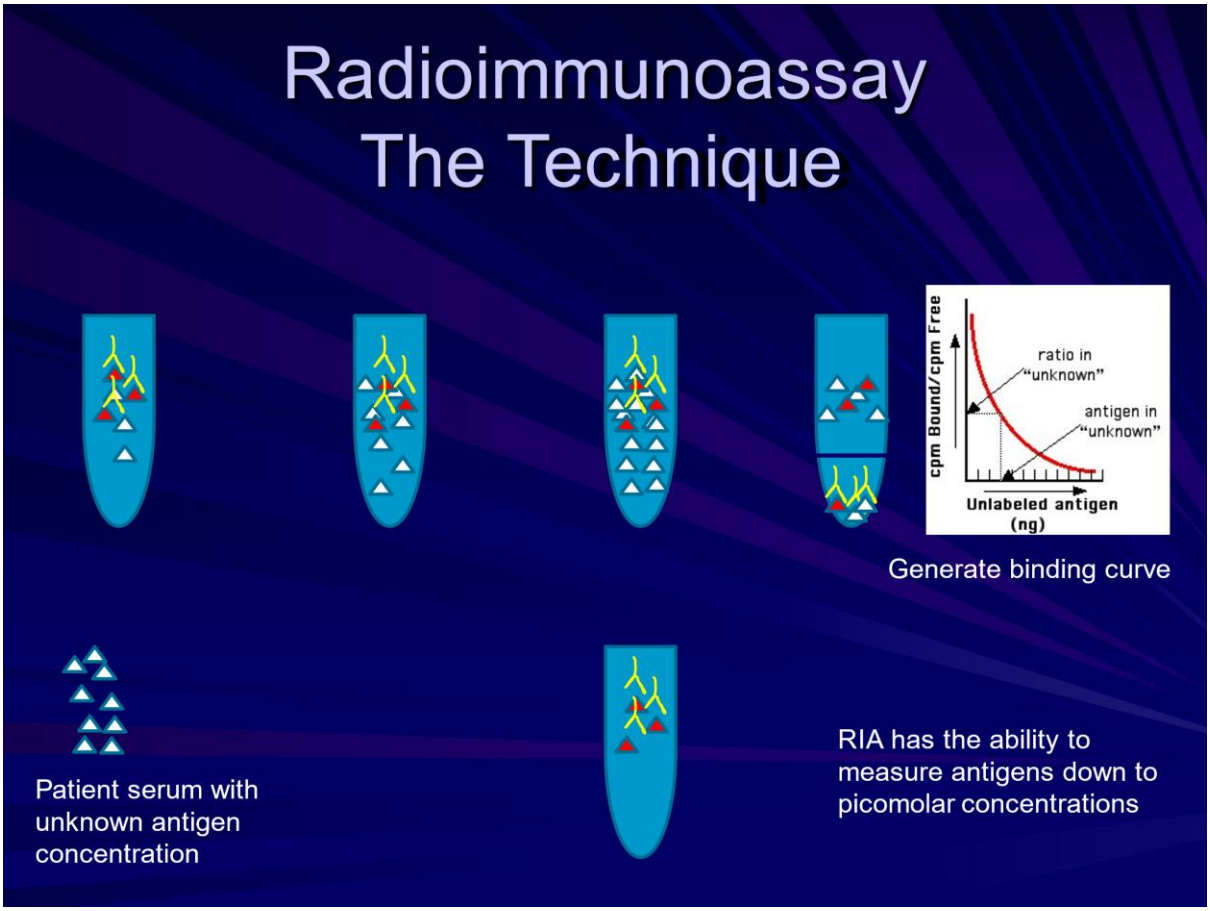
Using a variety of techniques, Berson and Yalow were able to demonstrate the ubiquitous presence of insulin binding antibodies in insulin treated diabetic subjects.

Yalow and Berson



This concept was so foreign to immunologists of the time that Dr. Yalow's paper was rejected by Science.

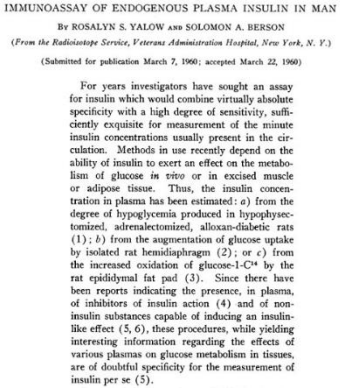
It was then sent to the Journal of Clinical Investigation where it was initially rejected there as well. The Journal editor Stanley Bradley said amongst other comments "The second major criticism relates to the dogmatic conclusions set forth which are not warranted by the data". Finally, the journal accepted this landmark study provided that the authors would remove the use of the word insulin antibody from both the paper title and the Conclusions.

The Legacy

The blood concentrations of many substances have been measured by radioimmunoassay including insulin, thyroxin, thyroid stimulating hormone, estrogens, testosterone, human chorionic gonadotropin, and gastrin.

"The radioimmunoassay principle is not limited to immune systems. The specific antibody can be replaced by any specific binding protein in plasma, a specific enzyme or tissue receptor site."

This is a truly universal vision and shows the importance and enormity of Berson and Yalow's discovery.



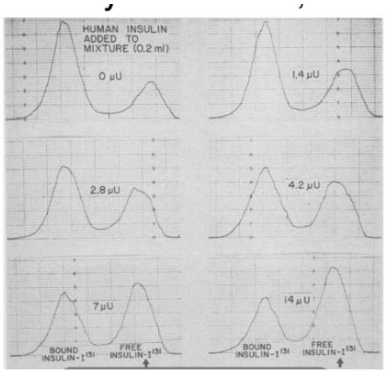
IMMUNOASSAY OF ENDOGENOUS PLASMA INSULIN IN MAN

By ROSALYN S. YALOW AND SOLOMON A. BERSON

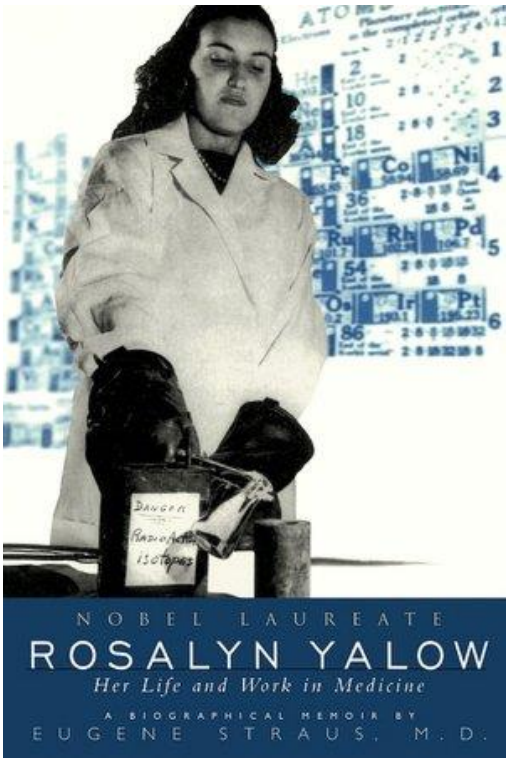
(From the Radioisotope Service, Veterans Administration Hospital, New York, N. Y.)

(Submitted for publication March 7, 1960; accepted March 22, 1960)

For years investigators have sought an assay for insulin which would combine virtually absolute specificity with a high degree of sensitivity, sufficiently exquisite for measurement of the minute insulin concentrations usually present in the circulation. Methods in use recently depend on the ability of insulin to exert an effect on the metabolism of glucose *in vitro* or in excised muscle or adipose tissue. Thus, the insulin concentration in plasma has been estimated: *a*) from the degree of hypoglycemia produced in hypophysectomized, adrenalectomized, alloxan-diabetic rats (1); *b*) from the augmentation of glucose uptake by isolated rat hemidiaphragm (2); or *c*) from the increased oxidation of glucose-1-C^{14} by the rat epididymal fat pad (3). Since there have been reports indicating the presence, in plasma, of inhibitors of insulin action (4) and of non-insulin substances capable of inducing an insulin-like effect (5, 6), these procedures, while yielding interesting information regarding the effects of various plasmas on glucose metabolism in tissues, are of doubtful specificity for the measurement of insulin per se (5).



III. PROMOTION OF WOMEN IN SCIENCE



Concerns about Discrimination of Women in Science:

Throughout her years of undergraduate and graduate education, Rosalyn Yalow always felt that she had to far exceed the efforts of her male fellow students in order to be recognized. Also, since obtaining funded positions in graduate education was extremely difficult at the time when she was a student, she never stopped campaigning for women in science. She herself was greatly inspired by the work of Marie Curie. At every opportunity Dr. Yalow pushed for greater opportunities and greater recognition for women in science, never having forgotten that, when she graduated from her undergraduate studies, it appeared that the only opportunities would be in either in elementary school teaching or stenographic work.

Rosalyn Yalow stands out as a model for all young women contemplating a career in scientific endeavor.

IV. Activities in Medical Physics Organizations

RAMPS:

The Radiological and Medical Physics Society of New York (RAMPS) was founded by a group of medical physicists in the New York City area. During the mid-1940's, physicists associated with medical institutions in the metropolitan New York City region commenced meetings to compare instrumentation and their measurements of the quantity of radioactivity in solutions in medical use. This was necessary for uniformity, and also for accuracy since the national standard available appeared to be inconsistent. This was just prior to the availability of megavoltage x rays and electrons, and the primary concern of the physicists was associated with the uses of radioactive nuclides. The clinical uses of iodine-131 and other radionuclides (phosphorus 32, yttrium-90, etc.) were being actively explored and agreement on the amount of activity being administered was essential. Such measurements led to the ''New York Millicurie," which served a vital purpose. By 1948the meetings of these medical physicists were on a scheduled basis with elected officers and records. Those initially active in RAMPS included Mones Berman, Hanson Blatz, Carl Braestrup, Giacchino Failla, Sergei Feitelberg, Elizabeth Focht, Hiram Hart, Lillian Jacobson, Robert Loevinger, Leo Marinelli, Eleanor Oshry, Edith Quimby, Edward Siegel, Aaron Yalow, Rosalyn Yalow, and others. This group established the measurement procedure for the ''New York Millicurie,' and their meetings served both scientific and professional functions. A constitution was written in 1954 by R. Yalow and J. Laughlin, and revised in 1957 by them. RAMPS has continued to grow from its modest beginning to its current membership of about 150 and conducts monthly meetings which are well attended. Their meetings usually include scientific presentations by a member or guest on physical aspects of treatment, diagnosis, nuclear medicine, or protection. Also, a symposium on a pertinent scientific topic is held annually. RAMPS welcomed the initiation of the AAPM and became a chapter in it.

When Rosalyn Yalow returned from Sweden in 1977 after receiving the Nobel Prize, she mesmerized the attendees at a RAMPS Meeting by describing many aspects of her trip to receive the award including meeting the Swedish Royal Family, considerations in choosing the appropriate formal fashion items for herself and Aaron, and a description of all of the events that took place in Stockholm.

AAPM:

The United State national organization of medical physics was established as the American Association of Physicists in Medicine (AAPM) in 1958. Both Rosalyn and Aaron Yalow were Charter Members.

V. LEGACY

Rosalyn Yalow died on May 30, 2011. She will always remain a hero to medical professionals in general for her outstanding work on radioimmunoassay and other scientific efforts, and to women in science for her tireless efforts to recognize the contributions of women and to ease the pathway for young women who wish to enter the many fields of scientific endeavor.

VI. FIGURES AND ILLUSTRATIONS

VII. REFERENCES

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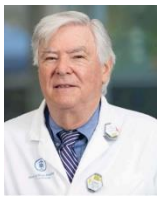
APPENDIX

Author Information



Lawrence N. Rothenberg, Ph.D. is Attending Physicist Emeritus in the Department of Medical Physics at Memorial Sloan Kettering Cancer where he is Director of the Medical Imaging Physics residency program. His main areas of interest in diagnostic radiology have included mammography, computed tomography, and education of radiology residents, medical physics students, and technologists. He is Past President of AAPM, Quimby Lifetime Achievement Awardee, Fellow of AAPM, ACR, ACMP, and HPS, and Distinguished Emeritus Member of NCRP.

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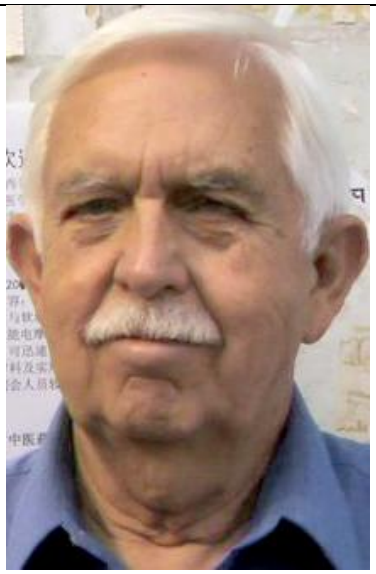
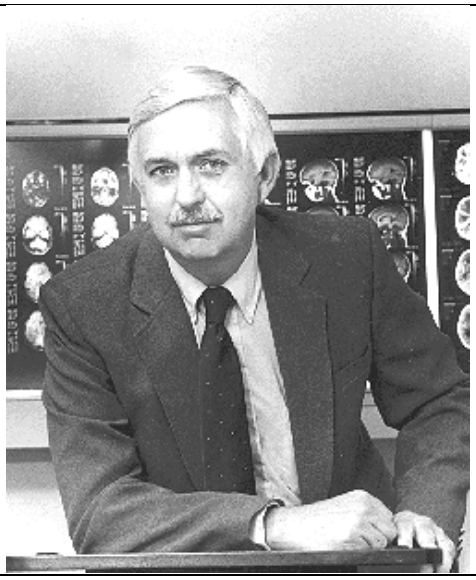
THE DOYENS OF MEDICAL PHYSICS:
PROFESSOR PERRY SPRAWLS – ONE OF THE TOP EDUCATORS SHARING VISUALS FOR TEACHING FROM A SMALL EMORY UNIVERSITY CLASSROOM TO CLASSROOMS AROUND THE WORLD

By Prof. Slavik Tabakov, Emeritus President IUPESM, President IOMP (2015-2018)





Prof. Perry Sprawls - a relatively recent photo and a photo from 1990s as Professor at Emory University

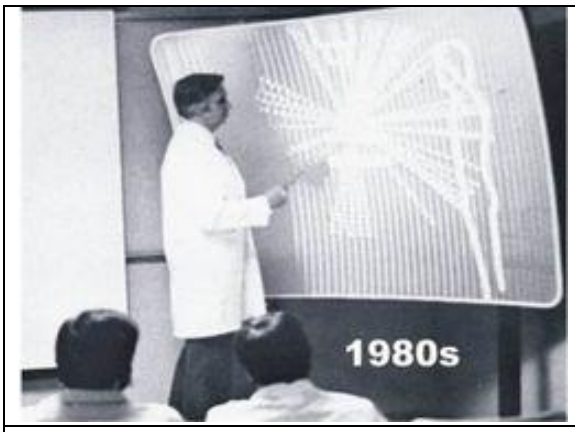
Thousands of medical physicists around the world use the excellent web site WWW.SPRAWLS.ORG - the site where Prof. Perry Sprawls has included his pioneering books on Physical Principles of Medical Imaging (especially X-ray Diagnostic Radiology) and Physical Principles of MRI. These books, written in late 20th century are still relevant with their excellent explanations of the methods and principles, but more importantly their superb explanatory diagrams have found place in many lectures and presentations. The extensive collection of visuals created throughout his career are now available for all to use on the website: Sprawls Shared Visuals for Teaching All these have been specially made by Prof. Sprawls to facilitate medical physics lecturing and are now classics in the profession. He introduced Computer Aided Teaching in radiology in 1980s and later introduced Teleteaching in the profession.

In 1994 Prof. Sprawls was invited to join the faculty of the ICTP College on Medical Physics in Trieste, Italy and from the following term he became one of its Co-Directors. He enriched the teaching there with his excellent visuals, which he continues to give to all students for free usage in their future teaching activities. In 2002 he, together with Slavik Tabakov, transformed the College into a "Train-the-Trainer" activity and hundreds of colleagues from Low and Middle Income (LMI) countries continue to use all College materials to start new teaching activities in their own countries. Alongside this Prof. Sprawls travelled to many countries to provide and help in the development of medical physics education programs in support of global healthcare. In 2003 he was awarded the inaugural IOMP Harold Johns Medal for Excellence in Teaching and International Education Leadership. He further pioneered teleteaching in the profession, making use of Internet tools for further disseminating medical physics education. In 2010 he received the AAPM Annual Award for Innovations in Education for his project: Collaborative Teaching; A model for Enriching the Medical Physic Learning Environment and in 2011 the Award for his development of A Model for Clinically Focused Physics Education.

In 2006 Prof. Sprawls joined the huge team of EMITEL project, developing the first e-Encyclopaedia of Medical Physics. He continues to take active part in the project and became one of the Editors of the Encyclopaedia. He continues with this role also in the recently published (2022) 2nd updated edition of the Encyclopaedia.

In 2012 Prof. Perry Sprawls and Prof. Slavik Tabakov were elected as Co-Editors-in-Chief of the IOMP Journal Medical Physics International (MPI) – a new Journal dedicated to educational and professional topics in the profession. This open access e-Journal quickly became one of the most read journals in the profession with

thousands of readers per month. In 2022 Perry Sprawls, together with Slavik Tabakov and Geoff Ibbott became the inaugural Co-Editors-in-Chief of the new journal Medical Physics International – History Edition, dedicated to the history of our profession.



Prof. Perry Sprawls as developer of Computer aided education in Radiology in the 1980s and pioneering teleteaching in the 2000s

Prof. Perry Sprawls (sitting in the middle) with faculty and students of the College on Medical Physics 2002

Perry Sprawls. was born on a farm in South Carolina, USA in 1934. After attending the local public schools, he enrolled in Clemson University obtaining three degrees – B.S. in physics, M.S. in nuclear science, and Ph.D. in bioengineering. After completing his military service and working for two years on the staff of a major research laboratory, he joined the faculty of Emory University in Atlanta, USA, for 45 years in the Radiology and Physics Departments.

After retiring from Emory University in 2005 and becoming a Distinguished Emeritus Professor, his family created the Sprawls Educational Foundations, www.sprawls.org , to support and provide free and open resources for medical physics education around the world.

The beginning of his career as a clinical medical physicist in the 1960s coincided with the introduction of most of the advanced imaging modalities: Mammography, CT, MRI, and Digital Radiography. Prior to that time, radiography and fluoroscopy, the two X-ray imaging modalities were relatively simple to operate with just a few technique factors to adjust. The newer modalities were all more complex with different physical principles and more adjustable factors affecting image quality and other factors including radiation exposure to patients. His work as a clinical physicist in a large hospital and affiliated clinics was collaborating with and helping the medical staff understand and optimize the procedures with these more complex imaging modalities. It was a learning opportunity in two ways. First, direct “hands-on” experience with the new modalities and their clinical applications, and second, an understanding of what physics topics radiologists and other medical professionals needed to know to effectively and safely use the imaging modalities.

Since these topics were not included in previous educational programs for radiologists, technologists, and medical physicists, there was a need for Continuing Education (CE) Courses on these topics. This became a major activity of Prof. Sprawls, especially in MRI. At Emory he was Director and principal faculty of the Magnetic Resonance Education Canter that provided CE courses attended by radiologists from throughout the USA and many other countries. He also provided courses in other countries in Europe, Central and South America, China and India.

Prof. Sprawls began his academic career at Emory University teaching general and nuclear physics in a traditional classroom as had been used for many years. The only "technology" was a writing board and a few pieces of dusty chalk. His concept of the traditional classroom was it as a "box" in which we enclosed students separating them from the physical universe they should be learning about. He realised there that classrooms needed "windows" through which the students could view elements of the physical universe as discussed by the teachers. This was to be the subject of much of his research and development projects throughout his career. The first activity, in collaboration with other faculty members, was to install image projectors in the classroom and the development of physics demonstrations that could be projected onto a large screen.

As Prof. Sprawls explains his work: Building on the concept that a knowledge of physics, especially medical physics, is a mental representation of the actual physical universe and is a complex network of images, concepts, verbal descriptions, and quantitative/mathematical relationships. A distinction is made between sensory concepts, especially visual concepts, and symbolic representations, words and mathematical symbols. The value of physics knowledge to support specific activities depends on the knowledge structure and is very different for different activities. For Radiologists and Radiology Residents the difference between getting good scores and passing examinations compared to conducting and optimizing imaging procedures. A knowledge of sensory concepts, especially visual, supports several functions The significance is how these knowledge structures are formed or learned. The symbolic representations can be learned in a traditional classroom with lectures and writing on a board or projected on a screen with an overhead projector. The formation of sensory concepts requires observation and viewing the elements and interaction of the physical universe, either directly or through appropriate visuals. It is the visuals that provide classroom "windows" through which the physical universe can be observed.

Prof. Sprawls further expands his activities into Collaborative Teaching, using the concept that learning is a natural human process that occurs when a learner/student observes and interacts with the immediate environment and is an ongoing and continuing process. Teaching is the process of helping someone learn and is in several forms. One way is the traditional classroom teacher, who interacts directly with the learners/students with lectures and discussions. The other way is a teacher who helps students learn by providing education resources, including textbooks, but of special interest here, visuals that can be used by the classroom teacher to provide more effective classroom presentations. This forms the concept of Collaborative Teaching.

His concepts for teaching medical physics are now used in almost all teaching in the profession where his specially made visuals have taken part in the education of thousands of students in medical physics. He continues to be active in the profession and apart from his work with a large international team in the updating of the Encyclopaedia of Medical Physics, he took part in the authorship of the book "Introduction to Medical Physics". He also continues to be Co-Editor-in Chief of the Journal MPI-History Edition.

Perry Sprawls the Historian: Especially in the more recent years, he has recognized the value of documenting and preserving the history of medical physics and related clinical applications. This was encouraged as most of the developments, that are now history, occurred during his career and he had memories of many and personal experience in some, including mammography, CT, MRI, the evolution of film-intensifying screen radiography and digital radiography. He is using his experiences, memories, and archive of documents from the past to publish articles on this history. Links can be found on the website, www.sprawls.org ,

Prof. Sprawls with his late wife Charlotte and their son Charles (a professional vocalist in New York) have always had special interest and supporters of classical music, with Perry serving as President of the local Opera.

Throughout much of his life, he has been especially active in the Baptist Church, in various leadership positions and educational activities. In his free time Perry cares for his excellent garden – developed on an initially barren place.

Prof. Perry Sprawls receives the ICTP Gratitude Plaque (in his 80s) and currently at his garden in Black Mountain, NC (in his 90s).

After retiring from the practice of clinical medical physics in the hospital and clinics, Dr. Sprawls continues using that valuable experience to support his activities an educator

THE DOYENS OF MEDICAL PHYSICS:
PROFESSOR LUCIANO BERTOCCHI – THE MAN WHO MADE ICTP A GLOBAL HOME FOR MEDICAL PHYSICISTS FROM LMI COUNTRIES

By Prof. Slavik Tabakov, Emeritus President IUPESM, President IOMP (2015-2018)


Prof. Luciano Bertocchi – a relatively recent photo and a photo from 1990s as ICTP Acting Director

There is hardly a medical physicist from the Low and Middle Income (LMI) countries, who has not been aware of the tremendous role, which ICTP has in spreading medical physics activities in all corners of the world. The International Centre for Theoretical Physics (ICTP) at Trieste, Italy has been opened in 1964 in Trieste by the Nobel Laureate in physics Prof. Abdus Salam (1926-1996). After Prof. Salam's death ICTP has been named Abdus Salam International Centre for Theoretical Physics. This unique institution, operating under the aegis of UNESCO, IAEA and the Italian Government, has always been an international hub for research, education and training.

Prof. Luciano Bertocchi has worked with Prof. Abdus Salam from the establishment of the ICTP. He and his colleague Giorgio Alberi initiated activities in the field of medical physics in 1982 when ICTP hosted an International Conference on the Applications of Physics to Medicine and Biology. This was followed by a second such conference in 1983 with 259 international delegates. Soon after this Conference Giorgio Alberi passed away and these activities were continued by Prof. Bertocchi. Thus the first workshop on Medical Physics with colleagues from LMI countries was organized in the same year, 1983. The success of these conferences, and the need of developing Medical Physics also in Third World countries, convinced ICTP that it was the right time to expand its training activities in the field of medical physics. Two more Workshops on Quality Control in Medical Physics X-Ray Diagnostic Equipment followed in 1985 and 1986, organized by Prof. Bertocchi and Dr Anna Benini (at that time IAEA Expert). This led to the opening of the College on Medical Physics in 1988 - a four week activity, which from its first run attracted 68 scientists from LMI countries. This extremely useful activity continues to this day and Prof. Bertocchi was its Local Co-Director until his 90th anniversary. Currently over 1500 scientists from 82 LMI countries have attended this regular (now biannual) ICTP College. Many of them have started medical physics activities in their own countries. This way the global impact of the College on Medical Physics has reached now a very significant part of the medical physicists in LMI countries, who are directly or indirectly related with ICTP.

In 2014 Prof. Luciano Bertocchi arranged the establishment of the unique Master programme in Advanced Medical Physics, which he inaugurated together with Prof. Renato Padovani and Prof. Renata Longo. This activity was based on a cooperation between ICTP and the University of Trieste with the strong support of the Italian Association of Medical Physics, and the IAEA. Thus the students from this Master programme not only attend full set of Master-level education modules, but also pass clinical training. So far over 200 students from LMI countries have graduated this Master programme.

Prof. Luciano Bertocchi (right) with students from the 3rd MSc cohort and ICTP and University of Trieste officials, 2017

Prof. Luciano Bertocchi (middle) with faculty and students from ICTP College on Medical Physics, 2024

Prof. Luciano Bertocchi was born in 1933 in a small village in the Alps - at the triple corner between Italy, Austria and Slovenia. The 500 inhabitants of the village speak 4 languages: Italian, German, Slovene and Friulano.

After the High School in Udine, Prof. Bertocchi graduated Physics in Bologna with a thesis in Dispersion Relations under the guidance of Giampiero Puppi. During his military service in Padova he was able to go to the Padova Physics Department, where he started his scientific cooperation with Sergio Fubini - a cooperation which marked his scientific career. In the Fubini group he achieved important scientific results: one was the relativistic Regge Poles derivation from the ladder Feynman Diagrams; another was the detailed phase behaviour of the scattering amplitude at the classical turning points. Luciano remembers that many years after this, somewhere in the 1980s he met Dr Michael Berry, known for the "Berry Phase". When he was introduced to him, Dr Berry commented: "Are you the Bertocchi, of the Bertocchi, Fubini and Furlan Paper? This is the paper where I found the inspiration for the phase, known as the "Berry Phase".

Prof. Bertocchi worked in Torino, where Fubini was Professor, and afterwords for two more years at CERN as a Research Fellow. In CERN he started a new phase in his scientific research: the multiple scattering of hadrons with nuclei – cooperating with Roy Glauber. In this area an experimental group from Trieste, directed by Giuseppe Fidecaro, was working at CERN on the high energy scattering experiment on deuterium (to check the interference between single and double scattering). Prof. Bertocchi and his late cooperator Giorgio Alberi developed the relativistic single and double relativistic scattering theory. The collaboration with the Fidecaro group was one of the reasons for Luciano's moving to the Trieste University after his CERN Fellowship. Another reason for this move was the scientific collaboration with Giuseppe Furlan. Also another reason was the fact that he would work in a city close to his native village. But the most important reason was the foundation in Trieste of the ICTP - the International Centre for Theoretical Physics (where he is associated to this day). Initially he was scientific consultant in ICTP, after this was for many years Deputy Director to Prof. Abdus Salam, and finally he was Acting ICTP Director (during the illness of Prof. Salam).

In Italy, a scientific career is always accompanied by teaching. Thus Prof. Bertocchi was lecturing courses in classical electrodynamics, in quantum mechanics, in the structure of matter. In 1972 he was appointed as Full Professor in Theoretical Physics. After this he was lecturing also Theoretical Nuclear Physics at the Trieste University. During this period, Prof. Edoardo Castelli was starting a group on experimental Medical Physics in Trieste. He convinced Prof. Bertocchi to include in the Nuclear Physics course a section on Imaging Methods in Medical Physics. This later evolved in a full course on Imaging Methods in Medical Physics. This in fact started

his interest in Medical Physics. Initially he started with a series of workshops in ICTP, and later in the form of two much bigger events. The first was the College in Medical Physics, established in 1988 and held every two years since this time. During the College in Medical Physics Prof. Luciano Bertocchi collaborated with the other Co-Directors over the years: Dr Anna Benini, Prof. John Cameron, Prof. De Guerrini, Prof. Mascarenhas, Prof. Perry Sprawls, Prof. Slavik Tabakov, Prof. Donald G Grey, Prof. Franco Milano, Prof. Renato Padovani and others.

Prof. Luciano Bertocchi's interest in medical physics education continued in the EU project EMERALD, where from 1995 he represented ICTP. This project created the first e-learning in medical physics and received the EU Award for vocational education – the Leonardo da Vinci Award in 2004. Later Prof. Bertocchi took part in the medical physics Conferences in ICTP (associated with EMERALD and its subsequent projects) - in 1998, 2003 and 2008. Recently (in his late 80s) Luciano became one of the authors of the book "Introduction to Medical Physics".

One of the most important contributions to the profession, led by Prof. Bertocchi, was the creation of the unique Master in Advanced Medical Physics – a cooperation between ICTP and the University of Trieste, supported by the IAEA. Starting in 2014 this Master programme, orientated to colleagues from LMI countries, runs every year. During the Master programme Prof. Luciano Bertocchi was for 10 years one of the main leaders, together with Prof. Renato Padovani, Prof. Renata Longo and others.

Alongside physics and medical physics Prof. Bertocchi was sportsman of international calibre in cross-country skiing. He was for 15 years member of the Italian University National Cross-Country Skiing team, taking part in 4 University Winter Olympic Games, where his team won twice the relay competition. He is also an expert in long ski running (cross-country ski marathon). He has made twice the enormous 90 Km ski races (in Norway and Germany), as well as 43 times the Italian 70 km ski race "MARCIALONGA". Prof. Luciano Bertocchi is indeed one of the 10 Lifelong Senators ("SENATORI A VITA") of the Marcialonga.

Prof. Luciano Bertocchi has always been close to his family - his late wife Liliana and his children, Elena and Bruno. Until his 90th anniversary he continued to lecture at the MSc in Medical Physics and to support the College on Medical Physics in ICTP. Part of his many awards is the inaugural Spirit of Salam Award of ICTP.

Prof. Luciano Bertocchi competes at the 70km Marcialonga cross-country ski competition (in his 80s) and part of his ski trophies

SEVENTY-FIVE YEARS OF ADVANCES IN PHYSICS AND ENGINEERING APPLIED TO MEDICINE IN EDINBURGH; 1936 -2010

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Abstract:
This paper reviews the main developments concerning the application of physics and engineering to medicine in Edinburgh from the 1930s to 2010, with brief mention of activity post 2010 for the purposes of continuity.

Keywords: Medical Physics, Medical Engineering, Bioengineering, Edinburgh

I. INTRODUCTION

Medical Physics in the UK mainly started with scientific support for the use of ionising radiation for diagnosis and therapy in the early years of the 20th century. However, physicists and engineers had been involved in medicine in many areas prior to this, including optics, electrophysiology and biomechanics [1, 2]. The Edinburgh Medical School was founded in 1726 and from its inception, teaching was influenced by the Newtonian scientific approach. Medical students attended lectures on physics in the university Natural Philosophy (Physics) department from at least the 1820s, with formal courses on physics principles for medicine (and 'medical physics') being presented from at least the early 1830s and a physics lecturer specifically appointed into the School of Medicine in the 1880s [1]. This was Alfed Daniell who taught to his own 1882 'Principles of Physics' textbook, later (1896) publishing a more focussed text, Physics for Students of Medicine. His successor, Dawson Turner, published a widely-used text, 'Manual of Practical Medical Electricity' in 1893, updated in the 1902 edition to add Röntgen Rays and Finsen Light, radiology having begun in Edinburgh in October 1898, so bringing us to the modern medical physics era.

The first half of the 20th century saw the growth of hospital physics and the first medical physics and medical engineering departments in the UK being established. The professional body for medical physics, the Hospital Physicists Association (HPA), was formed in 1943 with 53 members. One of those was Charles Murison, the first full-time hospital physicist employed in a Scottish hospital, who had taken up post at Edinburgh Royal Infirmary (ERI) in 1936, working single-handedly to support radiotherapy.

By 1957 there was established activity in Edinburgh in both medical physics and medical engineering, involving both the NHS and University. However, in comparison to other major teaching hospitals, Medical Physics had been slow to develop in Edinburgh. Dr (from 1966, Professor) John Greening (1922-2015) was appointed in 1957 to set up a joint NHS/University Department of Medical Physics and Medical Engineering (DMPME), which he led until his retirement in 1986. This initially combined the existing activities in medical instrumentation and radiotherapy physics, with sites at the ERI and the Western General Hospital (WGH). Subsequent growth in DMPME involved activities in rehabilitation engineering, nuclear medicine, ultrasound, MRI and biomechanics. Outside of DMPME a significant growth to 2010 was the rise of bioengineering, which is also discussed.

Separation of NHS and University activities took place in many departments across the UK in the 1990s and 2000s, often resulting in jointly funded departments splitting up. DMPME split into an NHS unit and an academic unit in 2002 and the latter was itself closed in 2012. By 2010 the original DMPME had undergone gradual fragmentation, mainly into clinically led centres. In addition, the early days of the DMPME had seen much clinical research undertaken within the NHS, often with little or no external funding. However, by 2010, a significant part of research was carried out by University staff with grant funding. At the time of writing, physics and engineering activities applied to medicine in Edinburgh are spread across many geographic and organisational areas, with the history also fragmented and in danger of being forgotten

It is hoped that this article will help keep alive the memory of the internationally leading work in applications of physics and engineering to medicine in Edinburgh over the 75 or so years prior to 2010.

II. RADIOTHERAPY PHYSICS

Although there would likely have been university physics involvement in the medical applications of X-rays and radium from soon after their discovery, Radiotherapy Physics existed formally from 1936 when Charles Murison was appointed, as noted above. He had worked for Metropolitan-Vickers on their pioneering work on continuously-evacuated 250 kV X-ray tubes and brought that experience to the orthovoltage X-ray treatment facility at ERI. There was also a radium unit at the ERI, since 1903 [3], formalised in 1929 as one of a network of National Radium Centres. When the DMPME was established, the Radiotherapy Department and its physics support had recently moved from the RIE to the new Oncology Department at the WGH. The new radiotherapy facility included a 2MV van de Graaff unit and a Metropolitan Vickers 4MV linear accelerator (linac), an 'Orthotron', installed in 1955. This was one of the first five linacs in the world to be used for radiotherapy, all in the UK [4]. Murison and others at the WGH were significant contributors to the development of practical methods of dosimetry and for radiotherapy planning and treatment using these new linacs [5]. To support the new facility, a team of physicists and mechanical engineers was recruited, beginning the expansion of Radiotherapy Physics in Edinburgh. Further accelerators were added, with increasing complexity requiring the employment of electronic engineers. In the 1980's a cyclotron was installed, with a separate team of physicists and engineers, providing a facility for neutron radiotherapy for several years [6]. By 2008 there were 7 linacs in the Oncology Department and approximately 35 physics and engineering staff. The NHS Radiotherapy Physics group were split out from DMPME in 1992 and incorporated into Oncology, as the Oncology Physics Department, headed by Tony Redpath, although academic links were continued within the university DMPME. Over the period covered by this review, significant developments were made in radiotherapy dosimetry (section III) and from the early 1970s in computer applications for treatment planning and delivery, led by Redpath and outlined here.

A. Development of an early computerised 2D planning system

A Digital Equipment Corporation PDP8 computer system with 16K memory and a floating point processor was purchased by the Radiotherapy Department in 1973, aiming to computerise and replace all the manual treatment planning processes. Redpath and Vickery wrote software for external beam planning in high-level language (Fortran IV) rather than assembler code, allowing it to be understood by physicists working in radiotherapy [7].

The treatment planning process is well defined, with its objective to achieve a high and uniform dose to the target while minimising the dose to organs at risk (OAR). A quadratic programming optimisation algorithm was incorporated into the planning software to achieve this [8]. The input data for the algorithm was calculated and its execution time was instantaneous, which was far superior to lengthy manual planning. None of this was available in other Oncology departments worldwide and by request the software was distributed to around 70 centres. It was used as a standard in several countries and was known as 'The Edinburgh Software'. It attracted commercial interest and was sold by two companies, Nodecrest (UK) and Varian (USA), running on the latest currently available hardware. It was the second most used treatment planning software worldwide for many years.

Redpath developed software for checking external beam calculations, using independent machine data from the initial calculation [9]. It worked for any treatment machine and required a small number of parameters to be set for the specific machine. If initial calculation and independent check disagreed by more than 5%, a warning was displayed, providing a final quality assurance check. This software was also distributed to centres in the UK.

Software was also written to reconstruct in 3D and calculate dose distributions for brachytherapy treatments using needle and seed implants [10]. Treatment of cervix/uterus using caesium sources with optimisation of the source positions was also included and vaginal applicators for this treatment were also designed.

B. Early computer-controlled beam data collection

Commissioning a linear accelerator for clinical use involves collection and processing of beam data. Manual collection was extremely time consuming. An automated system was developed in 1974 by Redpath, Bottrill and Nieman. The water tank's drive system was modified using stepping motors linked to a planning computer, to drive the detector remotely under software control. Detector signals were measured using analogue-to-digital converters on the computer [11]. Any X-ray beam size could be measured automatically in minutes at the points required to model it in the planning system. Software was developed to smooth and normalise the data and for transfer to the planning system database. This enabled beam commissioning measurements for a treatment machine to be performed in a day instead of weeks, as well as improving data accuracy and consistency. Redpath

then used beam modelling techniques to reduce the extensive measurement of all the beam data on a treatment machine, by developing software to generate the data using a small number of measured parameters per machine [12].

C. Treatment simulation and an early simulator-based CT system

In 1984, Redpath and Wright interfaced a Grinnell (GMR-275) image-processing computer to the image intensifier on a conventional treatment simulator to capture transmitted images and developed a set of image processing filters that could be applied to the images to enhance their quality [13]. This was designed to be performed in real time by the simulator radiographers.

CT scanners were then in their infancy and not available for radiotherapy planning. This project also developed a CT facility on the simulator [14]. A shaped filter was designed and fitted to the simulator head, to reduce the signal intensity in the transmitted image so that the dynamic range of the image intensifier was not exceeded. The signal reaching the intensifier was collimated by a 2cm slit. The simulator was rotated through 360º in a minute and the transmitted profiles captured every 1º. Software was written for the Grinnell processor to perform the image reconstruction for the slice, which took less than a minute. Although the images were not CT scanner quality, they were more than adequate for 2D planning, as internal structures could be delineated and the spatial accuracy was excellent and superior to previous methods [15]. This technique was taken up by commercial companies.

D. Development of a 3D planning system and dose calculation algorithms

The move to 3D planning took place with the wider use of CT scanners in radiotherapy. Redpath developed a 3D planning system, known as Virtsim, on a PC, such that any dose calculation algorithm could be 'plugged in'. Various useful features were incorporated, including: dose-volume histograms for any organ, beam's eye view, digital radiographs after the beam exited the patient, beam shaping using multileaf collimation and dose calculation in 3D with display on three orthogonal planes [16]. The software was distributed to several radiotherapy physics departments in the UK. It was ported to a UNIX workstation and sold by a commercial company in the UK (Nodecrest). In parallel, Redpath developed several 3D dose calculation algorithms [17-19]. The method used was based on the radiation properties of an X-ray beam and modelled the scatter distribution within a heterogeneous medium. Redpath and Thwaites tested the algorithm against measurement in a variety of heterogeneous situations, with the final version going through three modification stages with each one increasing accuracy. The time needed to calculate a 3D distribution was acceptable for treatment planning.

E. Intensity Modulated Radiotherapy (IMRT)

The availability of multileaf collimators on linear accelerators in the early 1990's allowed beam portals to be shaped with increased conformality. This enabled 'inverse planning', where the 3D patient dose distribution was specified and the shape of the beam portals and the beam intensity at any point within the portals determined. This could be treated as a classic optimisation problem. Redpath adapted a simulated annealing technique to find a solution where the objective was to obtain a uniform dose to the target volume subject to OAR dose constraints [20]. The variables used in the optimisation were the beam intensity at pixels in a map defining each of the beam portals, which led to a significant number of variables in the optimisation process, typically around 4000, with the algorithm requiring 10^6 iterations to converge. Because simulated annealing is an iterative technique, convergence in an acceptable time can be difficult. However, this took approximately 1 minute to execute and the algorithm was incorporated into Virtsim. In addition, Redpath developed a model to determine output factors for conformal megavoltage X-ray beams. It worked for dynamic wedging and for both static and dynamic multileaf collimated beams [21]. In breast cancer treatment using tangential opposed wedged beams, the shape of the breast means it is not possible to achieve a uniform dose distribution throughout the target volume. Redpath and Carruthers used Virtsim to calculate intensity modulated beams instead of using wedges. Patient studies demonstrated that noticeable improvements in dose uniformity could be achieved [22].

F. Adaptive radiotherapy for bladder treatment

Radiotherapy of the bladder presents a difficult problem due to movement and deformity, including of the target volume. The development of Virtsim (including IMRT) provided a tool that was not available on commercial planning systems, as it allowed the software to be modified to investigate specific problems resulting from conformal bladder radiotherapy. This led to collaboration (2003-2008) between Redpath and Muren (Bergen,

then Aarhus), arising from the latter's 2002-03 sabbatical in Edinburgh, with the major projects summarised below.

The clinical target volume (CTV) was outlined on a set of repeat CT scans taken weekly throughout treatment. After CT image registration, the superposition of these volumes produced an envelope in which the target volume was always present. Margins were applied in all 6 directions to enclose this envelope. In radiotherapy, isotropic margins were typically applied to the planning scan. Redpath developed an optimisation algorithm, again using simulated annealing, to determine the optimum margins required to minimise the high dose volume outside the envelope. The overall values of all 6 margins were determined from analysing 19 patients. Bladder movement and margins required were seen to be largest in the superior direction [23].

A study on 45 patients investigated if a concomitant IMRT boost dose to the tumour volume on all fractions was feasible [24], to give a 20% boost above the prescribed non-involved bladder dose. The optimisation was adapted to maintain the uniformity of dose in the non-involved bladder and fulfill the dose constraints on vital structures. This was found to be feasible in over 50% of patients and the approach was clinically adopted.

CT image guided radiotherapy (IGRT) was also used to investigate if shifting the isocentre in all of the 6 possible directions could reduce the margins required. The optimisation algorithm adjusted the margins, aiming to achieve full coverage of the target volume while minimising the high dose volume outside the target volume [25]. A marked reduction in the size of the margins from their commonly used isotropic values was shown. The target volume was reduced by approximately 30% and a reduction in dose to vital organs was also achieved.

A major challenge in radiotherapy for bladder cancer is to control and account for bladder motion. In an attempt to control bladder volume variation, a series of 20 patients were given fluid intake restrictions on alternative weeks of treatment. Weekly CT scanning was performed and the isocentre shifts required to obtain full target coverage were determined, using the available optimisation technique. The potential for a large margin reduction was shown if the bladder volume is controlled [25]. This work significantly improved the setup for bladder cancer treatment.

G. A uniform framework for objective assessment and optimisation of radiotherapy images: IQWorks

A 2010 PhD (Reilly) developed software and both hard and virtual phantoms, to perform quality assurance on digital imaging equipment in radiotherapy [26]. Named IQWorks, this expanded as a collaborative national and international project to provide medical physicists with automated image analysis software for use with DICOM test images in many other imaging areas, including CT, mammography and digital radiography [28].

III. Dosimetry

A. Fundamental radiation dosimetry

John Greening had begun significant research in London in fundamental radiation dosimetry for diagnostic radiology, radiotherapy and radiation protection, notably in the theory of cavity chambers. This was continued in Edinburgh [29-32]. He had a particular interest in low energy kV beam dosimetry [33] and a 1960s PhD programme (Tony Redpath) included calorimetry [34], ferrous sulphate dosimetry [35], ion chambers [36] and solid state devices [37]. In 1966, Redpath designed and built a calorimeter to determine microwatt energies of 10-30 kV X-ray beams, measuring temperature rises ~10^{-3} ºC/min [34]. It was used to calibrate the other dosimeters listed above for clinical dosimetry use. He was seconded to The Christie Hospital, Manchester in the early 1970s to develop a similar system to measure the dose output from a 14 MeV therapy neutron generator [38], where temperature rises an order of magnitude lower presented even greater measurement challenges.

Greening supervised Alan Nahum's 1975 PhD, arising from existing radiation dosimetry work in Edinburgh. Nahum developed one of the earliest Monte Carlo (MC) codes for applications in medical physics, modelling radiation transport for MV photon and electron dosimetry [39-41]. This pioneering work laid one of the key foundations for MC methods to develop into a major tool for radiation research and dosimetry and for its many later applications in clinical dosimetry worldwide.

The above work is folded into Greening's widely-used textbook on radiation dosimetry [42]. Greening was a member of the International Commission on Radiation Units and Measurements (ICRU) for 16 years, developing international recommendations for the safe and consistent application of radiation, particularly for clinical dosimetry and radiation protection. During his ICRU activity (1966-81) he was involved in Reports 12-39.

David Thwaites joined DMPME (Radiotherapy Physics) in 1980, direct from PhD and post-doc work on light ion stopping powers [43] and continued this analysis for materials of interest for dosimetry and medical and biological applications [44, 45]. Outcomes of this work were incorporated directly into ICRU recommendations for proton and He ion stopping powers [46] and those of other light ions [47], as source data for particle therapy, for other ICRU reports and for many practical and research applications.

B. Clinical radiotherapy dosimetry and dose protocols (codes of practice)

The neutron therapy facility mentioned in section II saw significant neutron dosimetry work by Jerry Williams and others, leading to his role in producing the European recommendations for neutron dosimetry [48]. Similarly, Edinburgh's first clinical electron beam linac was installed in 1980, beginning a programme of work on electron dosimetry and electron beam treatment applications, aiming to improve accuracy and consistency of clinical electron beam use for radiotherapy. This included ion chamber dosimetry, chamber correction factors, phantoms and measurement methods [49-52]. This was led by Thwaites and the work fed directly into new UK electron dosimetry protocols for clinical use, based on the National Physical Laboratory's air kerma primary standard [53] and then on its calorimeter-based direct-dose-to-water primary standard [54], as well as into national recommendations on secondary standard instruments to be used for clinical dosimetry [55].

C. Consistency of radiotherapy doses nationally and internationally, intercomparison and audit development

National and international radiotherapy dosimetry protocols (codes of practice) aim to ensure consistency of dosimetry between centres and between countries, so that radiotherapy delivery and patient outcomes are consistent and experience can be transferred with confidence between different places and within clinical trials. However, there is still potential for practice variations in application of protocols. Dose intercomparisons can check this. An early international example was a comparison between Edinburgh (John Law), Houston, USA and Umea, Sweden in 1970 [56]. The centres exchanged dosemeters (ion chambers, LiF and ferrous sulphate) for mutual measurements of stated doses. These agreed typically within 1%, providing confidence at that level. The implementation of different dosimetry protocols can also be directly compared in detail in a few centres [57]. Remote dose output checking systems, mainly using thermoluminescence dosimeters (TLDs) were begun in the late 1960s by the International Atomic Energy Agency (IAEA) to support low-and-middle-income (LMI) country radiotherapy facilities, but limited in scope. Also in the late 1970s, the USA began TLD-based dose checks, initially to support clinical trials [58, 59]. In the 1980s, systematic national dosimetry intercomparisons began in some countries, involving on-site visits and more extensive measurements.

A UK national megavoltage photon dosimetry intercomparison was organised and run from Edinburgh (Thwaites) in the late 1980s [60]. It was planned by an Institute of Physics and Engineering in Medicine (IPEM) working group and used ionisation chambers and specifically-designed phantoms to independently measure beam calibration reference doses, non-reference dosimetry parameters and multi-field treatment-planned dose deliveries, involving on-site visits to all UK radiotherapy centres. This was followed by a similar national electron dosimetry intercomparison, with measurements carried out by Nisbet [61]. The results gave significant confidence in UK clinical radiotherapy dosimetry, showing ratios of stated doses to independently measured doses very close to unity and with small standard deviations for the time. Various minor issues were identified for improvement and also one major issue. The latter was a miscalibrated Co-60 radiotherapy treatment unit, arising from an error at the time of a source change. This had resulted in patient overdoses at that centre which were not identified until the dosimetry intercomparison visit's measurements. This had significant impact on quality initiatives in radiotherapy (next section). The intercomparison methods were applied outside the UK [62].The general methodology and regional structure that was developed led to the establishment in the early 1990s of the on-going national radiotherapy dosimetry audit network [59], with Edinburgh continuing to lead the Scottish+ group and developing a range of other innovative audits [63]. This pioneering work and subsequent expansion have been summarised [59, 63]. It led to Thwaites joining IAEA radiotherapy dosimetry audit development groups from the early 1990s [64], to support the growth of radiotherapy (and of its complexity) in LMI countries, with significant progress taking place during the period of this review and Edinburgh acting as a testing site [65]. Remote audits were gradually expanded in scope from beam calibrations in reference conditions for megavoltage photon beams, to dose parameters in non-reference conditions and for electron beams. Later (post-2010) this led into audit methodology for remote testing of advanced radiotherapy treatment parameters, with the whole system summarised in a comprehensive IAEA document [66], and also guidelines for on-site dosimetry methods to investigate identified issues and to support whole radiotherapy centre clinical audit [67].

D. Quality management in radiotherapy, accuracy analysis and in vivo dose verification

The Co-60 beam miscalibration identified in the megavoltage dosimetry intercomparison led to significant attention being given to quality and accuracy in UK radiotherapy and eventually to the introduction of formal quality management systems in all departments. These same principles were subsequently incorporated into European guidelines on structure and methodologies for radiotherapy quality management and comprehensive quality assurance [68, 69]. This also led into an Edinburgh programme of work on analysis of accuracy required and achievable in radiotherapy, over the period from 1989-2018. The work (and interim references) in the period up to 2010 is summarised in a 2013 analysis [70]. This also included a systematic programme of in vivo verification of patient delivered doses, begun in the mid-1990s using diode dosimeters and developing novel

methodology and practical approaches [71-73]. The outcomes of this work were also incorporated into European guidelines [74].

E Other: Mammography dose and risk-benefit, image quality, small field radiotherapy dosimetry

Other significant dosimetry developments in the period of interest include John Law's work over 30 years or so. Law's work covered mammography system evaluation and quality control and mammographic image quality, aiming to minimise dose and improve quality [75], and consistency in mammography doses and the evaluation of dose-based risk versus benefit of breast screening [75, 76]. This work initially supported the Edinburgh breast screening trial, a pilot study begun in the late 1970s before the UK national breast screening trial commenced in the 1980s, and then continued to inform the national system.

Edinburgh acquired a linac-mounted cone-collimated stereotactic radiosurgery system in the mid-1990s, which began a programme for clinical stereotactic radiosurgery treatment of brain lesions and a linked small field dosimetry programme. This investigated linac head and phantom scatter factors, small field dosimetry systems and methodologies, treatment planning dosimetry and dose delivery verification, much as part of a PhD (McKerracher) [77, 80]. Its biggest immediate dosimetry impact, besides preparing the clinical service, was in its investigation and evaluation of small field detectors/dosimeters [81, 82].

IV. Medical instrumentation

The first biomedical engineer in Edinburgh was David Simpson (1920-2006). He undertook a PhD, 'The development of a method of following changes in the radio-opacity of the small bones of the hand' and then worked in the Department of Surgery from 1952. He developed a series of instruments including clinical blood pressure monitors [83-85], a skin resistance measurement device [86], fetal pulse rate monitor [87], an AV shunt for repeated haemodialysis [88] and a warning device for intravenous therapy [89]. He was an early advocate of patient monitoring stations in which several parameters (temperature, heart rate, pressure etc) were displayed simultaneously [90-92]. In 1962 following the thalidomide disaster Simpson was asked to set up a prosthetics unit, (see section V below).

Jim Neilson undertook his PhD on ECG analysis graduating in 1962 and worked in this area till his retirement. Work involved development of methods to continuously record ECG data from the patient on audio tape and then to analyse the ECG data by computer [93-96]. The work was patented [97, 98] and a spin-out company 'Reynolds Medical' was set up in 1972 to develop 24 Hour ECG recording and analysis [99-101]. The Pathfinder ECG analysis was the world's first commercial automated ECG analysis machine and was released in 1980. The patient wore an ambulatory device which recorded their ECG onto audio tape, a standard 90 minute tape operating at a much slower speed to allow 24 hours of recording. The audio tape was analysed by the computer to detect arrhythmias and other cardiac events. In Edinburgh the device was extensively used in cardiology research [102-106]. Reynolds Medical continued to operate until 2006 at which point the company was bought by OSI systems (Hawthorne, USA). At the time of writing the modern version of the Pathfinder device remains available to buy.

V. Rehabilitation engineering

A. The development of prosthetic limbs following the thalidomide disaster

In the late 1950s and early 1960s the drug thalidomide was prescribed to pregnant women to help with morning sickness and sleep. The drug led to the birth of thousands of babies with severe deformities, including severe stunting of arms and legs. Thalidomide was withdrawn in 1961. In Scotland some 100-150 children were affected. David Simpson was an established biomedical engineer and was asked to set up a unit to build prosthetics for the affected children. The 'Powered Prosthetics Unit' was set up in 1963. The unit moved to its long-term home at the Princess Margaret Rose Hospital in 1965.

Artificial limbs were attached to a frame which was contained within a harness or bodice. Movement of the prosthesis was achieved pneumatically [107-110]. An important realisation by Simpson was named 'extended physiological proprioception (EPP)' [111]. The idea was that, from the perspective of the child, the prosthesis becomes a part of the child's arm or leg. The child would seek to control the movement of the prosthesis in the same way that a person is able to control the movement of a tennis racket when striking the ball. The child would use what movement they had to control the movement of the leg or arm. Over the following decade a series of arm and hand prostheses were developed of increasing sophistication by Simpson and his colleagues [112-118].

The original Powered Prosthetics Unit evolved into the Bioengineering Unit with a wider remit around general support for rehabilitation.

B. Developments leading to the i-hand and i-limb

David Gow joined the Bioengineering Unit in 1984 and continued the work on prosthetic arms. The gas power source was replaced with an electrical source, movement was controlled by rotation of threaded shafts. While this was an improvement over the gas-powered arm, the full arm could only be built in an adult male version, plus the hand was relatively unsophisticated [120].

In the early 1990s there were limited powered solutions for a prosthetic hand. Gow developed a partial hand in which a small motor rotated a spiral shaft ('worm') which in turn was connected to a wheel. Movement of the wheel resulted in flexion of the digit. A partial hand was produced with separate motor/worm for each digit, consisting of 2 digits and a thumb. This was referred to as 'ProDigits' and patented [121]. This approach over time was scaled up to produce a full hand connected to an arm, called the Edinburgh Modular Arm System (EMAS) [120], which was also patented [122]. Much of the development of these devices had been performed within an NHS routine service setting, so the engineers involved were doing this work typically within 20% of their time, and at times with little institutional support. In 2003 Gow helped set up the company 'Touch Bionics' to further develop the technology and provide a sales platform. The prosthetic arm was called the 'i-limb' and the hand called the 'i-hand'. Touch Bionics was sold to Ossur Hf (Iceland) in 2015. These prostheses have proved very successful and have transformed the lives of thousands of patients throughout the world.

David Simpson and David Gow were internationally leading figures in rehabilitation engineering. An excellent review of the career, life and work of both is provided in the book 'Making Hands' [123] and in the web resource produced by Lothian Health Services [124].

VI. Nuclear medicine

Nuclear medicine encompasses a range of diagnostic and therapeutic techniques involving radioactive isotopes. Impetus for this area increased after WW2 with the availability of a range of isotopes produced by cyclotrons. These could be used locally or be packaged for delivery to centres without a local cyclotron. For imaging of patients the invention of the gamma camera in the 1950s was a key event. Developments in nuclear medicine were undertaken by Peter Tothill (joined DMPME in 1960, was Head of DMPME 1986-1988), Mike Smith (DMPME 1974-1986) and Jim Hannan (joined DMPME in 1975 and was Head of NHS Medical Physics 2002-2011).

A. Gastric Emptying

This technique, introduced in 1966, involves ingestion of radioactive isotope and imaging using a gamma camera. In Edinburgh, techniques were developed to monitor the early period of emptying using two different markers to simultaneously monitor solid and liquid emptying [124]. These are important issues for the effects of gastric surgery [126]. Methodological studies investigated the effect of different variables on emptying including posture [127], depth of the isotope from the camera [126] and the use of radioactive inert particles or radioactive digestible material [128]. The techniques were widely used in clinical studies [129-132].

B. Calcium and bone mineral measurement

Loss of bone mineral with age, especially following the menopause, can lead to fracture. Bone mineral is lost across all bones, but key areas for fracture are the spine, hip, wrist, knee, foot and ankle.

In Edinburgh methods for measurement of bone mineral content were developed based on irradiation of the patient with a radioactive source, with detection of the radiation after passing through the patient. The radiation is absorbed by the soft tissues and bone. As the bone mineral content decreases so the absorption by bone will be less. Single-photon techniques involving a single radioactive element were developed for measurements in the forearm and hand [133-135]. Dual-photon techniques were developed for measurements in the spine [136, 137].

The use of radioactive sources was superseded in the early 1980s by the use of X-ray sources. DEXA (dual energy X-ray absorptiometry) scanners became widely available in hospitals, with machines available from several manufacturers including Lunar, Hologic and Norland. Extensive assessment was undertaken, including comparing different commercial manufacturers [138-140] and scanning arrangements [141], investigating precision and accuracy using phantoms [142], and investigating the effect of body fat and weight [142-146].

Measurement of whole-body calcium was undertaken using neutron activation analysis. This involved irradiation of the patient by neutrons generated from a cyclotron, followed by detection of gamma rays in a whole-body counter [147]. Stable calcium-48 was turned into unstable calcium-49 by activation, which during decay produced a gamma ray. Several clinical studies were undertaken in osteo- and rheumatoid arthritis [148-151].

A review of the measurement of bone mineral and calcium was published by Tothill in 1989 [152].

C. Cardiac and pulmonary function

Techniques were developed for estimation of ventricular volume and cardiac output [153-156]. These involved injection of a radioisotope bolus, recording of gamma camera activity, and fitting of a gamma variate function to the activity-time curve. The cardiac output was estimated from the ratio of peak activity divided by the area under the curve. Modification of the bolus method was undertaken for measurement of the pulmonary blood volume, involving simultaneous monitoring of the activity time curve in the pulmonary artery and left ventricle [157]. These methods were used in a series of clinical studies on patients with pulmonary and cardiac disease [158-161].

VII. ULTRASOUND

Diagnostic ultrasound imaging involves high frequency (1-20 MHz) ultrasound waves which are transmitted and received using a hand-held device applied to the patient's skin. Ian Donald and colleagues (Glasgow) developed the first 2D ultrasound scanner for use in obstetrics [162]. This involved collaboration with Tom Brown, an engineer working for Babcocks, a company which worked on industrial flaw detection using ultrasound. In Edinburgh the Ultrasound section was led by Norman McDicken (1940-2024) who joined DMPME in 1972, becoming Professor and Head of DMPME (1988-2002). Other principal investigators relevant here are Steven Pye who joined as a PhD student in 1982 and was Head of the NHS Medical Physics unit (2011-2020), Peter Hoskins who joined in 1984 becoming Professor in 2012, Carmel Moran who joined in 1991 becoming Professor in 2018, and Vassilis Sboros who joined in 1996 becoming Associate Professor at Heriot Watt University in 2024.

A. Instrument development

Following his work in Glasgow, Brown worked in Edinburgh from 1970-73 on one of the first 3D ultrasound systems using a stereoscopic approach [163]. This was commercialised by Sonicaid as the Multiplane Scanner, however this was not commercially successful, and the product was discontinued in 1979.

Early ultrasound systems relied on manual scanning of a single element transducer in which the image was built up over several seconds. McDicken's group developed a series of ultrasound systems utilising mechanically swept transducers for real time imaging. The original rocker system developed in Glasgow involved a single element which was pivoted to and fro, giving a maximum frame rate of about 20/second. The follow up system developed in Edinburgh had 4 transducers mounted on a wheel enabling a higher frame rate suitable for fetal and cardiac imaging [164, 165]. These systems were commercialised by EMI (Emisonic 4262) and Nuclear Enterprises. The latter system was used in early studies of gastric emptying and motility [166, 167].

Other developments included visualisation of biopsy needle tips on the ultrasound image [168, 169], automatic gain control for B-mode imaging [170-172] and image processing for speckle reduction [173, 174].

B. Blood velocity measurement

Doppler ultrasound concerns the measurement of blood velocities using the Doppler effect. The history of Doppler ultrasound relevant to clinical practice centres around the development of real-time spectral Doppler (blood-velocity time waveforms), and real-time colour flow (2D images of blood flow) [175]. However, this technology is simple; it only measures a single component of blood velocity, that along the ultrasound beam, and it concentrates on measurement of maximum velocity. Blood flow may be highly complex, especially in disease such as atherosclerosis. Advances in Doppler ultrasound have been concerned with techniques for estimation of 2 or 3 velocity components and 2 or 3 spatial dimensions, and techniques which improve measurement accuracy.

For Doppler beams generated using a linear array the Doppler aperture is much larger than for pencil probes. It was shown that this leads to systematic overestimation of the maximum velocity [176-178] which occurs as a result of geometric spectral broadening [178]. The typical overestimation is 20-30%, but this is angle-dependent and machine dependent. It was shown that this creates the potential for mis-categorisation of patients for carotid surgery [177]. As the error is dependent on the geometry of the transducer it can be corrected using a string phantom to estimate the error as a function of depth in order to create a look up table of correction values. This method was used in subsequent work in Edinburgh to measure maximum velocity, and related quantities such as wall shear rate and volumetric flow, with high accuracy [178-181].

Calculation of blood velocity magnitude involves alignment of an angle cursor with the vessel wall, assuming that blood travels parallel to the wall. However, blood flow may be complex and velocity vectors may not be parallel to the wall. By measurement of 2 components of blood velocity it is possible to estimate both blood flow direction and magnitude automatically without the operator having to align a cursor. A dual-beam colour vector Doppler method was developed for estimation of the velocity magnitude and direction [182]. This was used to provide early evidence for spiral flow in arteries [182]. Vector Doppler systems were developed to provide angle-independent estimation of blood velocity in a stenosis phantom using spectral Doppler [178] and colour flow

[183]. A prototype commercial vector Doppler system was developed with ATL Ultrasound (Seattle, USA) which was trialled in phantoms [184] and normal volunteers [185] showing that spectral Doppler data was angle independent.

C. Ultrasound phantom development

Ultrasound phantoms are essential for the validation of Doppler ultrasound measurements of blood velocity. By the late 1980s there were established recipes for tissue mimics for B-mode imaging, but little work on phantoms for Doppler ultrasound. McDicken reported a flow phantom in which a gear pump was used to propel the blood mimic [186]. This phantom was extended [187] in which the gear pump speed was controlled by a computer enabling a wide range of realistic pulsatile flow waveforms to be obtained. Further progress required consideration of the acoustic properties of the materials which need to be tissue equivalent. Specifications for the components of a flow phantom were defined by IEC 61685 (2001). A blood mimic which met these requirements was developed by Ramnarine [188, 189] involving the use of nylon particles to mimic the red cells. This became the international standard blood mimic and is commercially available (Shelley Medical Imaging, Canada).

For a vessel mimic, the best commercially available material was C-flex, a rubber based material (Cole Parmer, Illinois, USA). This had the correct acoustic velocity but high attenuation. The problems of distortion of the Doppler beam led to the development of flow phantoms with no vessel, so called wall-less phantoms [190]. An acoustically matching vessel was created using PVA cryogel [191]. This material is prepared as a gel which undergoes hydrogen bonding following freezing and thawing. By adjustment of the number of freeze-thaw cycles the acoustic and mechanical properties can be controlled.

Non-planar carotid phantoms were created using a rapid prototyping technique. Clone phantoms were created. One phantom was transparent for use with optical measurement techniques including LDA and PIV [192]. The other phantom was manufactured using a wall-less approach for ultrasound [193].

Reviews by Hoskins discuss the specifications required for flow phantoms [194] and their design and use [195].

D. Cardiac imaging techniques

Tissue Doppler imaging (TDI) concerns the visualisation of moving tissues, especially the myocardium, and was developed by McDicken in a collaboration with Acuson (Mountain View, USA) [196]. TDI is similar to colour flow imaging of blood, but instead the colour image is related to the velocity of moving tissues. Adjustments are made to the machine settings to account for the lower velocities of the myocardium and the much higher Doppler signal strength compared to blood. In addition to 2D imaging it is possible to acquire TDI data along a single line and display this as a function of time [197, 198]. From the 2D TDI velocity data it is possible to estimate how much the tissue has stretched or compressed (strain) then from this the strain at each pixel as a function of time (strain rate) [198]. The TDI technique was patented by Acuson [199] and is available as standard on commercial ultrasound machines.

Intravascular ultrasound (IVUS) involves acquisition of ultrasound images from within the artery (or heart) using an ultrasound transducer mounted on a catheter. For coronary artery imaging the catheter is inserted into the femoral artery and pushed upstream to the heart. IVUS imaging is undertaken at frequencies of 20-40MHz for which the axial spatial resolution is 100-200μm. Radiofrequency (RF) data was acquired from atherosclerotic plaque excised from coronary arteries. A number of different features of the RF data were investigated for their ability to classify different regions of the plaque according to the histology; eg. ‘lipid’, ‘loose fibrotic tissue’, ‘dense fibrotic tissue’, ‘calcium’ [200-202]. These methods were incorporated into a commercial IVUS system for classification of plaque in-vivo (Volcano Corp, San Diego, USA).

E. Contrast agents

Early work in the field focussed on generation of basic science knowledge, engineering solutions (in signal and image processing) and assessment of clinical utility in cardiovascular disease and abdominal radiology. In the 1990s there was an emphasis on in vitro investigation on microbubble physical behaviour with a view to understand how to use ultrasound scanners in the diagnosis of cardiovascular disease and the variabilities associated with the administration of microbubble contrast agents [203-206].

In Edinburgh this work led to experimental physics investigations [207-210] which fed into theoretical investigations [211, 212]. The most important achievement was the first evidence that individual microbubbles produced scatter that could be detected by ultrasound imaging equipment [213]. This made Edinburgh one of the few research centres that investigated the acoustics of single microbubbles, undertaken using a novel acoustic setup for the measurement of single microbubble echoes. Using this methodology there followed fundamental research including acoustic studies on microbubble resonance [214], on decay/memory effects [215, 216], and on bubble behaviour inside capillaries [217] or next to a boundary [218]. These studies were key to understanding

microbubble scatter evolution in a real imaging setting, thus leading to signal processing research [219] and subsequently the development of in vivo ovine tissue model as a vascular regulation model and in order to generate new image analysis on perfusion quantification [221]. This research had a number of impacts, most importantly it paved the way to the generation of a new ultrasound field namely super-resolution ultrasound, where single microbubbles were tracked using image analysis tools in order to delineate their host vessels, thus creating very high resolution ultrasound meta images that are similar to those found in other fields such as super-resolution microscopy, astronomy and defence sensing.

VIII. MRI

MRI was the last of the major medical imaging techniques to gain widespread clinical use. Its origins can be traced to the discovery of magnetic resonance by Isidor Rabi (Columbia, USA) in 1938. The first MR image was produced in 1973 by Paul Lauterbur (Stony Brook, USA). Peter Mansfield (Nottingham, UK) developed echo-planar imaging, reducing imaging time to seconds which allowed future developments such as diffusion and functional brain MRI. John Mallard (Aberdeen, UK) developed the first MRI whole body scanner from which the first whole body image was produced in 1980 [222].

In Edinburgh a low field (0.08T) MRI system (M&D Technology, Aberdeen) was installed in 1984, under the leadership of radiologist Jonathon Best, with Mike Smith responsible for MRI physics. Developments included gated acquisition for cardiac imaging [223], methods for measurement of brain water [224], blood velocity imaging [225], and demonstration of pulsatile flow in cerebrospinal fluid [226].

Work on brain MRI was led clinically by neuroradiologist Joannna Wardlaw at the Western General Hospital [227]. A 2T Elscint MRI unit was funded from 1996, with the Brain Research Imaging Centre for Scotland opening in 1998. This system was replaced in the early 2000's by a 1.5T GE system that remained in operation until 2018 performing a wide range of clinical and technical development studies, principally focused on structural brain MRI. In the 2020 paper [227] Wardlaw comments that research using these units has changed stroke clinical guidelines worldwide, scanned >30,000 patients and led to >£120M research funding. There has been considerable physics support for these activities; prior to 2010 this was Ian Marshall (joined DMPME 1980, Head of the Academic Medical Physics Unit 2006-2012) and Mark Bastin (joined 1997). There were technical developments in MR spectroscopy [227-230], diffusion tensor imaging [231-236] and measurement of brain temperature [237, 238]. In addition to stroke, these methods were used in a range of clinical studies, including brain tumours [239], schizophrenia and bipolar disorder [240], and cognitive ageing [174], including via imaging of the Lothian Birth Cohort (LBC) of 1936 and discussion also of work on the 1921 LBC [241]. These techniques have all been further developed post 2010 and continue to be used in many clinical studies.

The use of MRI to measure blood velocity and wall shear rate are noted in section IX below.

IX. BIOMECHANICS

The term 'biomechanics' in the UK is often interpreted as part of rehabilitation engineering, usually involving gait analysis. The term used here is the wider international definition; 'the study of structure and motion of biological systems'. At the patient level this includes aspects of blood flow, the behaviour of arteries and the musculoskeletal system, surgical interventions and prostheses. Biomechanics is highly cross disciplinary and most work involves interactions between physicists/engineers and clinicians/biologists. Any one project will usually use 2-3 technologies, drawn from medical imaging, computational modelling, material science, metrology and others.

A. Heart valve development

Artificial valves were developed in Edinburgh by Norman McLeod [243-245] working in the Department of Physics with the initial version patented in 1970 [246] and an updated version in 1985 [247]. They were of a tilting design and tested extensively in a flow phantom and in animals, but were not commercialised for use in humans. Testing in a flow rig [248] used milk, with its clotting being used to mimic the build-up of thrombus on the valve surface [249-251]. This method was subsequently used to investigate commercial artificial valves [252].

B. Arterial biomechanics

A simple model of blood flow is that the velocity direction is parallel to the vessel wall, as noted in section VII.B. Flow in arteries may be complex; characterisation of a 3D flow-field requires 7 components; 3 spatial (x, y, z), 3 velocity (v_x, v_y, v_z) and time. In the 1990s ultrasound, MRI and computational fluid dynamics (CFD) had

sufficiently matured to enable the measurement of complex flow fields in-vivo and to estimate new flow-field quantities such as wall shear stress (WSS) which may be useful in clinical diagnosis.

Early work on colour flow vector Doppler involved sequential collection of data with the beam steered to the left followed by the beam steered to the right with vector compounding performed off-line. The initial application was the first ultrasound demonstration of spiral flow in the femoral artery of volunteers [182]. A single spiral shows as adjacent D-shaped regions of flow towards (in red) and away from the transducer (in blue). These techniques were used to demonstrate spiral flow in a cohort of volunteers [253]. Stonebridge went on to develop a prosthetic bypass graft which induced spiral flow, manufactured by Vascular Flow Technologies (Dundee).

Marshall developed MRI techniques for the measurement of the flow-field in carotid phantoms and the first MRI measurements of WSS [254-257]. It was shown that there was excellent agreement with the flow-field estimated using CFD. However estimated WSS was in error due to the difficulty in estimating the exact location of the vessel wall, and in estimating small velocities near the wall. Flow-field data was acquired in normal volunteers, from which standard flow-time waveforms were provided for the common, internal and external carotid arteries which have been widely used as input data in CFD studies [258].

For abdominal aortic aneurysm (AAA) rupture carries a 90% mortality rate and surgical repair is considered when the maximum diameter is greater than 5.5cm. It is known that diameter is not an accurate predictor of rupture and that there is a need for alternative measures. Studies initiated by Hoskins and Whyman investigated the use of AAA stiffness in rupture prediction. Stiffness was estimated using a combination of measured blood pressure and aneurysm wall motion measured using ultrasound. It was shown that stiff AAA are associated with increase in collagen and loss of elastin [259], however it could not be demonstrated that AAA stiffness was predictive of rupture [260]. It was thought that the assumed physical model (isolated uniform elastic ring) was too simple.

The failure of MRI to estimate WSS and of a simple model of AAA behaviour to predict rupture led to the idea that a combination of 3D imaging and computational modelling could be used to estimate WSS and tissue stress, as potential quantities for use in prediction of plaque and AAA rupture. This field was originally referred to as ‘image guided modelling’ [261] and later became known as ‘patient specific modelling’ (PSM). In Edinburgh, work on the development of protocols for PSM was undertaken in AAA using CT [262] and in carotid arteries using 3D ultrasound [263]. Studies on AAA WSS and rupture using PSM were undertaken later [264, 265].

C. Musculo-skeletal biomechanics and orthopaedic engineering

The rise in life expectancy has led to a significant increase in orthopaedic issues, as ageing populations experience a natural decline in bone health. Cumulative wear and tear on the musculoskeletal system, combined with age-related bone density loss, increases the risk of fractures, joint degeneration, and mobility issues. Court-Brown and Caesar [266] analysed the changing epidemiology of adult fractures by reviewing around six thousand fracture cases treated at the ERI and found that approximately 30% of fractures in men, 66% of fractures in women were potentially osteoporotic and predicted a significant rise in these. Their analysis also showed that osteoporotic fractures being primarily limited to thoracolumbar spine, proximal femur, proximal humerus and distal radius, was no longer correct; they identified 14 different anatomical locations where osteoporotic fractures were found to occur. In collaboration with Engineering the age-dependent mechanical response of bone to load was determined. A large sample of cadaveric bone specimens were subjected to mechanical tests to evaluate stiffness and strength – cortical (or compact) bone in tension [267] and trabecular (or spongy) bone in compression [268]. Mechanical tests were followed by examination of porosity, mineralisation and microstructure. The studies showed that mechanical properties deteriorated markedly with age.

Rising life expectancy also increases the need to undertake revision of previously replaced joints. Prosthetic components inevitably suffer wear over time, which also results in the degradation of the bone. Skeletal structures, which were adequate at the time of primary implantation, deteriorate severely and the bone stock left is diminished. A successful technique for hip revision surgery involves use of morselised allograft bone, which is compacted into the bone defects and new prosthetic components are then cemented into the grafted bed. If initial stability of the new components is ensured, the grafted bone is then slowly re-incorporated and remodelled, reconstituting the host skeleton. Ensuring stability requires that the bone graft can sustain shear forces. It was common practice to use relatively large bone particles, often called croutons, for grafting. Pioneering work at Edinburgh, using basic geotechnical engineering concepts, showed that graded graft particle mix (i.e., mix of particles of different sizes) and washing the graft enabled better compaction and strength [269, 270]. Lab experiments showed that the graft behaviour was strongly dependent on the compaction blows applied during surgery [271]. These also demonstrated that graft was a time dependent material (deformation was not instantaneous on load application) and led to the development of the first ever computational model that included post-elastic response [272]. Computer simulation was used to evaluate and optimise short term stability of revision hip replacements which included bone graft [273, 274]. These studies showed that simulation could replicate clinically observed migration (i.e., the movement) of the cup in the acetabulum. One of the most biofidelic numerical models of the human pelvis [275], which, for the first time included muscular and ligamentous supports,

was developed in Edinburgh (Pankaj's group) and showed that stresses in the pelvis were far more uniformly distributed than previously estimated. After 2010 Edinburgh established itself as a major centre for computational biomechanics research in orthopaedics.

X. BIOENGINEERING

The term 'Bioengineering' was coined in 1954 by Heinz Wolff, and the last 25 years have seen the very considerable rise of this area internationally. 'Bioengineering' refers to work that integrates engineering and biology, whereas 'biomedical engineering' refers to work aimed at providing solutions in the medical arena, but the 2 terms are often used interchangeably. An embryo Bioengineering Unit was set up in the School of Engineering in Edinburgh University in 2006. This became an Institute in 2014 headed by Alistair Elfick. The biomechanics work described in section IX was an early example of biomedical engineering in Edinburgh. A few of the other themes of work in bioengineering to 2010 are briefly described below.

A. Raman spectroscopy and related techniques

A number of optical spectroscopic techniques were developed for applications in live cell imaging and characterisation of samples of biological material. Raman spectroscopy involves induction of scattered light which contains information specific to the scattering tissues. Modifications to basic Raman spectroscopy are coherent anti-Stokes Raman scattering (CARS) and tip enhanced Raman scattering (TERS). In CARS a coherent light source is used to increase Raman scattering resulting in improved sensitivity. In TERS a small tip is positioned close to the tissue or material of interest. The tip enhances the scattering by a huge factor, and scanning of the tip allows 2D images of the surface of a material to be acquired. Developments of both TERS and CARS have been undertaken [276-281] with potential applications in many cells types [282, 283].

B. Implantable devices

An implantable device is one which is inside the patient with no wired connection to the outside. Alan Murray and colleagues developed a miniature RF transmitter which generated signals which could be picked up outside the body [284]. As part of a multi-centre collaboration an electronic pill was developed whose intention was to be swallowed and pass through the gastrointestinal system providing real time data on temperature, pH, conductivity, and dissolved oxygen [285]. In practice the pill was 1.6cm in diameter and 5.5cm long making swallowing difficult. A device for drug delivery was developed for the skin [286] and the eye [287]. The idea was that the device is implanted under the skin or eye. The drug is housed in cells whose seal could be broken by remote RF activation allowing controlled delivery over an extended period of time.

XI. POST 2010

Up to 2010, the vast majority of work involving the application of physics and engineering to medicine arose from the original DMPME or its offshoots, continuing Greening's legacy. Post 2010 is a rather different story. Research in Radiotherapy Physics is ongoing, led by Prof. Nailon. Bioengineering has established groups at both Edinburgh University and at Heriot Watt University. Large groupings of physicists, engineers and computer scientists are based in clinical and preclinical centres supporting work in MRI, PET, CT, ultrasound and retinal imaging, all under the umbrella of 'Edinburgh Imaging'. There are also activities in informatics, artificial intelligence, computational medicine and other areas. Thus, whilst no longer under one administrative umbrella, applications of physics and engineering in medicine continue strongly into the future in Edinburgh.

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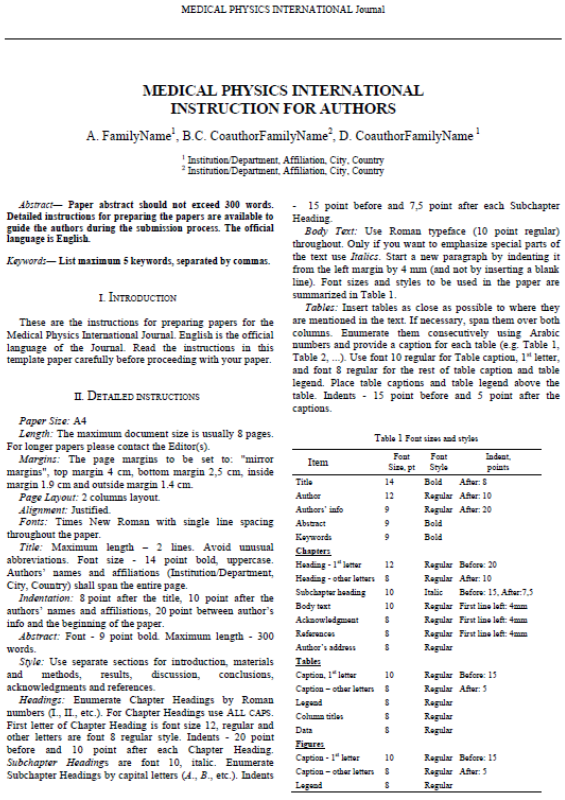

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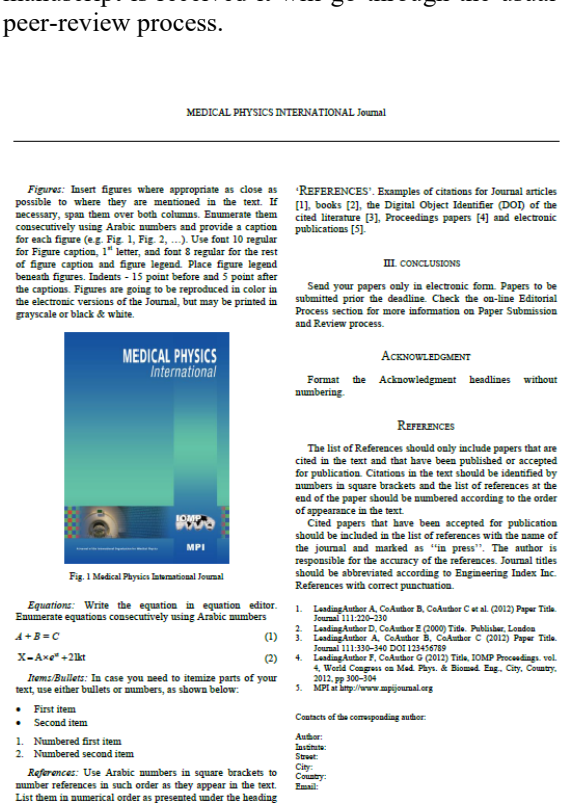

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