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].

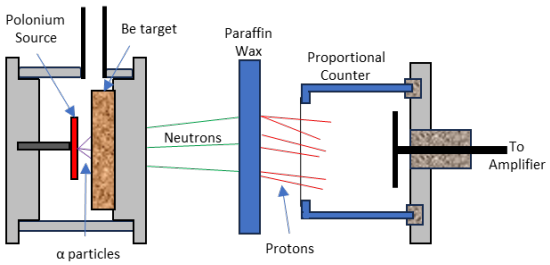

Fig 2. Schematic of Chadwick's apparatus with which he detected the neutron.

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.

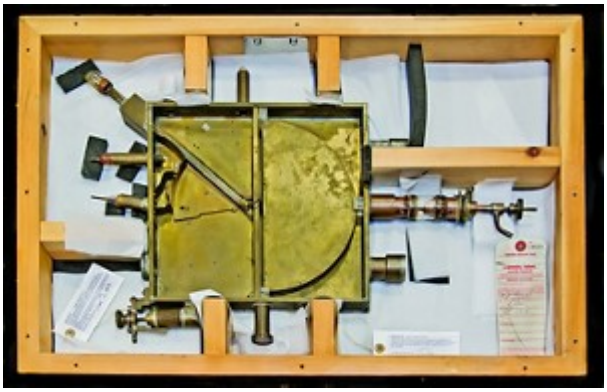

Fig. 7. Lawrence and Livingston's 11-inch cyclotron which produced an energy of 1.2 MeV.

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.

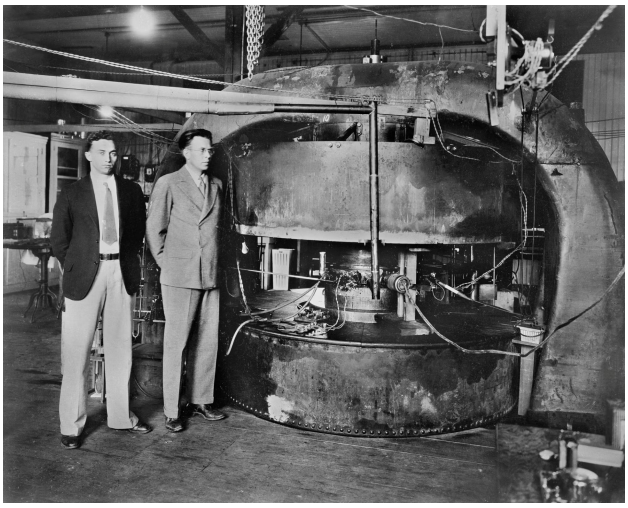

Fig 8. Livingston (left) and Lawrence with the 27-inch cyclotron.

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.

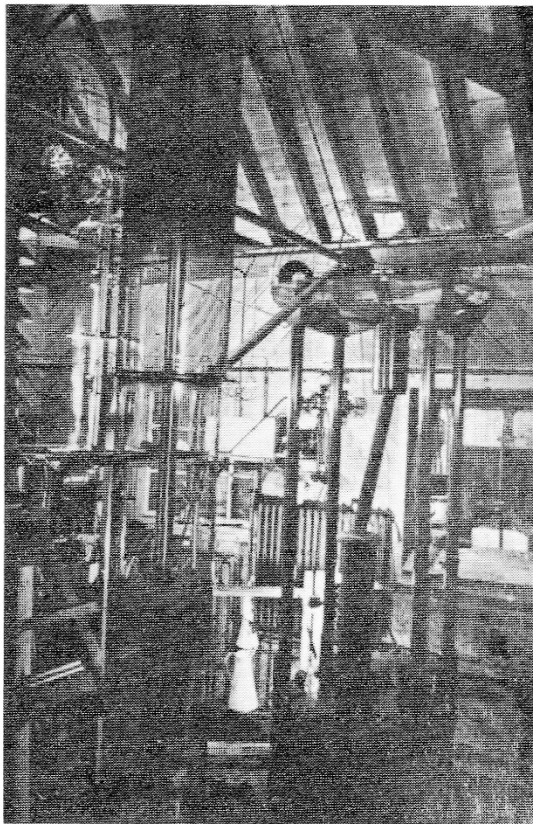

Fig 11. Gray's Cockcroft-Walton accelerator housed in a wooden hut in the grounds of Mount Vernon Hospital in North London.

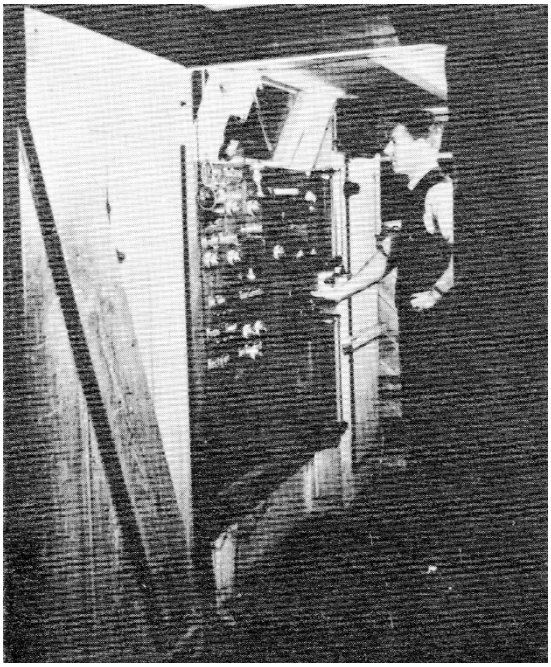

Fig. 12. Gray at the controls of his accelerator.

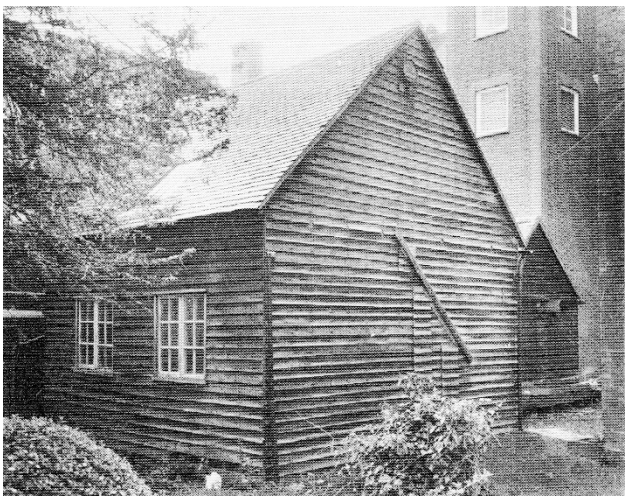

Fig. 13. The wooden hut in the grounds of Mount Vernon Hospital that housed Gray's D-D accelerator

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.

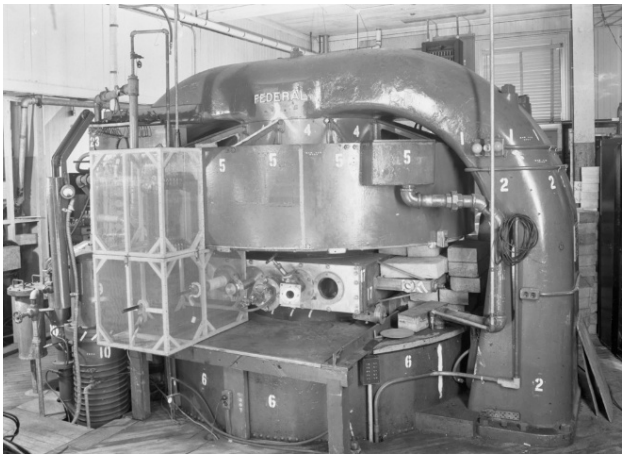

Fig 14. The 37-inch cyclotron used to treat the first patients with neutron radiation therapy. The magnet was the same one used for the 27-inch cyclotron.

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.

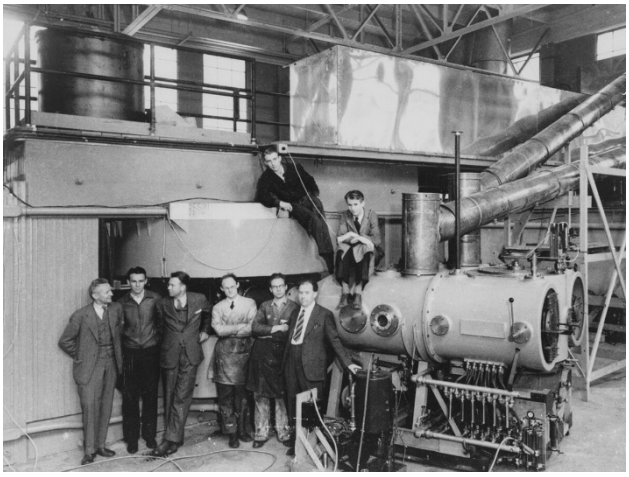

Fig. 16. Lawrence (third from left) with his colleagues and the 60-inch cyclotron.

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).

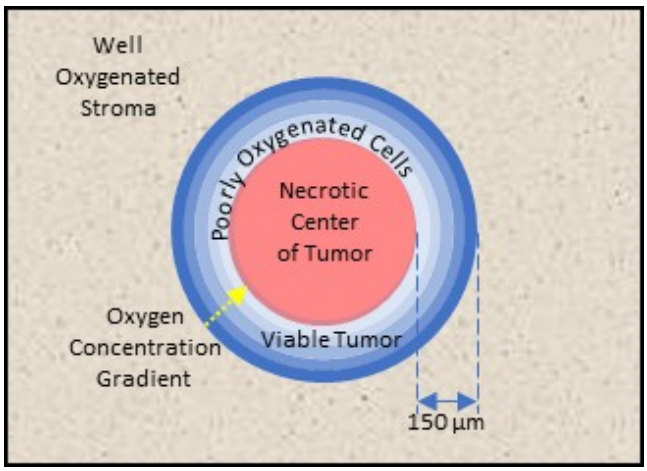

Fig. 17 Schematic representation of Thomlinson and Gray's study of bronchial carcinoma histological sections.

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

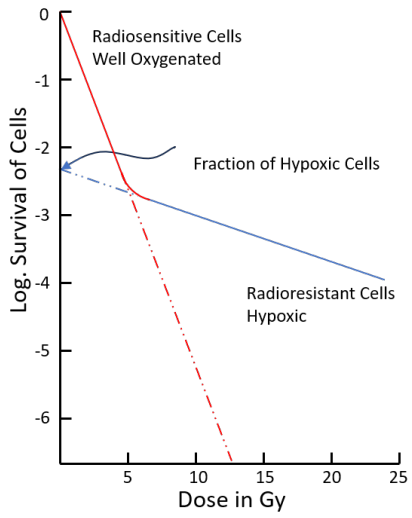

Fig. 18. Log survival curve showing how two cell populations of differing radiation sensitivity result in a breaking cell survival curve. In the Powers and Tomach experiment they were able to demonstrate the existence of hypoxic cells in a mouse tumor. The fraction of hypoxic cells in this hypothetical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

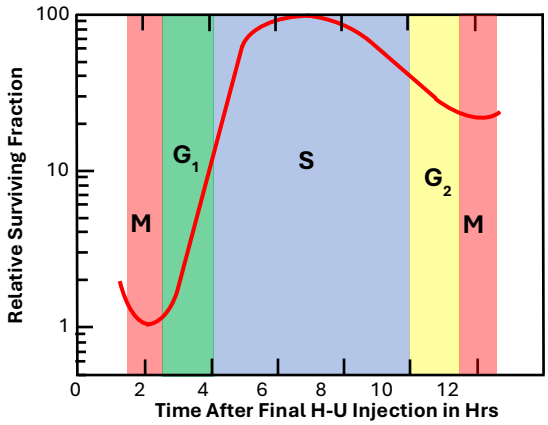

Fig. 19 Typical curve of cell survival vs phase of cell cycle. M - mitosis, G_1-first gap, S - DNA synthesis, G_2 – second gap. In this hypothetical example S-phase is 100 times more resistant than mitosis.

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.

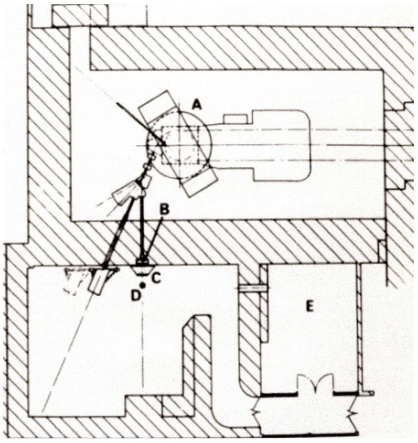

Fig. 20. The treatment room at the MRC Cyclotron Unit. A - cyclotron, B - Be target, C - protective cone and wood collimator system, D – patient skin position and E – control room.

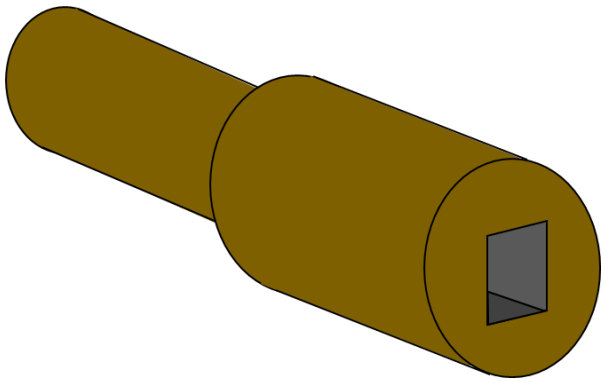

Fig 21. Schematic of the wooden aperture inserts used at Hammersmith Hospital. Similar apertures, constructed from various attenuating materials, were used in many of the early neutron therapy facilities

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.

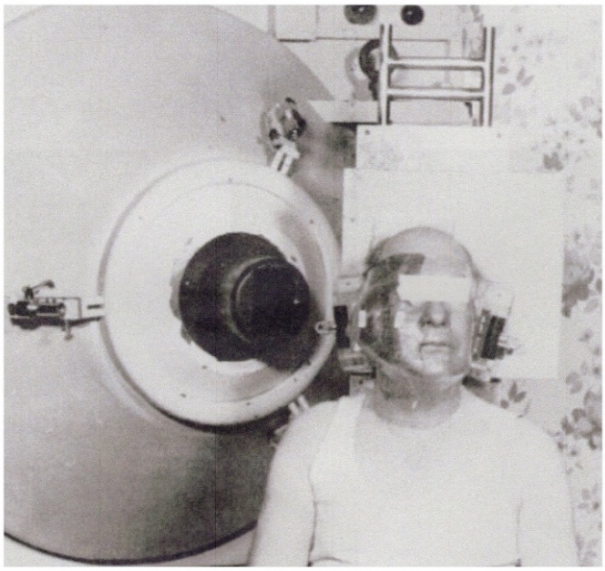

Fig. 22. A head and neck patient positioned for treatment in a seated position. The wooden collimator is seen inserted into the protective cone.

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.

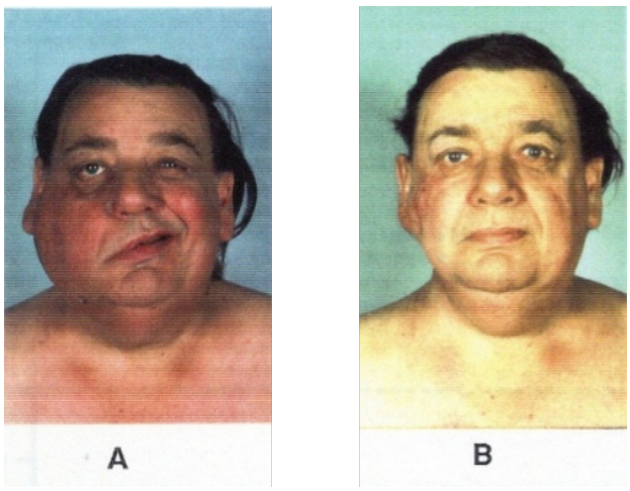

Fig. 24 A patient with neutron therapy by Dr. Catterall. A- A large parotid tumor causing paralysis of the 7th nerve. B- After treatment. Tumor regressed and facial nerve recovered fully. Patient died 3 years later of general metastases.

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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