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*Medical History*

# PROTON BEAMS AND NOBEL LAUREATES

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**Running Title:** Proton Beams

## INTRODUCTION

Physicists and physicians at Queen's University Belfast and Harvard University are both currently engaged in long-term efforts in using accelerated protons to optimize therapy. The Bragg effect of accelerated protons and controlled changes in cellular oxygen tension are promising therapeutic modalities, as recognized by the 2019 Nobel Prize in Physiology or Medicine recently awarded jointly to Harvard Researcher William G. Kaelin, Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza (a Harvard College Alumnus) for "their discoveries of how cells sense and adapt to oxygen stability"[1,2,3,4,5,6,7,8]. This Medical History is an account of my[1] observations as both a participating physician and a thirty-four year survivor of malignancy treated by accelerated proton therapy .

## MAGNUS SMEDAL, PROTONS

While stationed at Harvard's Fifth General Hospital at Musgrave Park near Belfast in 1942[9], Major Smedal taught its staff about cyclotrons and Bragg Peaks. His wartime Army service merited three Battle Stars for his service over Omaha Beach, Normandy, and the Rhineland[10]. Post-war, Smedal became co-chair of the Radiotherapy Department at the Massachusetts Institute of Technology's (M.I.T.) High Voltage Research Laboratory associated with Boston's Lahey Clinic and President of the New England Roentgen Ray Society (Table 1). Wisconsin born, Smedal had received his M.D. from Harvard. He had worked closely

| TABLE 1. PROTON BEAM DEVELOPMENT | |
|---|---|
| 1932 | Joseph Rotblat begins atomic research |
| 1935 | James Chadwick Nobel Prize "The Neutron and Its Properties" |
| 1937 | Scattering of neutrons, Rotblat's doctoral thesis (suggested by Niels Bohr)<br>First cyclotron built at Harvard University for research in nuclear physics |
| 1938 | Rotblat splitting of uranium atom |
| 1940 | Otto Frisch and Rudolf Peierls blueprint for atom bomb, consult with Rotblat and Chadwick<br>Frisch moved to Liverpool University |
| 1942 | Smedal of MIT at Musgrave Park, Belfast |
| 1946 | Robert R. Wilson, "Radiological Use of Fast Protons", *Radiology* 47:487-91 |
| 1948 | Chadwick to Cambridge University<br>More advanced cyclotron built at Harvard funded by U.S. Office of Naval Research (ONR) |
| 1949 | Joseph Rotblat appointed as Professor of Physics at St. Bartholomew' s Hospital, London; held Chair until 1976. |
| 1956 | Reconstruction of Harvard Cyclotron-160 MeV external beam |
| 1957 | Windscale radioactive fire at Sellafield, Cumbria |
| 1959 | Radioactive fire at Liverpool Street Station, London |

**Table 1** Proton Beam Development

with M.I.T. Professors John J. Trump and Robert J. Van de Graaff, developer of the Van de Graaff generator, a particle accelerator used in physics research, but with limited clinical applications[9].

1 This and subsequent first-person references are to the first author.


**Figure** 1 Bragg Stamp. Diamond Jubilee commemoration of Sir William (1860-1942) and Sir Lawrence Bragg's Nobel Prize in Physics. In 1915, Lawrence's brother, Robert, was killed at Gallipoli.

Peak effects and focus and distance of protons were described by the Braggs during their sojourn in Adelaide, Australia in 1903 and 1904[4,11,12](Fig. 1) (Table 2). On 7 January 1904, William H Bragg spoke at the Tenth Meeting of the Australasian Association for the Advancement of Science at Dunedin, New Zealand[13], home ground of Ernest Rutherford, who was

| TABLE 2. NOBEL PRIZE AWARDEES CONTRIBUTING TO DEVELOPMENT OF CLINICAL USE OF PROTON BEAMS | |
|---|---|
| **YEAR** | **AWARDEE/S** |
| **1908** | **Ernest Rutherford** |
| **1915** | **William H. Bragg and Lawrence W. Bragg** |
| **1922** | **Niels Bohr** |
| **1935** | **James Chadwick** |
| **1939** | **Ernest Lawrence** |
| **1979** | **Allan M. Cormack and Godfrey N. Hounsfield** |
| **1989** | **Norman F. Ramsay** |
| **1995** | **Joseph Rotblat** |

**Table 2** Nobel Prize Awardees contributing to Development of Clinical use of Proton Beams

also presenting a paper[14] (Fig 2) (Table 2). Bragg's address was titled , "Some recent advances in the theory of the ionization of gases"[13].

## THE BRAGGS

The Bragg family had lived for many years in the County of Cumberland where in the 1820s John Bragg married Lucy Brown, who was then living near Belfast. Around 1840, when William, the eldest of their four children was twelve, John Bragg was lost at sea between Belfast and Cumberland. In 1846, John and Lucy Bragg's second son, Robert John went off to sea as an indentured apprentice until the late 1850s, when he bought a farm, Stoneraise Place, near

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**Figure 2** Lord Rutherford, OM, FRS, of Nelson (1871-1937). Oil on canvas, 152.8 cm x 101.5 cm, 1934, by Sir Oswald Hornby Joseph Birley (1880-1952), No. G-826-2, National Art Gallery, New Zealand, courtesy of the Alexander Turnbull Library, Wellington. Born in New Zealand in 1871, in October 1907 Rutherford left McGill University for the Professorship of Physics at Manchester. Rutherford became the world's first successful alchemist when he turned nitrogen into hydrogen, protons and oxygen. In 1919, Rutherford was elected Cavendish Professor of Experimental Physics at Cambridge University. In 1938 Lord Rutherford was succeeded by Sir (William) Lawrence Bragg, who with his father Sir William had shown that "Protons have a well defined range, with a sharp increase of ionization at the end of the range that is the 'Bragg peak'."

Wigton in Cumberland, in the parish of Westward. In 1861 he married Mary Wood, the daughter of the Vicar, the Rev. Robert Wood and his wife. On July 2, 1862, Mary Wood Bragg gave birth there to the first of their three sons, William Henry[4,11,12,15].

## CYCLOTRONS

In 1929 plans for the first cyclotron came from Ernest Lawrence of Berkeley, California[16]. By 1937 cyclotrons were functioning in Boston at both Harvard University and M.I.T. Also described by Smedal, was the work of Cockroft and Walton in the Cavendish Laboratories at Cambridge University, who had, like Joseph Rotblat in Warsaw, split atoms[17](Table 1) (Table 2).

## NOBELIST, FRS, SIR JOE

In 1937, Joseph Rotblat was appointed Associate Director of the Atomic Physics Institute of the Free University of Poland, having completed his doctoral dissertation at the University of Warsaw in the same year on inelastic neutron scattering. That year he married Tola Gryn, a student of Literature. His doctoral degree was awarded in 1938[17]. Rotblat learned of the work of Otto Hahn and Fritz Strasseman, who had communicated their results on neutron bombardment of uranium to produce barium to Lise Meitner and her nephew Otto Frisch, who deduced that uranium nuclei had been split. Through associations with the Curies, Joseph Rotblat was invited to study in Paris, but accepted the invitation of James Chadwick[18] (Fig. 3) (Table 2), protégé since High School of Ernest Rutherford then Professor of Physics, Victoria University of Manchester[19] (Fig. 2). Chadwick asked Rotblat to join him at Liverpool University, where

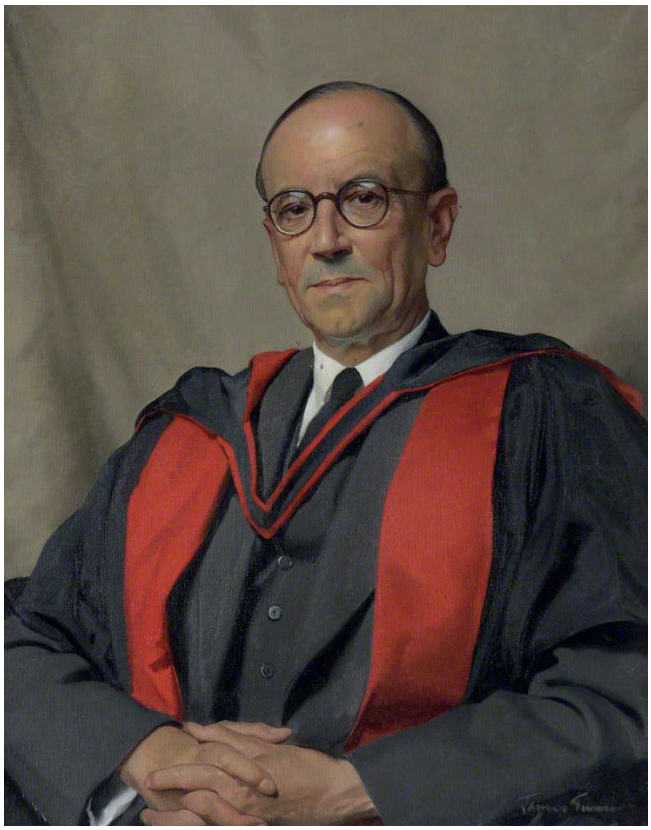

**Figure** 3 Sir James Chadwick, CH, FRS (1891-1974). When at Manchester High School Chadwick solved one of the experiments set by local Professor of Physics Ernest Rutherford (Fig. 2). Leader of the British scientists at Los Alamos, he was awarded the U.S. Medal for Merit in 1946. Chadwick and his wife remained in the U.S. until he returned to Cambridge University as Professor of Human Philosophy and Master of Gonville and Caius from 1948 to 1958. Portrait by Herbert James Gunn (1893-1964), oil on canvas 74 x 61 cm, No. GC0043. Reproduced with permission.

he was building a cyclotron for the study of basic nuclear reactions. Rotblat arrived in Liverpool on 18 April 1939; Tola remained in Warsaw because of her husband's small Liverpool stipend. Rotblat returned in August of 1939 to bring Tola back to Liverpool. An attack of appendicitis prevented her from travelling even though all the necessary documents had been arranged, and Joseph Rotblat returned to Liverpool alone on 31 August 1939, just before the German invasion of Poland. Over the ensuing months her husband did everything in his power to arrange Tola's rescue, but in 1941, British Intelligence uncovered her murder in the Madjanek concentration camp on the outskirts of Lublin. This information was not communicated to Rotblat, who only learned of her death in 1945 from his sister: Joseph Rotblat never remarried[17]. Magnus Smedal had been briefed in 1941 about Tola's death.

## WORLD WAR II

In 1943, FDR and Churchill agreed that Britain should join the U.S. endeavor known as the Manhattan Project to produce the atomic bomb. James Chadwick (Fig.3) and Joseph Rotblat were recruited to join the project at Los Alamos, New Mexico, although Rotblat's entry was delayed due to his Polish citizenship. Harvard's cyclotron was moved to Los Alamos in 1943[20]. Chadwick was Head of the British Delegation: Robert R. Wilson, a protégé of Ernest Lawrence and Robert Oppenheimer, became head of the Cyclotron Group (R1) and later the Head of the Research Division of the Manhattan Project at Los Alamos[20]. After World War II, Harvard made Robert R. Wilson, manager of the Harvard cyclotron in the Manhattan Project at Los Alamos, New Mexico, a non-tenured Associate Professor of Physics. In 1946, in his seminal paper in *Radiology* on the potential therapeutic advantages of proton beams and their focused Bragg Peaks, Robert R. Wilson wrote: "The range of a 125 Mev proton in tissue is 12 cm, while that of a 200 Mev proton is 27 cm. It is clear that such protons can penetrate to any part of the [human] body"[21]. After a year, he moved to Cornell and thence to the U.S. National Fermi Laboratories in Illinois, where he later became Head.

## RICHARD, NOT ROBERT

Putney-born Richard Wilson earned his BA and D.Phil at Christchurch, Oxford. In 1955, Richard and his wife Andrée moved to Harvard's Physics Department where Richard was appointed Mallinckrodt Professor of Physics[22].

## ROTBLAT, POST LOS ALAMOS

At the end of 1944, Joseph Rotblat resigned from the Manhattan Project on political, humanitarian and scientific grounds, and returned to the University of Liverpool, succeeding James Chadwick as head of Nuclear Physics as the Chadwicks had remained in the U.S.[17,23].

Rotblat's work at Liverpool emphasized the medical applications of radioactivity. In 1949 Rotblat applied for and was awarded the chair of Professor of Physics for London University at St. Bartholomew's Hospital Medical College. He held these titles from 1950 until his retirement in 1976[17,24,25,26] (Fig. 4). Joseph Rotblat's resignation from the Manhattan Project was grounds for ongoing American suspicion and he was denied entry to the United States for many years.

## WINDSCALE AND BELFAST, 7-11 OCTOBER 1957

Less than forty miles from the farm near Wigton, Cumbria

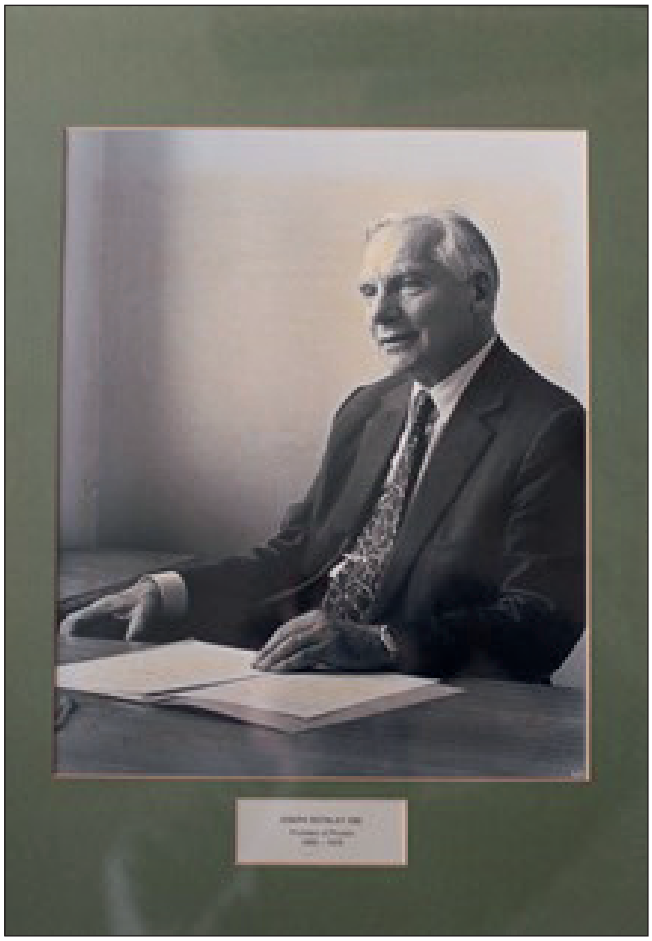

**Figure** 4 Sir Joseph Rotblat, KCMG, FRS, Professor of Physics, 1950-1976. From the Archives of St. Bartholomew's Hospital, London (No. SBHT1965) and reproduced with their permission. After World War I, Joseph Rotblat first attended a vocational school and helped support his family by working as an electrician. After discovering the evening classes at the Free University of Warsaw he earned a diploma and then a degree, and studied at the Radiological Laboratory of the Polish Scientific Society, where he drew the attention of Professor Ludwick Wertenstein. Wertenstein's collaboration and experience with Rutherford and Chadwick at Cambridge's Cavendish Laboratory did much to further Rotblat's career:Nobel Peace Prize, 1995.

where William H. Bragg was born almost a century earlier, the most serious nuclear disaster in British history took place in October 1957 at the Windscale facility, Sellafield,

Cumbria[27,28,29]. At Sellafield the radioactive plumes from the burning atomic piles were subjected to light winds from the northeast: winds aimed at the 160 miles to Belfast. Early on October 11, 1957, the wind freshened and veered from the north and then blew from the northwest for twelve hours. Belfast was saved but both Newcastle-upon-Tyne, Liverpool and Harrow on the Hill received significant radiation as did the Low Countries and Scandinavia. Professor Rotblat, at St. Bart's in London, was consulted. Milk, seaweed and St. George's Channel plaice were found to be slightly radioactive[28,29,30,31,32]. My father[9]as a former Bart's trainee of Professor of Surgery George E. Gask, DSO, CMG (1875-1950)[33], consulted with Professor Rotblat as to where Ernest Rutherford's tidal currents and drainage maps for the United Kingdom were kept[17,24]. Coastal Command of the RAF provided them. Eating seaweed was proscribed until further notice.

## RADIOACTIVE FIRE IN LONDON

On May 29, 1959, at 7:25 a.m. as Chief Resident at Bart's, I answered the Disaster Phone in Admissions. There was a radioactive cloud of smoke headed west from Liverpool Street Station London Parcels Division[34]. Twenty uniformed Metropolitan fire fighters from Bishopsgate, accompanied by Liverpool Street Station Officer Philip O'Hare and escorted by Metropolitan police arrived at Admissions. Safety precautions were ordered by Mr. J.K.H. Cunningham, Assistant Chief Officer of the London Fire Brigade[34]. I summoned help from Professor Rotblat at his Highgate home. He brought Geiger counters and radiosensitive emulsions[24]. Meanwhile, Bart's nurses and orderlies tagged clothes bags with corresponding fire-fighters' numbers and surnames. Station Officer Philip O'Hare, told me that he thought two lead containers of thorium X[35,36] stored in the parcels office enroute to hospitals had burst and burned during the fire which was now contained. Rotblat surveyed the very low contamination of the firemen accompanying Station Officer O'Hare and ordered the Metropolitan Police to take them to their homes where they were to rest for at least twenty-four hours. O'Hare's hands and forearms were washed five times and the measured thorium X radioactivity declined with each washing. The subsequent health of O'Hare was monitored by Dr. Robert M. MacKenna, Head of Dermatology at Bart's.

On Washington's Birthday in February 1960, my wife and I went to the American Embassy in Grosvenor Square to obtain Immigration Papers to work at the Massachusetts General Hospital in my case and Boston Children's Hospital in hers[37]. The Embassy was closed so we returned later that same week. The U.S. State Department officer that interviewed us said "No visas". I told him to get his boss which he reluctantly did. The supervisor looked at our dossiers and said "Yes to both". When I returned to Bart's I was told the initial refusal was because Professor Rotblat had been, and was still banned from the U.S. on the directive of F.B.I. Director J. Edgar Hoover, in part because of his departure from Los Alamos in 1944. Later the Kennedy Administration overrode this ban.

## BOSTON 1960

I arrived at the Massachusetts General Hospital at 7:30 a.m. on July 1st, to be told I was late and directed immediately to my first U.S. patient, a disordered teenager, who bit me. Nick Zervas, then a junior neurosurgeon, threatened the teen with a carotid needle and we proceeded successfully[38].

In 1961, at the age of 27, I was made Head of Neurosurgical Anaesthesia with Professor J.C. White continuing as Head of Neurosurgery. He was soon to be succeeded by William H. Sweet, former Rhodes Scholar, gifted pianist, and Senior Neurosurgeon at the University of Birmingham, UK[39].

My promotion was prompted by John E.A. O'Connell (1906-2001), Head of Neurosurgery at Bart's since 1946[40,41]. In 1935 O'Connell had won a Rockefeller Foundation Fellowship to Ann Arbor to work with Max Peet and thence to Chicago to train with Percival Bailey. During this Fellowship, John O'Connell was "proud to have met Harvey Cushing"[42]. O'Connell returned to Bart's in 1937 to become a Chief Assistant to Sir Geoffrey Keynes. During World War II, O'Connell worked on the Neurosurgical casualties of London's Bombing Blitz; in this he liaised with William Sweet at Birmingham.

John O'Connell, friend and supporter of Rotblat, was twice Hunterian Professor, also President of the Society of British Neurological Surgeons. In 1958, O'Connell operated on the first pair of his six craniophagus twins[41]. Always most courteous, John O'Connell was a devoted and skilled fly-fisherman[40].

## BOSTON

From my point of view, the most taxing of cases were induction of general anaesthesia outside the M.I.T. nuclear reactor and maintenance during the boron-capture nuclear bombardment[43]. With the help of E.P. Richardson, Jr., Head of Neuropathology and Larry Martin, Massachusetts General's Deputy Director, we succeeded in getting the U.S. Federal Government to close the Harvard-M.I.T. boron capture programme.

## ADVANCES WITH PROTON BEAMS

For May 25, 1961 Raymond Kjellberg, Assistant in Neurosurgery, Massachusetts General Hospital asked me to anaesthetize a two-and-a-half-year old girl with a malignant tumor of the central part of her brain in preparation for proton therapy[20,43,44]. This first anaesthetic was "a remarkable feat"[44,45]. Her airway was challenging and the Bragg Peak effect was said to be more effective if the arterial oxygen tension was low[45]. The protons were delivered in "three fractions over several weeks and the total dose was 8,000 rads"[44]. These Bragg effects shrank the tumor which had been resistant to chemotherapy and conventional deep X-ray therapy, by 80 percent. I found Dr. Kjellberg and the

physicists, Directors of the Third Harvard cyclotron, Richard Wilson and Norman Ramsay to be both fascinating and congenial (Table 1)(Table 2).

Norman Ramsay, like myself, a Clare Cambridge University graduate[46,47], later asked me about our Harvard colleague for twenty years Jim Watson and his sojourn in 1952-1953 almost next to my student accommodations in Clare Memorial Court, "M" for me and "R" for Jim Watson[48]. I said that I had there been introduced to Lawrence Bragg, successor to Lord Rutherford as Head of the Cavendish Laboratory[49]. Jim Watson referred to Sir Lawrence Bragg only as "My Boss"[48,49]. Max Perutz[50], who helped us with some hemoglobin work[51,52] has confirmed that it was in Jim Watson's suite of Clare rooms that "My Boss" wrote the Nobel Committee Recommendation for the Double Helix, DNA, for Watson's Nobel Prize[49]. A delayed Nobel Prize in Physics was awarded to Norman Ramsay in 1989 for Atomic Time Keeping[47]. The GPS system of widespread and essential deployment has ensued.

Norman Ramsay has written "our Post-doc Allan Cormack was paid from our funds, and we knew he was boondoggling some on the evenings." "Well, it turned out that Cormack was doing calculations on his own." What he was doing was developing the theory for CT-Scans[46,53]. Cormack's Nobel Prize was shared with Electrical Scientist Sir Godfrey Hounsfield of EMI[54] knighted in 1981 and memorialized by the quantitative description of radiodensity known as the Hounsfield Scale[55] (Table 2). Rarely if ever has this "Boondoggle" been surpassed in its benefits and dangers for humanity.

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