Lobar Pneumonia Treated by Musgrave Park Physicians

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Lobar pneumonia treated by Musgrave Park physicians

John Hedley-Whyte, Debra R Milamed

Accepted 5 January 2009

SUMMARY

In the decade 1935-45 the treatment of lobar pneumonia in the developed and warring world underwent a series of evolutions—anti-sera, specific anti-sera, refinement of sulphapyridine drugs, sulphapyridine and anti-sera, the introduction of penicillin for bacteriology, then ophthalmology, and then for penicillin-sensitive bacterial infections such as lobar pneumonia with its many Cooper types of Streptococcus pneumoniae. Penicillin for civilian use was essentially banned in World War II, a ban that early in 1941 two Musgrave Park physicians tried to circumvent. Strict secrecy on the details of penicillin production was enforced. The treatment option chosen by the Musgrave Park physicians in 1941, and the non-availability of penicillin led to sequelae affecting the post-Belfast careers of both patient and physicians.

KEY WORDS: Sera, Sulpha, Penicillin

INTRODUCTION

At the start of his 1944 Campbell Oration1, the newly knighted Alexander Fleming (Figure 1) mentioned his 40-year collaboration and mentorship with Ulsterman Sir Almroth Wright. He thanked his friend, housemate and long-time collaborator Victor Douglas Allison, Queen’s MB, later DSc. Allison had been the JC White Lecturer in Bacteriology, Queen’s University6. After working with Wright and Fleming, as a Beit Memorial Research Fellow, he became a Senior Consulting Pathologist to Belfast City Hospital and the Northern Ireland Hospitals7. Fleming also recalled his World War I service with the Professor of Medicine 1921-50 at Queen’s University6. After working with Wright and Fleming, Cushing was in 1926-27 to train Hugh Cairns11, later Nuffield Professor of Surgery at Oxford, at the Peter Bent Brigham Hospital, Boston. Cairns, in 1942, both abridged and amplified Cushing’s experience12. Lee was to train Professor Maxwell Finland at Harvard13-15. Fleming, Keith and Thomson were frequent golfing companions at Wimereux where their golfing feats incurred Wright’s displeasure, but did not strain their friendship. Sir Almroth Wright maintained his high regard for the trio. Fleming, when out of sight behind a dune, had dropped a “somewhat self-important Colonel’s ball” so as to fake a hole in one, and demand the customary sequelae of drinks on the Colonel16.

In his Campbell Oration, Fleming mentioned neither the secret work on penicillin in the United States since his visit to New York in 1939, nor the efforts of two Musgrave Park 31st General Hospital doctors to obtain penicillin in March 194117. One of the pair, Max Rosenheim, later President of the Royal College of Physicians and enabled with an FRS, had also in March 1941 asked the Wright-Fleming group for advice on Type XIV anti-pneumococcal serum7.

WORLD WAR II BELFAST

In March 1941, under optimal circumstances, the preferred treatment regimen for lobar pneumonia was to determine as expeditiously as possible the Cooper type of infecting pneumococcus: to take a blood sample for culture was advised18. Before these results were obtained, polyvalent pneumococcal antiserum could be given intravenously with caution14. This done, a loading dose of sulphapyridine, then called M and B 693, was given, generally by mouth18,19. Sulphathiazine was thought to have less toxicity, but was new and expensive (Table I). The patient’s hydration, nutrition and mental attitude needed to be bolstered during the course of the treatment.
The Allies had by June 1944 achieved their objective of ensuring that their Forces had enough penicillin to treat expected casualties in the Normandy landing and breakout. Fleming's Penicillin notatum (NRRL 1249), isolated 1929, was a producer only in surface culture. NRRL 1249 did not produce when submerged. After searching all over the world for Penicillin notatum-chrysogenum which could produce when submerged, the best strain proved to be from a cantaloupe in a Peoria, Illinois fruit market (NRRL 1951). Mutation sequence began on the best substrain, 1951-B25, Demerec of the Carnegie Institution of Washington's Cold Spring Harbor Laboratory, developed a superior X-ray mutant 1951-B25 X1612 which was commercially produced, but was superseded by strain Q-176, which was an ultraviolet-produced mutant derived from X-1612 by the University of Wisconsin. Fleming's mold NRRL 1249 produced 2-4 Oxford Units per ml, 1951-B25. Q-176 produced 750 times Fleming's mold. The United States efforts to ramp up the production of penicillin during World War II was given funding priority equal to the Manhattan project to develop uranium and plutonium bombs. Secrecy was strictly observed.

Sareen Sally McElroy was a trained nurse, the twin daughter of a County Mayo farmer. The Flemings were very happily married from 23rd December 1915, when Alexander was on leave from his duties in Boulogne with Ulstermen Sir Almroth Wright and Thomson until Sareen's terminal illness and death on 29th October 1949.

Both Musgrave Park physicians Benjamin Rycroft and Max Rosenheim knew penicillin was extremely effective against pneumococcal (now called streptococci pneumoniae) infections, and that penicillin did not appear to cause nausea, vomiting, heart arrhythmias and diarrhoea, as did M and B 693. Both Rosenheim and Rycroft knew that penicillin was being produced at Oxford and in New York at Columbia University, in a manner that took over many rooms.

What Rosenheim did not know was whether specific type XIV anti-pneumococcal serum was available. My father kept his copies of The Medical Annual in the library of our Dunmurry Lane home. The 1940 edition, which I inherited from him and still possess, has a section on “New Pharmaceutical Products”.

### Table I:

#### Sulphonamides In Order Of Therapeutic Introduction

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<th>No.</th>
<th>Name</th>
<th>Formula</th>
<th>Description</th>
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<tr>
<td>1.</td>
<td>Prontosil</td>
<td>C₁₂H₁₄CIN₅O₂S</td>
<td>Developed by the Bayer team of H. Hörlein and G. Domagk who filed German patent application No. 607537 in 1932.</td>
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<td>2.</td>
<td>Sulphanilamide</td>
<td>SO₂⁻ - NH₂</td>
<td>First synthesized by P Gelmo in 1908. The Tréfouëls advanced work on the therapeutically active component of Prontosil and published their results in 1935.</td>
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<tr>
<td>3.</td>
<td>Sulphapyridine</td>
<td>C₁₁H₁₁N₃O₂S</td>
<td>Also known as M and B 693. N Grillet of Rhône-Poulenc ordered AJ Ewins of their subsidiary, May and Baker, to work with their chemists G Newberry and M Phillips. LEH Whitby was recruited to test sulphapyridine by Ewins in 1936.</td>
</tr>
<tr>
<td>4.</td>
<td>Sulphathiazole</td>
<td>C₉H₉N₃O₂S₂</td>
<td>Only sulphadiazine, C₁₀H₁₀N₄O₂S, was obtainable in Belfast and could have been used instead of sulphapyridine (M and B 693).</td>
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<tr>
<td>5.</td>
<td>Sulphadiazine</td>
<td>C₁₀H₁₀N₄O₂S</td>
<td>The production of sulpha drugs, such as trimethoprim, C₉H₆N₂O₂S, has remained close to World War II levels with increased veterinary and animal husbandry use.</td>
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<tr>
<td>6.</td>
<td>Trimethoprim</td>
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Throughout this Medical History, “I” or “my” refers to the first author.
Lobar pneumonia treated by Musgrave Park physicians

Table II:

Ophthalmologists And Pre-March 1941 Penicillin Human Therapy

1. Drs Frederick Ridley and SR Craddock reported experimental extraction on April 10, 1929, of a concentrated penicillin. Ridley was later a colleague of Rycroft at Moorfield’s Hospital, London.

2. Professor Alexander Fleming, late in 1929, treated Dr KB Rogers, an assistant to Sir Almroth Wright. Pneumococcal conjunctivitis was promptly and completely cured.

3. Dr Cecil G Paine, a St. Mary’s graduate, grew his own penicillin from Fleming’s strain and in 1933 with ophthalmologist Albert Nutt successfully treated ophthalmitis neonatorum at Sheffield Royal Infirmary. From 1932-35 Howard Florey was Professor of Pathology at Sheffield.

4. CG Paine, for his eighth case, successfully treated with penicillin a colliery manager who had an intraocular foreign body and pneumococcal infection. Successful extraction was enabled.

5. On October 15, 1940 Dr Martin H Dawson of Columbia University, New York, NY, began to treat three patients with retinal Roth spots due to subacute bacterial endocarditis, with Columbia-manufactured penicillins. By May 6, 1941, Dawson’s group had treated a total of four patients.

6. On February 12, 1941, Dr Charles Fletcher of the Nuffield Department of Medicine at Oxford University started penicillin treatment on policeman Albert Alexander, aged 43. Following a rose scratch, post-left-eye exenteration, Alexander developed endophthalmitis and orbital cellulitis. Treatment was initially successful but Alexander died on the 15th March 1941 after Oxford’s supply of penicillin had been exhausted.

Fig 2. Sir Benjamin William Rycroft, OBE, FRCS, 1902-67. Photograph by Walter Bird. Reproduced with the permission of Moorfields Eye Hospital and UCL Institute of Ophthalmology solely for this Medical History.

Educated 1919-24 at St. Andrews University. After qualifying, he practiced as a general practitioner in Bradford, Yorkshire, from where, starting about five years later, he studied ophthalmology in London during the week, returning to work in Bradford at the weekends. On this regime he was admitted FRCS in 1931 and moved as Clinical Assistant to Sir Stewart Duke-Elder, knighted 1933, at St. George’s Hospital. Benjamin Rycroft published his first paper on human corneal transplantation in 1933. From 1940 to 1942 he served in the 31st General Hospital at Musgrave Park. Torpedoed and rescued on the way to Algeria, he later advised Allied Mediterranean Command for which he received the OBE. Rycroft published the first book in the English Language describing corneal grafts. Sir Benjamin’s obituary says “he rode to show-standard and hunted”. He was an accomplished organist, and “all his life he maintained an interest in the piano”. As Honorary Consultant to the Zoological Society of London, he operated on tigers and horses among other animals. Rycroft, Examiner in Surgery to Queen’s University, Belfast, encouraged by Dickie Hunter, asked candidates in surgery at Queen’s viva questions enabling.

Preparations”. The section on “Antipneumococccic Sera (Rabbit),” Lederle, covers the ‘higher types’ of pneumococcal pneumonias for which horse sera have not previously been available. Supplies of antisera are now available in 20,000 unit vials for all the 32 Cooper types except Types XV, XXV, XXVI, and XXX. These vials are manufactured by Lederle Laboratories Inc., New York, NY. Literature on application to the distributors CF Thackray Ltd, Park Street, Leeds. In March 1941, Type XIV was not available on demand in a timely manner from Lederle, New York, nor from the Leeds distributor. The reason that rabbits had supplanted horses was that production of the “higher types” of antipneumococccic serum killed about a third of the horses. This high equine mortality was not experienced in producing lower types I, II and III; in these “original” types equine production probably had higher profit margins. There were more patients for types I, II and III and greater production from the sensitised horses.

As a result of his telephoned investigations, Rosenheim discovered Squibb was about to release “Antipneumococccic Rabbit Serum Type XIV”. Type XIV lobar pneumonia was then relatively uncommon in the United Kingdom. One New York-based study reported type XIV pneumococcus as comprising 16.1 percent of lobar pneumonias in children, but only 2.6 percent in adults. Type XIV produced mortality rates as high as 14 percent in children and 23 percent in adults without bacteremia, and 28 percent in children and 69 percent in adults with bacteremia.

Disease Course

On a stormy dawn early in March 1941, I awoke in my bedroom at Windy Ridge, Dunmurry Lane with pain in my right side. I called my father who came in his dressing gown and then returned with a stethoscope. After listening to my chest, he brought a glass of water, and told me to drink it, and that he would get Rycroft whom I already knew. I asked why I needed an eye doctor. “He kept the city of Bradford in order as a GP”, my father replied. Rycroft arrived about an
hour later and took a venous blood sample and several throat swabs (Figure 2, Table II).

Later, a tubby, cheerful man appeared in civilian clothes and said to me and my nurse, “I am Max” (Figure 3). He told me that the next three to five days would be like climbing a mountain. I would probably get more breathless and the pain in my right chest was best put up with. He then listened to my chest and said “Angus and the eye doctor are right”. Max gave me an intravenous injection which he said had been made by Sir Almroth Wright and Professor Fleming2 and left, saying he would be back when he had checked up on the eye doctor. A few hours later Rycroft appeared with some pills he made me swallow (Figure 4). Rycroft said in future he would announce his arrival by playing on the piano in the room beneath my bedroom.

That evening I asked my father who Max was, to be told he was a Salopian Johnian.52 The nurse, who was from Sligo, said that Max was very nice. “Where was he from?” my father replied, “The Massachusetts General Hospital”. So I asked if he was an anaesthetist. “No, he was Belton Pollard Fellow with Albright and Bauer,” my father replied52. Late the next day Max reappeared and said he had made a lot of people work including Angus and the eye doctor, so he was going to give me back some of my own medicine—so started my intravenous course of Type XIV antipneumococcal serum32.

Max Leonard Rosenheim was President of the Royal College of Physicians, London.

Max Leonard Rosenheim was President of the Royal College of Physicians of London from April 1966 to April 1972. In May 1968 he presided over the 450th Anniversary of the College in a meeting held jointly with the American College of Physicians in Boston, Massachusetts. Educated at Shrewsbury School and St. John’s College, Cambridge. At University College Hospital by pioneering the treatment of urinary infections with mandelic acid48 and hypertension with pentamethonium,50,51 he pioneered major advances in therapeutics. Max led a Professorial Unit at UCH judged second to none. His Military Service started at Musgrave Park in 1941. replied, “The Massachusetts General Hospital”. So I asked if he was an anaesthetist. “No, he was Belton Pollard Fellow with Albright and Bauer,” my father replied52. Late the next day Max reappeared and said he had made a lot of people work including Angus and the eye doctor, so he was going to give me back some of my own medicine—so started my intravenous course of Type XIV antipneumococcal serum32.

At the age of fifteen, his father being vicar of St. Mary’s Church, Crumlin Road, Belfast, Wright entered Royal Belfast Academical Institution from where he proceeded to TCD reading English, French, German, Spanish and Italian. This Instonian won the Gold medal in his BA in 1882. He also read medicine concurrently. He qualified MB from TCD in 188332.

Aged 23, Almroth Wright went to Leipzig to study with Cohnheim, and later Ludwig and Weigert. He returned to the United Kingdom to become pathologist to the Brown Animal Sanatory Institute. John Scott Burdon Sanderson, later knighted and Regius Professor of Medicine at Oxford, was the Brown Institute’s first superintendent. He was followed as superintendent by Sir Roy, Victor Horsley and CS Sherrington. When Roy became head of Pathology at Cambridge University in 1886, he appointed Wright Demonstrator in Pathology51. Roy soon sent Wright to von Recklingshausen in Marburg. After proposing the citration of blood he was offered and accepted the Professorship of Pathology at the Army Medical School at Netley. He was thirty-one. This Army appointment led to the flowering of one of the most productive and influential careers of the last century. In 1902, Wright became Professor of Pathology at St. Mary’s Hospital Medical School. Friendly with Arthur J Balfour, Lord Haldane and G Bernard Shaw, Wright was both knighted and elected FRS in 1906. At St. Mary’s he mentored and nurtured Alexander Fleming for almost forty years. Wright and Fleming, together with SR Douglas, founded and ran the Vaccine Laboratory of the Department of Therapeutic Inoculation. Until after the end of World War II, the Inoculation Department had control of their own patient beds at St Mary’s52.
are dead". Max said he had also been talking with Wright's people at Mary's. They had reminded him how to do a Quellen reaction and a precipitin test to type the pneumococci. He said they had no spare penicillin. "Try Oxford and New York," advised Sir Almroth. So he had given that job to Rycroft, "Because eye-doctors couldn't get into trouble because of the Duke (Figure 5). Ophthalmologists know more about penicillin than anyone else". "Good-bye," said Max. "Go to a college on the Backs of the Cam".

1941 UNITED STATES IN ULSTER

I never saw Max in uniform during his posting to Musgrave Park. When I asked for an explanation, I was told, “Because he was dealing with the Yanks.” The next month after my pneumonia, April 1941, was the time of the Belfast blitz. The still neutral US War Department issued RAINBOW-5, which detailed the deployment of 30,000 US troops in Ulster. On June 12, 1941, the construction contract for US bases and hospitals in Northern Ireland was signed. Rosenheim, with his recent Harvard experience advised on what Harvard's Fifth General Hospital and other US Medical Services would require. He liaised with Professor WWD Thomson for WWD’s own experience at Boulogne’s Fifth General Hospital in World War I.

THERAPEUTIC ALTERNATIVES

To determine the pneumococcal type from the samples obtained by Rycroft, Rosenheim used concurrent techniques described by Lionel Whitby, Pathologist to the Middlesex Hospital. “Type may be determined by an immediate direct method, by mouse inoculation or by agglutination of a culture.” In the direct method, a small fleck of fresh sputum is well mixed on a slide with a drop of the type I, II or III serum. “After the serum has penetrated into the sputum, a cover-slip is placed over the preparation and it is examined with the 1/6th lens and x10 eyepiece. The capsule of an organism, when in contact with its own specific serum, becomes swollen and the organism itself loses its definition.”

“The white mouse is very susceptible to pneumococcal infection, and if inoculated intraperitoneally with a sample of pneumococcal sputum, not only are the mucus and the cellular elements liquefied, rendering the pneumococci free, but the cocci also multiply rapidly.” The peritoneal cavity of the mouse is aspirated after four hours and the direct method repeated. Under microscopic examination, the capsule of the diplococcus is swollen by its own specific serum. If no swelling occurs, as it did not in my case, the search continued with expensive specific serum for the remaining known, as of 1932-1941, twenty-nine types.

Rosenheim then used mouse inoculation as described by Whitby and obtained evidence of agglutination of a mouse heart blood sample. A suspension of the culture is tested for agglutination in dilutions varying from 1:1 to 1:20 with each of the type-specific sera. The tubes should be incubated in a water bath for one hour at 37°C. The peritoneal washings of an incubated mouse can also provide a suitable suspension for this test. Further confirmation that the infecting pneumococcus was type XIV was provided by the precipitin reaction using the polysaccharide haptene known as Specific Soluble Substance, or SSS from urine.
As Whitby states, “Recognition of the characteristic change requires much practice”74. This was the justification for Rosenheim’s telephone calls to Professor Thomson and to Whitby’s and Wright’s groups. Agreement was reached that the infecting pneumococcus was type XIV. Where was Whitby’s and Wright’s groups. Agreement was reached that the infecting pneumococcus was type XIV. Where was the antiserum? And did it need to be given as well as the specific anti-serum and the sulphapyridine (M and B 693) were given as early as possible in the course of the lobar pneumonia14,15.

In 1939, an annotation in this journal on the treatment of pneumococcal infections stated that for a child of seven, an initial dose of M and B 693 of 1.5 0.5g tablets should be followed by 1 tablet every four hours. The Ulster Medical Journal continues, “It is of importance even with this brand of drug that every case should be typed.” “Physicians...may wish to supplement their treatment ...with administration of specific serum”79. In 1940 a study from Birmingham showed that the mortality in 1,685 successive patients, with lobar pneumonia admitted to the Dudley Road Hospital dropped from 20.5 percent in 1936 and 1937 to 5.3 percent after the introduction of M and B 693. In Birmingham, type I pneumococcus predominated 43%, type III 16%, type II 11%, type XIII 5%. The other types were “encountered only sporadically and types XIII, XIV, XXII, XXVI and XXX not at all”80. In Los Angeles, California, in the five years from January 1934 through December 1938, type XIV lobar pneumonia represented only 1% of 1,469 consecutive cases of lobar pneumonia84. Things were different in Harlem, NY, where type XIV had been shown to be a virulent pneumococcus “selecting by preference infants and young children, in whom the pneumonias are usually of long duration—it is especially prone to invade the blood and prove fatal”85 (Figure 6).

PERSONAL SEQUELAE

My parents complained of the paltry British Army pay. So I asked the cost of my treatment. The M & B 693 sulphapyridine cost £1 per day. My illness cost “a fiver”. The anti-sera were free samples. “The Germans invented a dye called prontosil, for which Professor Domagk was awarded the Nobel Prize in ’3922,65,66 (Figure 7). The French24 stole it and the English improved it so you got better and did not go pink or blue”83. I later asked what a Quellen test was and why Mary’s had XXX not at all”18. In Los Angeles, California, in the five years from January 1934 through December 1938, type XIV.

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<td>June 1942</td>
<td>10</td>
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<td>Jan. 1944</td>
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<td>June 1944</td>
<td>750,000</td>
<td>5,000</td>
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Production figures derived from Lord Florey’s Antibiotics published in 194948 and US figures declassified in stages post-World War II4. The 150-fold increase in US production from June 1943 to D-Day was largely due to irradiation procedures. War-time secrecy and patent protection inhibited and delayed US to British Empire information transfer4. The University of Toronto delivered approximately 1,000 Oxford Mega Units to Canadian Armed Forces in May 194446.
My father wrote to the Dragon Preparatory School on Bardwell Road, just north of Oxford University. Father was told that they were full. So when my father next met his friend Hugh Cairns, Nuffield Professor of Surgery at Oxford, he claims he made him feel guilty for procrastinating on the release of penicillin for me. The excuse was they had "run out on a rose scratch case". If I had been given the penicillin I would have been the third patient in the first Oxford series30 (Table III). Professor Cairns, as propitiation, said he would call on the Lynams (Hum and son Joc, co-Head-Masters), and there would be no trouble. I entered the Dragon as a boarder in September 1942 to learn that the most prominent of the Oxford Dons that founded the school in 1877 was a Mr George, who thereafter had his Dragons both male and female: all to be aged seven to thirteen. We Dragons aspired to "robust informality and relaxed vigour"71.

Max Rosenheim left Belfast to become officer in charge, Medical Division, in various countries in the Middle East and North Africa, ending his Army service as a Brigadier General and consulting physician to the Allied Land Forces South East Asia52.

At one of our teas or Sunday lunches that the Cairns family gave me at their home around the corner from the Dragon School, I asked why Max had been sent so far away. Professor Cairns replied, "Because of your penicillin". "But I didn't get any, and anyhow Rycroft did the asking." "Yes, but we all knew Max was behind it". Professor Cairns then said "Did you know Rycroft had to swim for awhile on the way to North Africa? He was torpedoed and they had trouble picking him up"35. He's good at using penicillin72.
Dr. E. Cairns and Old Dracenian David Cairns and I were joined on occasion by Charles Florey who became a Dragon in January 1945 after returning from being evacuated to Yale to live with John and Lucia Fulton in Connecticut. Fulton, Sterling Professor of Physiology\textsuperscript{10}, had been a Rhodes scholar at the same time as Florey. Cairns, like Florey from Adelaide, was friendly although not contemporaries. I remember Cairns’ assistant Captain Calvert\textsuperscript{13} handing the tea around on at least one occasion.

In preparation for Cambridge in 1951, I suggested I try to manipulate the sulphonamides. I was allowed to work in the chemistry Laboratories of King’s College, Newcastle-upon-Tyne. I read Lionel Whitby’s classic papers\textsuperscript{26,53,69} about which I was told to go to a college on the Backs. I fancy Clare”. “I thought of my reply. “When I was seven, Professor Rosenheim was applying to Downing. On the train to Cambridge I had my treatment by Max and Ben. He then asked whether I was applying to Downing. On the train to Cambridge I had thought of my reply. “When I was seven, Professor Rosenheim told me to go to a college on the Backs. I fancy Clare”. “I shall talk to Henry and tell him to make up his mind.” Sir Henry Thirkill during his long mastership of Clare was a reigning Vice-Chancellor. In July 1960, when I arrived at Harvard, Walter Bauer, Head of Medicine at the Massachusetts General Hospital, knew of my treatment by Max and Ben. So did Max Finland who was to become head of Harvard’s Thorndike Laboratory and George Richards Minot Professor of Medicine (Figure 9). Finland was contacted by Rosenheim in 1941, and again after my wife Tess\textsuperscript{27} and I started work in Boston.

When we were doing rounds and combating infection in our Harvard Intensive Care Units, Max Finland advised us\textsuperscript{78-83}. On the enoblement of Max Rosenheim, Finland remarked to my physicians in Belfast, Cambridge, London and Boston\textsuperscript{57} and by parental and uxorial admonitions.

The authors have no conflict of interest.

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