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Medical History

Lobar pneumonia treated by Musgrave Park physicians

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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 sulpha drugs, sulpha 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 Oration[1], 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 University[6]. 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 Hospitals[7]. Fleming also recalled his World War I service with the Professor of Medicine 1921-50 at Queen's, WWD Thomson, knighted in 1950[3,6,8].

When they returned to take the Belfast-Larne train, the Flemings discovered they were missing his lantern slides and lecture notes[3]. The Ulster authorities and British security knew that since 1941 all details of antibiotic production by the World War II Allies had been strictly classified secret. The train was delayed; the Larne to Stranraer ferry's escort rescheduled. The notes were found, vetted, and restored to Sir Alexander. The Flemings were then allowed on their way back to London and Allison's Highgate house where Allison kept a pied à terre for visits from Cardiff where he was stationed. The Flemings had been bombed out of their Chelsea home[2].

WORLD WAR I: FLEMING, THOMSON AND WRIGHT

Captain Alexander Fleming had worked under Colonel Sir Almroth Wright's command from 1915 to 1918 at Boulogne[2,7]. Captain WWD Thomson and Captain N Keith of Canada, later of the Mayo Clinic, were junior officers in this Unit devoted to the study of Allied War Wounds and their infection. Harvard's US 5th General Hospital was also stationed in Boulogne with Professor Harvey Cushing as Commanding Officer, and Professor Roger Lee as Chief of Medicine. Both were friends of Wright's group, and Cushing collaborated in Wright's work on war wounds[9,10]. In 1919 Harvey Cushing was awarded an honorary MD by Queen's, Belfast[10]. Cushing was in 1926-27 to train Hugh Cairns[11], later Nuffield Professor of Surgery at Oxford, at the Peter Bent Brigham Hospital, Boston. Cairns, in 1942, both abridged and amplified Cushing's experience[12]. Lee was to train Professor Maxwell Finland at Harvard[13-15]. 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 Colonel[16].

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 1941[17]. One of the pair, Max Rosenheim, later President of the Royal College of Physicians and enobled with an FRS, had also in March 1941 asked the Wright-Fleming group for advice on Type XIV anti-pneumococcal serum[7].

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 advised[18]. Before these results were obtained, polyvalent pneumococcal antiserum could be given intravenously with caution[18]. This done, a loading dose of sulphapyridine, then called M and B 693, was given, generally by mouth[18,19]. 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

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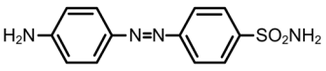
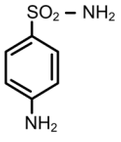
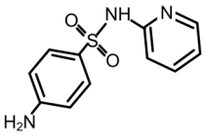
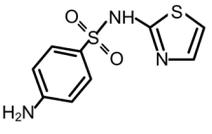
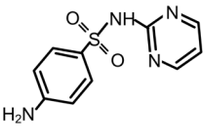
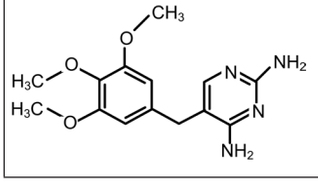
Fig 1. Professor Sir Alexander (1881-1955) and Lady (Sareen) Fleming on the steps of 25 University Square, Belfast just after D-Day[2,3].

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)[4]. 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[4,5]. Fleming's mold NRRL 1249 produced 2-4 Oxford Units per ml, 1951-B25. Q-176 produced 750 times Fleming's mold[4]. 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[4]. 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[2].

disease[28]. 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[29]. Both Rosenheim and Rycroft knew that penicillin was being produced at Oxford[30] and in New York at Columbia University,[17] "in a manner that took over many rooms".

TABLE I:

Sulphonamides In Order Of Therapeutic Introduction

1. PRONTOSIL  **2. SULPHANILAMIDE**  **3. SULPHAPYRIDINE (M and B 693)** 	1. Prontosil, $C_{12}H_{14}ClN_5O_2S$ [20,21] was developed by the Bayer team of H. Hörlein and G. Domagk who filed German patent application No. 607537 in 1932[22]. 2. Sulphanilamide, $C_6H_8N_2O_2S$ [23] was first synthesized by P Gelmo in 1908. The Tréfouëls advanced work on the therapeutically active component of Prontosil and published their results in 1935[24]. 3. Sulphapyridine, $C_{11}H_{11}N_3O_2S$ [23] was 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[25]. LEH Whitby was recruited to test sulphapyridine by Ewins in 1936[26].
4. SULPHATHIAZOLE  **5. SULPHADIAZINE**  **6. TRIMETHOPRIM** 	4,5. In March 1941 sulphathiazole, $C_9H_9N_3O_2S_2$ [23] and sulphadiazine, $C_{10}H_{10}N_4O_2S$ [23] were obtainable in Belfast and could have been used instead of sulphapyridine (M and B 693). 6. The production of sulpha drugs, such as trimethoprim, $C_{14}H_{18}N_4O_3$, [23] has remained close to World War II levels with increased veterinary and animal husbandry use[27].

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

* Throughout this Medical History, "I" or "my" refers to the first author.

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[35,36]. Benjamin Rycroft published his first paper on human corneal transplantation in 1935[37]. 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[36,38]. Rycroft published the first book in the English Language describing corneal grafts[39]. Sir Benjamin's obituary says "he rode to show-standard and hunted"[35]. He was an accomplished organist, and "all his life he maintained an interest in the piano"[35]. 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 on wild animal surgery[40,41]. The average adult female tiger requires a number 15 Magill-type tracheal tube[41,42].

Preparations". The section on "Antipneumococcic Sera (Rabbit), Lederle, covers the 'higher types' of pneumococcal pneumonias for which horse sera have not previously been available"[31]. "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"[31]. 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 antipneumococcic 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 "Antipneumococcic Rabbit Serum Type XIV"[32]. 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[33].

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[43]. 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[2].
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 ophthalmia neonatorum at Sheffield Royal Infirmary[44,45]. From 1932-35 Howard Florey was Professor of Pathology at Sheffield[45].
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[44,45].
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 penicillin[2,17,46]. By May 6, 1941, Dawson's group had treated a total of four patients[46].
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[2].

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[34]. 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"[35], my father replied. Rycroft arrived about an

Fig 3. Professor Lord Rosenheim of Camden, KBE, DSc, PRCP, FACP, FRS, 1908-72. Oil on Canvas by Judy Cassab, CBE, AO, 1972. 2008 Artists Rights Society (ARS), New York/VI$COPY, Australia. Reproduced with permission of the Artists Rights Society, solely for this Medical History, from the Heritage Centre, Royal College of Physicians, London.

Max Leonard Rosenheim was President of the Royal College of Physicians of London from April l966 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[47]. Educated at Shrewsbury School and St. John's College, Cambridge. At University College Hospital by pioneering the treatment of urinary infections with mandelic acid[48] and hypertension with pentamethonium[49,50] 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.

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 Fleming[2] 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

Fig 4. Sir Almroth Edward Wright, KBE, MD, FRCPI, FRS (1861-1947). Oil on canvas, 1934, by Sir Gerald Kelly, KCVO, PRA, LLD (Cantab and TCD). Reproduction courtesy of St. Mary's Hospital Archives (Imperial College Healthcare NHS Trust), London.

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 1883[2,7]. 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 CS Roy, Victor Horsley and CS Sherrington. When Roy became head of Pathology at Cambridge University in 1886, he appointed Wright Demonstrator in Pathology[51]. 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's[2].

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 replied[52]. 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 serum[32]. I asked what Rycroft had been forced to do. "Argue with Oxford," was the reply.

The next day but one, Rycroft changed his piano tune from "Smoke Gets in Your Eyes" to "The Blue Danube". He came upstairs and said, "John, you are better or Max's army career is over before it begins". "Yes, I am," I replied. "Can I go and see my pony?" "Not yet." Max reappeared somewhat later. He said he had called Whitby[53-56]. I replied, "My ancestors there

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[53-57]. 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[61]. Rosenheim, with his recent Harvard experience advised on what Harvard's Fifth General Hospital[34] and other US Medical Services would require. He liaised with Professor WWD Thomson[8] for WWD's own experience at Boulogne of Harvard'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"[54]. 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"[54].

"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"[54]. 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[54].

Fig 5. Sir Stewart Duke-Elder, GCVO, MD, DSc, FACS, FRCS, FRCP, FRS (1898-1978). Oil on canvas by Ruskin Spear, reproduced with the permission of Moorfields Eye Hospital and UCL Institute of Ophthalmology, solely for this Medical History.

"The Duke" was Surgeon Oculist to Their Majesties Edward VIII, George VI, and Elizabeth II. Educated at St. Andrews and London Universities, Howe Lecturer, Harvard University, 1930, Craig Prizeman, Belfast, 1952. Brigadier General 1940-46, later Consulting Ophthalmic surgeon to the British Army, 1946-61. Married in 1928 Phyllis Mary Edgar, MB, BS (London), who helped her husband with his legendary texts[58,59] including his Craig Prize Oration[60]. Ruskin Spear also portrayed Lord Ashby, Vice Chancellor of Queen's Belfast and Master of Clare.

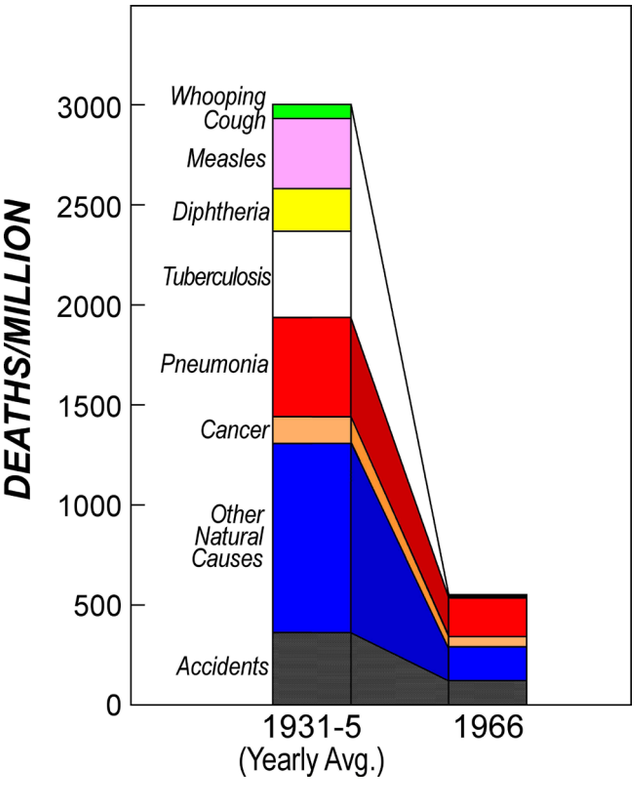


Fig 6. Comparison between childhood death rates before and after the introduction of sulphanilamide and antibiotic chemotherapy. Figures were provided by the Association of the British Pharmaceutical Industry to Professor Ronald Hare[43].

Fig 7. Otto Dix: Portrait of Professor Gerhard Domagk, MD, DSc, FRS (1895-1964), oil on canvas, 1953. Art Collection, Bayer AG, Leverkusen, Inv. No. 0474. © 2008 Artists Rights Society (ARS), New York/VG Bild-Kunst, Bonn. Reproduced with permission of the Artists Rights Society/VG Bild-Kunst solely for this Medical History.

Gerhard Domagk was born in Laagow, Brandenburg, Germany, and trained at the University of Kiel Medical School and at Münster for post-graduate studies. In 1927 Domagk was appointed Director of Research in Experimental Pathology and Bacteriology at Bayer. In 1928, he was concurrently appointed Professor of Pathology at Münster. After testing many azo-compounds, Domagk added a sulphonamide group to chrysoidine and produced in 1932 prontosil[67] which in 1936 saved the life of Franklin Delano Roosevelt Jr. at the Massachusetts General Hospital[68]. A few months before, in 1935, at the Pasteur Institute in Paris, the husband and wife team, Jacques and Thérese Tréfouël, showed that sulphanilamide, which they synthesized, was the active component of prontosil, and less toxic than the larger molecule[24]. In 1937 and 1938 Lionel Whitby published his classic papers on 4-(p-aminobenzine-sulphonamide) pyridine treatment of pneumococcal pneumonia in mice and humans[26,69]. Domagk was awarded the Nobel Prize for Medicine in 1939 but Hitler, having imprisoned him for a week, forbade its acceptance[22]. In 1947, Domagk gave his Nobel Oration in Stockholm[70]. The Caroline Institute never paid Professor Domagk the monetary prize[22].

As Whitby states, "Recognition of the characteristic change requires much practice"[54]. 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 the antiserum? And did it need to be given as well as the sulphapyridine (M and B 693) they had already started me on, or should sulphathiazine, or even sulphadiazine[62,63] be given? (Table I). These sulphonamides are not bacteriocidal in therapeutic doses. Max Finland's group at Harvard in the previous year had shown that results were better if both the specific anti-serum and the sulphapyridine (M and B 693) were given as early as possible in the course of the lobar pneumonia[14,15].

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"[19]. 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"[18]. 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 pneumonia[64]. 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"[33] (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 '39[22,65,66] (Figure 7). The French[24] stole it and the English improved it so you got better and did not go pink or blue"[31]. I later asked what a Quellen test was and why Mary's had had to coach Max. "To discover you are Type XIV". So I asked why I was Type XIV. "Because you probably kissed someone". "I don't kiss girls". "John, you had better go to the Dragon School."

TABLE III:

Penicillin Production In The USA, UK and Australia

Monthly Production In Oxford Mega Units			
Date	USA	UK	AUSTR
Jan. 1942	2	<1	
June 1942	10	20	
Jan. 1943	100	100	
June 1943	5,000	700	
Jan. 1944	100,000	2,000	3,000
June 1944	750,000	5,000	6,000

Production figures derived from Lord Florey's *Antibiotics* published in 1949[44] and US figures declassified in stages post-World War II[4]. 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 transfer[4]. The University of Toronto delivered approximately 1,000 Oxford Mega Units to Canadian Armed Forces in May 1944[43].

Fig 8. Professor Sir Lionel Whitby, CVO, MC, MD, DSc, LLD, FRCP. 1895-1956. Oil on Canvas by Waldron West, photographed by Chris Titmus, Hamilton Kerr Institute, Fitzwilliam Museum, Cambridge. Reproduced by permission of the Master and Fellows of Downing College, Cambridge, solely for use in this Medical History.

Sir Lionel Whitby was educated at Bromsgrove and Downing College, and is here portrayed in his Cambridge MD gown. He was a Royal Fusilier in 1914, later machine gun officer in Serbia, Gallipoli, Salonika and a hero at Passchendale, where he was awarded the Military Cross as a Major. In 1918 he was severely wounded and had to have a leg amputated. After the Natural Sciences Tripos he was Freeman Scholar at the Middlesex: in 1929 as Assistant Pathologist he attended King George V in his serious illness[55]. It was largely Whitby's work that led to the success of sulphapyridine (M and B 693) in the treatment of pneumococcal pneumonia[26,53,69]. In World War II Whitby was in charge of the Army Blood Transfusion Service and also treated Prime Minister Churchill's 1943-44 infections[74]. Lady Whitby was a physician and consummate hostess. Her husband was Visiting Professor of Medicine at Harvard and Cutter Lecturer in 1946. Sir Lionel died after an operation at the Middlesex[55].

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 series[30] (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].

Fig 9. Joe Waldbillig, MAXWELL FINLAND (1902-1982), Oil on canvas, Harvard Art Museum, Fogg Art Museum, Harvard University Portrait Collection, Harvard Medical School, H826. Photo: Imaging Department President and Fellows of Harvard College.

Born near Kiev, in the Ukraine, Max graduated from Boston English High School, and gained a scholarship to Harvard College, where he became a chemist under the tuition of Professors James Bryant Conant, later President of Harvard University, and Louis Fieser[75,76]. In 1922 Max entered Harvard Medical School and subsequently interned on the 2nd Medical Service of the Boston City Hospital. He was promoted to "pneumonia resident", but he also worked in Professor Milton Rosenau's Department of Preventive Medicine and Hygiene where anti-pneumococcal serum was being produced. He remained at the Boston City Hospital and became Head of its Thorndike Memorial Laboratory, and George Richards Minot Professor of Medicine at Harvard Medical School. Harvard and Boston City Hospital severed almost all relationships in 1973, and the Thorndike moved to the Harvard Medical School campus. Maxwell Finland was elected a member of the US National Academy of Sciences. In 1982 Harvard granted him an honorary DSc, an unusual honour for its own faculty. The citation read "A distinguished and loyal son for (over) sixty years"[75].

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 Asia[52].

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 penicillin[72].

Dragon Elizabeth Cairns and Old Draconian 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[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[73] 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[26,53,69] about which Max had called Whitby a decade earlier (Figure 8). I was having trouble getting accepted by Clare. My father suggested I ask to see Whitby, Master of Downing and Regius Professor of Physic. In Master Whitby's sitting room we discussed 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 one-man admissions process. On January 15th, 1952, he had written to Harrow, with a copy to my father, "Hedley-Whyte's performance in the Clare Entrance was very poor indeed…I am wondering whether he is likely to be able to tackle the Natural Sciences Tripos." Thirkhill relented; Whitby was 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 Tessa[77] and I started work in Boston.

When we were doing rounds and combating infection in our Harvard Intensive Care Units, Max Finland advised us[78-83]. On the enoblement of Max Rosenheim, Finland remarked to our team, "In medicine there is only one great Max, and now he is Lord Max".

WHO ON PNEUMOCOCCAL VACCINES

Recently there has been increased emphasis on prevention of pneumococcal pneumonia, especially in children, the elderly and the chronically ill. In 2007 the World Health Organization (WHO) attested to the success of antipneumococcal vaccination and strongly recommended 7-valent pneumococcal conjugate vaccine (PCV-7), which was effective against 65-80% of serotypes associated with invasive pneumococcal pneumonia disease in young children from western industrialized populations. This WHO Position Paper pointed out the variability of coverage among populations in developing countries and noted progress in the development of vaccines with wider serotype coverage[84]. Recently serotype 19A strep. pneumoniae was shown to account for over 28% of invasive pneumococcal disease in Alaskan children under two years of age. Serotype 19A was not countered by the PCV-7 these children had received[85]. A 23-valent pneumococcal polysaccharide is the subject of an October 2008 WHO Position Paper[86] and is now endorsed against a moving target of invasive pneumococcal disease[87].

POSTSCRIPT

Memory, while obviously fallible, is said to be most reliably implanted at seven years of age. My recall has been aided by my father Angus' notes on the course of my lobar pneumonia, which are on pages 5,6 and the inner cover of his copy of Osler's Medicine which had survived bombing in Rennes on June 17th, 1940.[34] Memory was reinforced in later years by meeting with my physicians in Belfast, Cambridge, London and Boston[47] and by parental and uxorial admonitions.

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