### Citation

### Accessed
August 28, 2017 11:03:26 AM EDT

### Citable Link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:4732014

### Terms of Use
This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)
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 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, a pied à terre for visits from Cardiff where he was stationed. 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 home2.

WORLD WAR I: FLEMING, THOMSON AND WRIGHT
Captain Alexander Fleming had worked under Colonel Sir Almroth Wright’s command from 1915 to 1918 at Boulogne2,7. Captain WWD Thomson and Captain N Keith of Canada, later of the Mayo Clinic, were junior officers in
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.

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.

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...”

---

**Table I: Sulphonamides In Order Of Therapeutic Introduction**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sulphonamide</th>
<th>Formula</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Prontosil, C₁₂H₁₄CIN₅O₂S</td>
<td>20,21</td>
<td>Developed by the Bayer team of H. Hörlein and G. Domagk who filed German patent application No. 607537 in 1932.</td>
</tr>
<tr>
<td>2.</td>
<td>Sulphanilamide, C₆H₈N₂O₂S</td>
<td>23</td>
<td>First synthesized by P. Gelmo in 1908.</td>
</tr>
<tr>
<td>3.</td>
<td>Sulphapyridine (M and B 693), C₁₁H₁₁N₃O₂S</td>
<td>23</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, C₉H₉N₃O₂S₂</td>
<td>23</td>
<td>Obtainable in Belfast and could have been used instead of sulphapyridine (M and B 693).</td>
</tr>
<tr>
<td>5.</td>
<td>Sulphadiazine, C₁₀H₁₀N₄O₂S</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Trimethoprim, C₁₄H₁₈N₄O₃</td>
<td>23</td>
<td>Production of sulpha drugs, such as trimethoprim, has remained close to World War II levels with increased veterinary and animal husbandry use.</td>
</tr>
</tbody>
</table>

---

Throughout this Medical History, “I” or “my” refers to the first author.
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 ophthalmia 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 penicillin. 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.

As a result of his telephoned investigations, Rosenheim discovered Squibb was about to release “Antipneumococcic 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 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 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 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 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. 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.

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.
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 pneumonia44. 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”19 (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”31. I later asked what a Quellen test was and why Mary’s 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>
<thead>
<tr>
<th>Table III: Penicillin Production In The USA, UK and Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monthly Production In Oxford Mega Units</strong></td>
</tr>
<tr>
<td>Date</td>
</tr>
<tr>
<td>Jan. 1942</td>
</tr>
<tr>
<td>June 1942</td>
</tr>
<tr>
<td>Jan. 1943</td>
</tr>
<tr>
<td>June 1943</td>
</tr>
<tr>
<td>Jan. 1944</td>
</tr>
<tr>
<td>June 1944</td>
</tr>
</tbody>
</table>

Production figures derived from Lord Florey’s Antibiotics published in 1949 and US figures declassified in stages post-World War II. 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. The University of Toronto delivered approximately 1,000 Oxford Mega Units to Canadian Armed Forces in May 194444.

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 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 sulphadiazine23 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 pneumonia14,15.
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.

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.
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, 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 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 about which chemistry Laboratories of King’s College, Newcastle-upon-Tyne. I read Lionel Whitby’s classic papers about which

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 about which

12. Cairns H. Head injuries in war, with special reference to gunshot wounds, including a report on the late results in some of Harvey Cushing’s cases of 1917. War Med 1942;5(2):772-85.

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. 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. A 23-valent pneumococcal polysaccharide is the subject of an October 2008 WHO Position Paper and is now endorsed against a moving target of invasive pneumococcal disease.


76. Hedley-Whyte ET. On being a pathologist: how does one plan a career, or does one? Human Pathol 2008;39(9):1269-74.


