Lobar Pneumonia Treated by Musgrave Park Physicians

Citation

Permanent 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

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
Medical History

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, 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 sequela of treatment 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, 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.

When they returned to take the Belfast-Larne train, the Flemings discovered they were missing his lantern slides and lecture notes1. 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 was often shortened. 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 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

David S Sheridan Professor of Anaesthesia and Respiratory Therapy, Harvard University, 1400 VFW Parkway, Boston, MA 02132-4927. USA.

This work was supported by the David S Sheridan Professorship of Anaesthesia and Respiratory Therapy, Harvard University.

Correspondence to Prof Hedley-Whyte

john_hedley-whyte@hms.harvard.edu
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, \textit{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 \textit{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 \textit{“New Pharmaceutical Disease”}. Throughout this Medical History, “I” or “my” refers to the first author.

---

**Table I:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sulphonamides In Order Of Therapeutic Introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Prontosil, $\text{C}_12\text{H}_14\text{CIN}_5\text{O}_2\text{S}$, was 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, $\text{C}_6\text{H}_8\text{N}_2\text{O}_2\text{S}$, was first synthesized by P. Pelmo in 1908. The Tréfouëls advanced work on the therapeutically active component of Prontosil and published their results in 1935.</td>
</tr>
<tr>
<td>3.</td>
<td>Sulphapyridine, $\text{C}_11\text{H}_11\text{N}_3\text{O}_2\text{S}$, 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. LEH Whitby was recruited to test sulphapyridine by Ewins in 1936.</td>
</tr>
<tr>
<td>4.</td>
<td>Sulphathiazole, $\text{C}_9\text{H}_9\text{N}_3\text{O}<em>2\text{S}<em>2$ and sulphadiazine, $\text{C}</em>{10}\text{H}</em>{10}\text{N}_4\text{O}_2\text{S}$, were obtainable in Belfast and could have been used instead of sulphapyridine (M and B 693).</td>
</tr>
<tr>
<td>5.</td>
<td>Trimethoprim, $\text{C}<em>{14}\text{H}</em>{18}\text{N}_4\text{O}_3$, has remained close to World War II levels with increased veterinary and animal husbandry use.</td>
</tr>
</tbody>
</table>
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 1935. 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.

As a result of his telephoned investigations, Rosenheim discovered Squibb was about to release “Antipneumococcic Sera (Rabbit)”. 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 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.

Table II:

**Ophthalmologists And Pre-March 1941 Penicillin Human Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drs Frederick Ridley and SR Craddock reported experimental extraction</td>
</tr>
<tr>
<td>on April 10, 1929, of a concentrated penicillin. Ridley was later a</td>
</tr>
<tr>
<td>colleague of Rycroft at Moorfield’s Hospital, London.</td>
</tr>
<tr>
<td>Professor Alexander Fleming, late in 1929, treated Dr KB Rogers, an</td>
</tr>
<tr>
<td>assistant to Sir Almroth Wright. Pneumococcal conjunctivitis was</td>
</tr>
<tr>
<td>promptly and completely cured.</td>
</tr>
<tr>
<td>Dr Cecil G Paine, a St. Mary’s graduate, grew his own penicillin from</td>
</tr>
<tr>
<td>Fleming’s strain and in 1933 with ophthalmologist Albert Nutt</td>
</tr>
<tr>
<td>successfully treated ophthalmia neonatorum at Sheffield Royal Infirmary</td>
</tr>
<tr>
<td>From 1932-35 Howard Florey was Professor of Pathology at Sheffield.</td>
</tr>
<tr>
<td>For his eighth case, successfully treated with penicillin a colliery</td>
</tr>
<tr>
<td>manager who had an intracocular foreign body and pneumococcal infection.</td>
</tr>
<tr>
<td>Successful extraction was enabled.</td>
</tr>
<tr>
<td>On October 15, 1940 Dr Martin H Dawson of Columbia University, New</td>
</tr>
<tr>
<td>York, NY, began to treat three patients with retinal Roth spots due to</td>
</tr>
<tr>
<td>subacute bacterial endocarditis, with Columbia-manufactured penicillia.</td>
</tr>
<tr>
<td>By May 6, 1941, Dawson’s group had treated a total of four patients.</td>
</tr>
<tr>
<td>On February 12, 1941, Dr Charles Fletcher of the Nuffield Department</td>
</tr>
<tr>
<td>of Medicine at Oxford University started penicillin treatment on</td>
</tr>
<tr>
<td>policeman Albert Alexander, aged 43. Following a rose scratch, post</td>
</tr>
<tr>
<td>left-eye exenteration, Alexander developed endophthalmitis and orbital</td>
</tr>
<tr>
<td>cellulitis. Treatment was initially successful but Alexander died on</td>
</tr>
<tr>
<td>the 15th March 1941 after Oxford’s supply of penicillin had been</td>
</tr>
<tr>
<td>exhausted.</td>
</tr>
</tbody>
</table>

As a result of his telephoned investigations, Rosenheim discovered penicillin a colliery manager who had an intraocular foreign body and pneumococcal infection. Successful extraction was enabled.

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 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 Johnian52. 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. 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 Whitby53-56. 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 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. 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 Whitby53-56. 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.
specific anti-serum and the sulphaspyridine (M and B 693) were given as early as possible in the course of the lobar pneumonia\textsuperscript{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 \textit{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”\textsuperscript{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”\textsuperscript{10}. 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\textsuperscript{14}. 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”\textsuperscript{19} (Figure 6).

\textbf{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 1939\textsuperscript{22,65,66} (Figure 7). The French\textsuperscript{24} stole it and the English improved it so you got better and did not go pink or blue”\textsuperscript{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.”

\begin{table}[h]
\centering
\caption{Penicillin Production In The USA, UK and Australia}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Monthly Production In Oxford Mega Units} & \textbf{USA} & \textbf{UK} & \textbf{AUS} \\
\hline
\textbf{Date} & & & \\
\hline
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 \\
\hline
\end{tabular}
\end{table}

Production figures derived from Lord Florey’s Antibiotics published in 1949\textsuperscript{49} and US figures declassified in stages post-World War II\textsuperscript{4}.

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. 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”.

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.

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”. He’s good at using penicillin.
Dr. Lionel Whitby's classic papers about which manupulate 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 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." Thirkill 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 and I started work in Boston.

When we were doing rounds and combating infection in our Harvard Intensive Care Units, Max Finland advised us to "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 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." Thirkill 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 and I started work in Boston.

When we were doing rounds and combating infection in our Harvard Intensive Care Units, Max Finland advised us to "Remember Cairns' assistant Captain Calvert handing the tea around on at least one occasion.

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. Memory was reinforced in later years by meeting with my physicians in Belfast, Cambridge, London and Boston and by parental and uxorial admonitions.

The authors have no conflict of interest.

REFERENCES

12. Cairns H. Head injuries in war, with especial reference to gunshot wounds, including a report on the late results in some of Harvey Cushing's cases of 1917. War Med 1942;2(5):772-85.
Lobar pneumonia treated by Musgrave Park physicians

64. Moore JF, Thomas RE, Kistler M, Leland RM, Hallstone VE. Pneumococcal pneumonia: analysis of the records of 1,496 patients treated in the Los Angeles County Hospital from 1934 through 1938. Arch Int Med 1940;66(12):1290-316.

© The Ulster Medical Society, 2009.


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


86. 23-valent pneumococcal polysaccharide vaccine. WHO position paper. Wkly Epidemiol Rec 2008;83(42):373-84.