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Medical History

Tuberculous Scrofula: Belfast Experience

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SUMMARY

The Belfast blitzes of 1941 are blamed in our family for the scrofula of my younger brother and sister and myself. Guinea pigs and rabbits at Musgrave Park proved that each of us had bovine derived TB infection caused by failure to pasteurize milk when tuberculin-tested milk was not available. The clinical head of Harvard Medical School's anti-tuberculosis effort contacted his boss, Professor Maxwell Finland, who ascertained from Selman A. Waksman that his antibiotic streptothricin was bacteriostatic against TB but too toxic for humans. Finland, born 1902, knew Waksman (born 1888) well, each having emigrated from the Czarist-ruled Ukraine. Waksman , in 1942, had hopes for an analog to streptothricin he intended to name streptomycin: an antibiotic from *Actinomyces griseus* which had been culture-isolated in 1916 for his M.Sc. thesis. Streptomycin was still 6-9 months away from animal testing. The same Actinomyces species was also able to produce actinomycin C and D that was later supplied to Professor Sidney Farber of Harvard to start successful human cancer chemotherapy.

INTRODUCTION

In the spring of 1942 at Windy Edge, Dunmurray Lane, Ryki and I* were reading *Gray's Anatomy*. We came to Arnold's nerve, the auricular branch of the vagus. Ryki was my brother's god-father, Major Benjamin Rycroft[1,2]. He began to stare at my right ankle. He must tell the Yank Badger of his suspicions. Badger had arrived as the Chief of Medicine of Harvard's U.S. 5th General Hospital[3]. He had landed at Larne in March 1942, a year after the Luftwaffe blitzes of Belfast[2,4].

Ted Badger, came to my father, his commanding officer[3] at Musgrave Park, to say that the CO's three children had scrofula. My father brought Badger from Musgrave Park to Windy Edge, and our neck glands were palpated and our chests auscultated. My sister, Sarah, was 4 ½ years old and my brother Michael 20 months. I was 8 ½ years of age. Badger said that the skin lesion over my right Achilles tendon might be scrofulous. My mother was told the preliminary diagnosis. She said we had always been given milk from tuberculin-tested cows, or milk that had been pasteurized. During the blitzes this had not been possible, so our milk had been boiled by our cook, Kitty Lee.

CONFIRMATION OF DIAGNOSIS

Badger, as Harvard's chief tuberculosis clinician under Professor Max Finland[1], knew the importance of finding the "index case"[5]. He also knew that scrofula might be caused by exposure to human TB, but in our cases was more likely to be bovine. In humans the incubation period during childhood could be a year or more. The fact that we three children were diagnosed simultaneously suggested to Badger a strong infecting dose.

Badger asked me if anyone had coughed over me. He then asked if a cow had coughed over me. I laughed and said "No". He next asked if any of the three of us had kissed a local cow. "No." Did we like milk? "Yes." Had we been given boiled milk? "Only at the time of the blitzes." Our cook, Kitty Lee, and our nurse were then examined. They were, and had been, in perfect health. Badger then asked them if the milk had always been brought to a boil before being given to us. An awkward silence ensued. Kitty Lee said that once during the blitzes, when the regular tuberculin-tested milk, or guaranteed pasteurized milk could not be delivered, the milk for the nursery had been taken before her wood-fire had really warmed the local substitute. At very least, our milk should have been heated to 62º C for 30 minutes or 72ºC for 15 minutes. These were the rules of the Belfast Cooperative Society promulgated in 1913, said my father[6].

MANAGEMENT

What to do? Badger suggested that he preferred to use American equipment, methods and personnel. My father was in a delicate situation. The British were threatening him with court martial for purchasing illegal Éire and border-produced food for his command, the now- Allied Military Hospital at Musgrave Park[3,7]. The Whiteabbey TB Hospital scandal was being exploited by the left-wing politician Harry Midgley[4].

In 1908 TB was made a notifiable disease in Northern Ireland[6,8]. The United States authorities were convinced, not without reason, that United Kingdom TB incidence was a disgrace. In 1932, a Cattle Disease Committee was established, which reported in 1934 that approximately thirty percent of U.K. cows were tuberculous[9,10]. In Ulster, control of bovine TB was, during the period 1935-40 better than in Scotland, but not as successful as in England and Wales[10,11]. The Registrar-General's Annual Report for 1941 cites death rates from tuberculosis as 1.04 per 1,000 in Northern Ireland, 0.73 for England and Wales, 0.85 for Scotland and 1.24 for Éire[12]. According to Lionel Whitby[13], in the U.K. 5 years

* This, and all other first-person references are to the first author.

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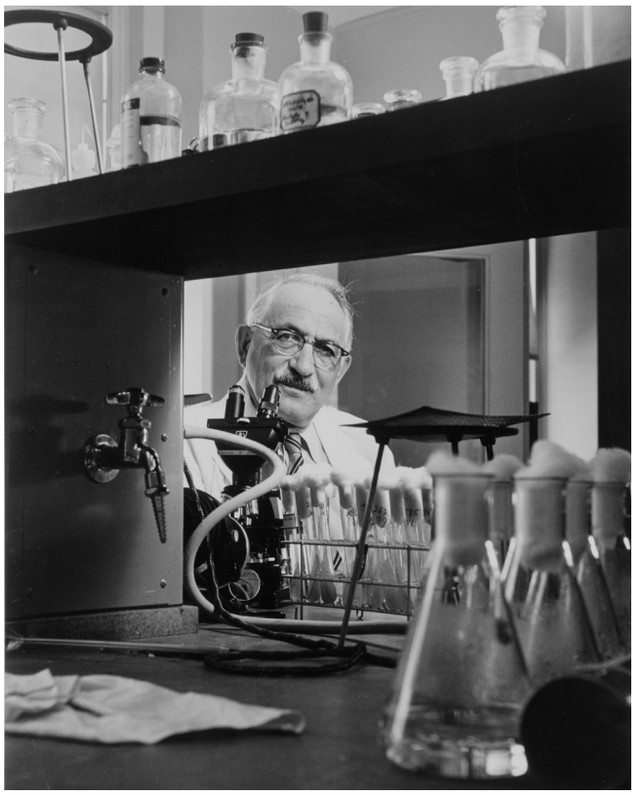

Fig 1. Selman Waksman by Philippe Halsman, gelatin silver print on paper, 1954. Image/Sheet: 34.7 x 27.4 cm (13 11/16 x 10 13/16"), mat: 71.1 x 55.9 cm (28 x 22"). National Portrait Gallery, Smithsonian Institution; gift of Steve Bello in memory of Jane Halsman Bello, © Philippe Halsman Archive, NPG.2004.45. Born in Prikula, near Kiev, on July 22, 1888, Selman Abraham Waksman matriculated in 1910 as an extern from the 5th Gymnasium in Odessa. Next year, having won a New Jersey State Scholarship, he entered Rutgers University[16,17]. In 1916, his seminal paper on Streptomycin[18,19] won him his M.Sc. degree from Rutgers. He became a U.S. citizen and was appointed a Research Fellow at the University of California, Berkeley. The University of California granted his Ph.D. in Biochemistry in 1918. The remainder of Selman Waksman's career was spent at Rutgers. He was elected to the U.S. National Academy of Sciences in 1942. Selman Waksman visited Ireland once, in 1946. He was confined with his wife Deborah to "a boarding house in Adare" in County Limerick's Golden Vale for three full days. "We were herded like cattle and told to wait. The facilities, especially the food, were very poor"[17]. After release, the Waksmans met their physician son, Byron, in Frankfurt-am-Main, where he was stationed in the U.S. Service after his having received his M.D. degree in 1943 from the University of Pennsylvania[17]. In 1952, Selman Waksman received the Nobel Prize in Physiology or Medicine. The Nobel Committee cited his work on "the microbiological population of the soil, sulphur oxidation by bacteria, microorganisms and soil fertility; decomposition of plant and animal residues, nature and formation of humus; occurrence of bacteria in the sea and their role in marine processes; production and nature of antibiotic substances; and taxonomy, physiology and biochemistry of the actinomycetes"[20]. After Stockholm he was decorated by the Japanese Government with the Second Order of Merit with the Grand Gordon of the Rising Sun and received in audience by the Emperor. He and his wife were invited to dinner at the home of H.I.H. Prince Takahito Mikasa, where plans for establishment of the Japan Waksman Foundation were formulated[21]. Selman Waksman died on August 16, 1973. Deborah, his devoted wife of 57 years, and a most talented musician, died a year later. They are buried at Wood's Hole, Cape Cod, Massachusetts. Byron, their son, an only child, joined the staff of the Massachusetts General Hospital before accepting chairs at Yale and in New York. He has returned to Harvard as a Visiting Scientist at the Center for Neurologic Diseases, where he is now the Doyen of Neuroimmunology and Mentor Extraordinaire[16,17].

before World War II, 70 percent of scrofula was caused by bovine TB. With bovine TB bacteria, rabbit intravenous inoculation leads to death within two months. Inoculation with human TB almost always leaves the rabbit unharmed[13]. When inoculated with bovine TB, guinea-pigs die in about six weeks. With human TB inoculation, the guinea pigs usually survive six months[13].

Badger said that it would take a week or so to assemble the necessary diagnostic equipment and the U.S. tuberculin for the Mantoux tests. Badger continued by saying that the British needles were blunt[14]. As to the tuberculin purity, did my father not know of the Lübeck "massacre of the innocents"—72 babies killed by contaminated tuberculin?[15]

Benjamin Rycroft[1] knew of our presumed scrofula. He asked Badger to ask his Boston boss Max Finland[1] to enquire whether the large Waksman group (Figure 1) at Rutgers University had any of their soil-derived antibiotics (Tables 1 and 2) ready to treat his godson. Rycroft and Badger knew that in 1932 the U.S. Federal Government and TB Foundations had given Professor Selman A. Waksman substantial support to find an antibiotic cure for tuberculosis[53]. This funding was continuing as were the Rutgers'[19,22-49] and Johns Hopkins'[54-56] publications.

Max Finland replied to Badger that it was a waste of time to do Mantouxs and that he "should put me on M and B 693 (Table 3) but not my brother and sister--she could take halibut-liver oil pills". My TB had spread, but theirs appeared localized. With fresh air and cod or halibut-liver oil my younger brother and sister would cure themselves: in our adulthood there would be a 5 percent chance of recrudescence[5].

Max Finland also told Ted Badger that Waksman had hopes for his newest antibiotic, streptothricin[37,42] and that Waksman was now concentrating on *Actinomyces griseus* which he had culture-isolated 26 years before for his Rutgers M.Sc.[19]. This, Waksman proposed to rename streptomycin and have tested, hopefully, on patients by two Mayo Clinic doctors[17,59-61].

Professor Waksman's son Byron, a medical student at the University of Pennsylvania, was now telling his father, relayed Max Finland, to quit treating tuberculous guinea pigs and rabbits and start on humans.

We awaited the U.S. equipment to needle biopsy our cervical glands and my right Achilles tendon[62-64] and appropriate swabs for our tonsils. The Musgrave Park guinea pigs and rabbits were thereafter inoculated and later autopsied. Bovine TB it was.

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TABLE 1:

Publications of S.A. Waksman related to Development of Antibiotics, 1916-1943

YEAR	JOURNAL	REF
1916	Soil Sci	19
1918	J Infect Dis	22
1919	Soil Sci	23
1937	Soil Sci	24,25,26
1939	Soil Sci	27
1940	J Bacteriol	28
	Proc Soc Exptl Biol Med	29
	Soil Sci	30
	Chronica Botanica	31
1941	Proc Soc Exptl Biol Med	32
	J Bacteriol	33
	Bacteriol Revs	34
1942	J Pharmacol Exptl Ther	35
	J Biol Chem	36
	Proc Soc Exptl Biol Med	37,42
	Soil Sci	38,39
	J Bacteriol	40
	Science	41
1943	J Bacteriol	43,45,47
	Proc Soc Exptl Biol Med	44
	Mycologia	46
	Proc Natl Acad Sci (US)	48,49

Rycroft, on a visit to Windy Edge, told us we had the King's Evil, which could be cured by a Royal laying-on of hands. My father said he had asked Arnold Stott (Figure 2), physician to the Royal Household, to take over our management. "Second best to His Majesty," rejoined Rycroft.

After inoculation with the aspirate from my neck, the guinea pig and rabbit were unharmed, but became symptomatic when inoculated with aspirate from the lupus over my right Achilles tendon. My supratendinous aspirate was of bovine tuberculous origin. I was asked by Badger if I had ever been bitten on the right ankle by my brother or sister. " They had neck pathology, not facial," said Rycroft. My ankle healed after a fortnight of the sulphonamide treatment, which was then terminated.

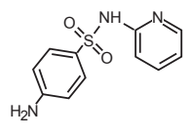
Remembering my reading lessons of the spring, I asked General Arnold Stott in September 1942 whether he had discovered Arnold's nerves in the hiding place of earwigs. "No, it was a German, Friedrich Arnold (1803-90)[70]. He died when I was your age," my Doctor Arnold retorted.

Arnold Stott took over our surveillance until 1952. Stott was a Governor of Wycombe Abbey, my sister's boarding school[67].

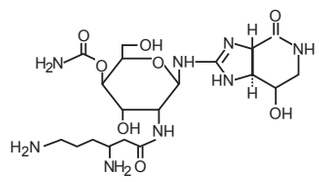
TABLE 2:

1. *SULPHAPYRIDINE (M and B 693)*[1,50] $C_{11}H_{11}N_3O_2S$
2. *STREPTOTHRICIN*[50] $C_{19}H_{34}N_8O_8$
3. *STREPTOMYCIN*[50] $C_{21}H_{39}N_7O_{12}$
4. *PAS (PARA-AMINO SALICYLATE SODIUM)*[51,52] $C_7H_6NNaO_3.2H_2O$
5. *ISONIAZID*[50] $C_6H_7N_3O$

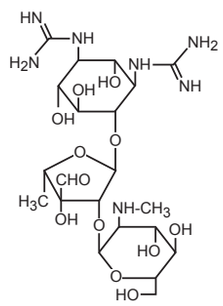
1. SULPHAPYRIDINE (M and B 693)



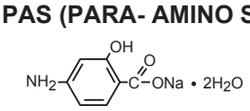
2. STREPTOTHRICIN



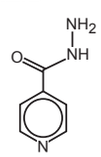
3. STREPTOMYCIN



4. PAS (PARA- AMINO SALICYLATE SODIUM)



5. ISONIAZID



Our upbringing was in no way constrained. Our schools were told by Sir Arnold Stott, from 1946 KBE, that we were in no way infectious. My sister's scrofulous neck glands were excised by a Newcastle-upon-Tyne surgeon, Ronald Watts, FRCS, Edin.—inelegantly but successfully, said my father. Stott agreed and my sister refused plastic surgery. My brother Michael's tonsils were removed. He awoke from the chloroform shouting "John's done this to me!" Not true, but

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Fig 2. Sir Arnold Walmsley Stott, KBE, FRCP (1885-1958), by Walter Stoneman © National Portrait Gallery, London, and reproduced with their permission (No. x166999). Arnold Walmsley Stott was born at Oldham, Lancashire on July 12, 1885, and educated at Rugby School, Trinity College Cambridge, and St. Bartholomew's Hospital[65,66,67]. He was trained in Cardiology by Sir Thomas Lewis. Stott was recalled to Barts as Chief Assistant in Pediatrics, and then successively appointed to the Honorary Staffs of the Royal Chest Hospital and the Westminster Hospital. Stott served in both World Wars: in the First as a Major and in the Second as a Major-General. During World War II he was Consultant Physician to his second BEF and after evacuation from Dunkirk Adviser in Medicine to the U.K. Emergency Medical Service[66]. Stationed in Escrick Park near York with my father, they together inspected numerous war-time hospitals. From 1942 to late 1944 there were constant complaints from the RAF and the American Army Airforce that wounded bomber crew were not under the control of Airforce doctors. Air Vice-Marshall Geoffrey Keynes[14] moved stored blood to bomber stations and constantly visited them[68]. Stott and my father were often responsible for vetting those about to be placed in occupied Europe. Together with Elliott Cutler, Moseley Professor of Surgery at Harvard[3], and General Paul R. Hawley[69], Stott and my father planned the medical and surgical staffing for the consequences of the D-Day landings[69]. The initial medical D-Day landing meeting, according to my father's diary, was on Friday, March 5, 1943, at Thirlstaine Hall, Cheltenham, Gloucestershire. Stott used to regale me, my brother, and sister with apparently spontaneous topical rhymes seemingly based on the extraordinary activities of my brother's god-father, Benjamin Rycroft and his friend Dicky Hunter[1,2]. One of Hairy Ryki's rhythmical heroes was Ulsterman Harold Alexander, later Earl.

Stott joined the Council of Wycombe Abbey girls' school to which "He was a good friend"[67] in May 1951, and chaired the Council from 1953 through 1956. He was married for 47 years to Lily Holland. Their only son, J.R.W. Stott, was a long-time Rector of All Souls, Langham Place and Chaplain to Her Majesty the Queen. Her father, King George VIth, had appointed Arnold Stott, Physician to the Royal Household in 1937[66].

Badger had concluded that maybe it was the Belfast blitzes' infected milk, so we blamed the Germans.

FOLLOW UP

During the 1940s and early 1950s, Stott would examine us and recite his 'Ryki' ballads about Rycroft's war and horsemanship and the snakes and wild animals in Rycroft's Number 35 Harley Street consulting rooms. We heard from Stott of Rycroft's successful human corneal grafts[1] later of his use of Waksman's actinomycin D (NSC-3053) to treat certain eye tumors.

On July 1, 1960 my wife[71] became Sidney Farber's intern; we soon were told of Selman Waksman's 1954 arrival at the Boston Children's Hospital with 300 mg of actinomycin D (NSC-3053). The "little vial" was delivered and Waksman and Farber "started work immediately. To our great pleasure," writes Professor Farber, "we quickly found—that this was the most powerful antitumor agent"[72,73]. Within a few months, childhood Wilms' and Ewing's tumors were being cured. For gestational choriocarcinomas actinomycin was combined with Methotrexate, NSCF-740, glutamic acid, N-F-[[2,4-diamino-G-pterdinyl]methyl] methylamino]benzoyl][74]. Farber always gave credit to Gerhard Domagk's[1] group's work on animal tumor treatment with actinomycin C[75].

From 1960, Ted Badger was my caring Boston physician[76]. In 1969 our singles tennis match at The Country Club unmasked his need for an aortic valve replacement. The replacement at the Massachusetts General Hospital was entirely successful and led to a memoir and critique[77,78]. Badger lived another ten years, but would never again play tennis against me[79].

PARTIAL IMMUNITY

Is bovine TB disease protective against subsequent infection with human TB? This question has been debated since Koch's description of the bacterial causes of human and bovine tuberculosis[80]. My father did not seem to mind my boyhood conversations with Eric Arthur Blair at Greystone, Stockton-on-Tees, the home of the O'Shaughnessy's[14]. Laurence Frederick O'Shaughnessy, with whom my father had grown up, was known as Eric O'Shock from an early age. O'Shaughnessy was the famous Eric then, not his sister Eileen's husband, Eric A. Blair. Eric O'Shock's death at the Dunkirk evacuation of the second BEF was mourned by both the Allies and the Axis. He had been Sauerbruch's favourite assistant in Berlin[81].

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TABLE 3.

Treatment Of Tuberculosis

YEAR PUBLISHED	DRUG	RESULTS
1937[1,57]	Sulphapyridine (M and B 693)	Limited usefulness
1940[29,31]	Actinomycin	Very toxic; not for paediatric use[17]
1942[41]	Clavicin	Less toxic[17]
1942[41]	Fumigacin	Less toxic but less active[17]
1942[37]	Streptothricin	Delayed toxicity; active against bacteria[17]
1944[58]	Streptomycin	Similar to streptothricin, less toxic[17]

In his 1954 autobiography[17] Waksman reported the isolation of actinomycin in 1940, clavicin and fumigacin in 1941, streptothricin in 1942 and streptomycin in 1943. Publication followed within the year.

Eric Blair in 1942 and 43 questioned me at Greystone about horse herd behaviour. He was writing *Animal Farm* as George Orwell†. We discussed the intelligence ranges of Clover the intelligent mare and Mollie the flighty but beautiful mare. I emphasized the leadership roles of mares and their territorial and herd behaviour. My mother told me not to get too close to this coughing Old Etonian. My father said I was protected by my Ulster infections.

George Orwell died of a pulmonary bleed from his TB on 21st January 1950, having had severe reactions to two successive but aborted courses of streptomycin. Eileen had died on March 29, 1945, and is buried in Jesmond Cemetary near my wife's grandparents.

When I was house physician at Barts to Chest Physician Neville C. Oswald[83], he taught "that middle class doctors and nurses were protected by having had the King's Evil." Is this protection more powerful than BCG vaccination? The Harvard Technology Assessment Group chaired by Professor Fred Mosteller[84,85] could not come to a conclusion on this issue[86].

For the years 2003-2008 in some hospitals with access to the full range of drugs, the hospital mortality in patients admitted with tuberculosis is one in three[87]. In parts of South Africa the incidence of multi-drug resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (EDR-TB) is 72 per 100,000 health care workers; for the general population it is 6 per 100,000. Nosocomial infection of nurses is rampant[87]. The World Health Organization has reported an estimated 440,000 incident cases of MDR tuberculosis worldwide in 2008[88,89]. The World Health Association's (WHO) twelve recommendations for the control of TB must be implemented[90].

Sixty-nine years after the scrofula diagnosis I have a calcified cervical gland, my sister's neck scars are just visible, and my brother's cervical adenopathy seems to have had complete resolution. They have approved this Medical History.

† Mr. Blair told me the inspiration for Animal Farm's revolt of the animals was a carthorse on Hampstead Heath who went exactly where he wanted despite the wishes of his human leader. In Orwell's introduction to the Ukrainian edition of Animal Farm[82], he wrote that the horse was mistreated. He never mentioned equine ill-treatment to me.

ACKNOWLEDGEMENTS

We thank Professor Douglas E. Eveleigh of Rutgers University for his assistance. H. Boyd Woodruff[18, 28-30, 32,33,37-40] will receive the U.S. National Academy of Sciences 2011 Award for the Industrial Application of Science. Woodruff is being honored during the 148th Annual Meeting for "leading the development of multiple antibiotics, vitamin B_{12} and the avermectins, the latter revolutionizing parasite treatment in livestock and humans."

The authors have no conflict of interest.

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