ORDINARY MEETING

Monday, 13th April 2015

TUBERCULOMUCIN: A FORGOTTEN TREATMENT FOR TUBERCULOSIS

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Early in 2011, Dr Charlotte Jones, a retired general practitioner living in Monmouth, contacted Professor Tim McHugh, Director of the Centre for Clinical Microbiology at University College London, and a world leader on tuberculosis drug development.[1] Dr Jones related an extraordinary story of a treatment for tuberculosis developed 100 years previously in Prague by her grandfather, Friedrich Weleminsky (1868–1945, Fig 1).

Figure 1. Friedrich Weleminsky (1868–1945). Courtesy Charlotte Jones

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The treatment, tuberculomucin, was widely used throughout Austria, Germany and Eastern Europe, but on the eve of its commercial production in 1938 by a Belgian pharmaceutical company, Hitler annexed the Sudetenland, the German-speaking regions of Czechoslovakia, and Weleminsky and his family fled to London.

They brought with them cultures of tuberculomucin, which they continued to produce in the kitchen of their West Hampstead home and which was used illicitly in the early years of the Second World War by Weleminsky's daughter to treat sanatorium patients in Surrey. Dr Jones herself was successfully treated with tuberculomucin in the late 1940s after catching tuberculosis whilst a medical student at the Royal Free Hospital, London. She was able to provide a number of her grandfather's academic papers, as well as articles published in German by physicians who had used tuberculomucin in clinical studies in man and animals.

The increasing prevalence of multi-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis, and the limited armoury of anti-tuberculosis drugs, have established an imperative to explore all routes to new treatments for this major global health problem. The most recent statistics from the WHO for 2013, estimated 480,000 global incident cases of multi-drug resistant TB (MDR-TB) although only 97,000 were started on treatment. An estimated 9% of patients with multi-drug resistant TB had extensive drug resistance.[2] As a result, historians and scientists at UCL are collaborating on a project to determine the context in which tuberculomucin was originally produced and tested, the circumstances in which it was ultimately "forgotten", and to produce tuberculomucin in sufficient quantities to characterise its properties and test its efficacy in killing *Mycobacterium tuberculosis*. Preliminary research suggests that tuberculomucin has both bactericidal and immunomodulatory modes of action which do not overlap with current treatments.

Clinical drug-resistant strains of *Mycobacterium tuberculosis* are highly transmissible and drug resistance beyond extensively drug resistant TB is increasingly being reported although the concept of "totally drug resistant" to describe TB strains with advanced resistance is disliked by TB specialists, not least because of the effect that a label of "incurable" has on patients, contacts and caregivers.[3] Nevertheless, the futility of current treatment in extensively drug resistant TB has resulted in significant numbers of these patients in the Western Cape Province of South Africa for example, being discharged back into the community where average survival is under two years. Since almost a third are smear-positive at discharge, they pose a high risk of transmission,[4] and recent reports of XDR-TB in health care workers have begun to emerge.[5]

Tuberculosis has always been associated with poverty, under-nutrition and co-existing diseases, which makes treatment very challenging. Whilst up to 90% of urban populations in the 19th century are estimated to have harboured the bacillus, only about 10% developed TB,[6] although in cities like London this was a big problem. Nevertheless, about 20% of tuberculosis cases in the pre-chemotherapeutic era spontaneously resolved, which supports the notion of immune-mediated clearance.[7] In the current crisis, researchers believe there is a potential role for immune-modulating therapy in which the immune system is realigned or redirected to deal more effectively with the invading *Mycobacterium tuberculosis*.[8] This is the premise on which Tuberculomucin-Weleminsky was developed.

Friedrich Weleminsky, second assistant to the head of the Institute for Hygiene at the German University of Prague,[9] published in 1912 his discovery of a new treatment for tuberculosis, which he named tuberculomucin (Tbm).[10] Tuberculomucin had been eight years in production and derived from strains of *Mycobacterium tuberculosis* cultured in purpose-made Kappenkolben (swan-necked flasks) that allowed aeration with minimal evaporation over many years incubation.[11] The growing medium was a

weak alkaline glycerine peptone beef broth (bouillon) from which the zoogloea (gelatinous film produced by the bacteria) was skimmed every three weeks. It was only after removing 20 such films that the cultures produced immunogenic substances powerful enough to prolong the life of test animals. During the fourth year a metabolic product of the active bacteria in the form of a mucin protein was observed and this was shown to be the therapeutic component of what became known as tuberculomucin. As ever with TB, the guinea pig was Weleminsky's laboratory animal. His trials were meticulously recorded, with every guinea pig listed, along with the changes that occurred throughout the treatment. It was guinea pig number 1769, infected with human tuberculosis on 3rd July 1909, and treated with tuberculomucin, that was the first to survive.[12]

Weleminsky was aware of the possible confusion between tuberculomucin and Robert Koch's tuberculin, and sensitive to the controversy associated with the early documented adverse reactions to tuberculin. Koch had announced his potential cure for tuberculosis in 1890 at the Tenth International Congress for Medicine in Berlin, just eight years after his discovery of the causative bacillus. Koch explained the action of tuberculin in experimentally-infected animals as causing necrosis in infected tissues, which consequently deprived the bacteria of nutrients and led to their death. Tuberculin was therefore intended to affect the tissues – by turning them into infertile soil – and not the bacteria. Christoph Gradmann calls this "a bacteriological variation of a scorched-earth strategy."[13] Unfortunately, its use in TB patients proved extremely harmful in many cases as it often led to reactivation of old foci of infection, as well as severe systemic reactions and occasionally death. Furthermore, the severity of the reaction did not appear to be related to the dosage, and tuberculin soon came to be regarded as unpredictable.[14]

Given the importance of tuberculosis in fin de siècle Europe (Koch's own estimates for Germany were six to eight sufferers in every thousand of the population),[15] there was a heightened imperative in the German-speaking world to produce tuberculin variants that could potentially immunize against and cure tuberculosis. This research activity was embedded within the intellectually vibrant and globally influential schools of bacteriology, immunology, and therapeutics that emerged in Imperial Germany alongside the German pharmaceutical industry. Further impetus was provided by the financial rewards from commercialization of vaccines and antibacterial therapies[16] as well as rivalry between German and French science.

Friedrich Weleminsky, as a Czech Jew in an increasingly anti-Semitic academic environment, and having been turned down in 1906 for an associate professorship at his own university,[17] would undoubtedly have been wary of crossing swords with the great and the good or indeed to be seen as exploiting his discovery for personal gain.[18] Nevertheless, it is clear from the testimony of his descendants and from his own published articles that Weleminsky passionately believed in the exclusivity and efficacy of his product above other tuberculosis treatments, and that his laboratory and clinical work was well designed and meticulously executed.[19] Weleminsky always drew distinctions between tuberculin and tuberculomucin, as did the two pharmaceutical companies that began producing tuberculomucin in sample batches during the mid-1920s.[20] Yet there *are* similarities between tuberculomucin and Koch's original tuberculin (known as "old tuberculin" OPD),[21] which was the preparation used in the early research in the microbiology laboratories at the Royal Free Hospital to replicate as far as possible Weleminsky's work. Old tuberculin is believed to contain identical mucin fragments as those described for tuberculomucin.[22]

Although we have now identified at least 60 papers written in German, in which tuberculomucin's use was described in humans, very little information reached the

English-speaking scientific world. There are very few articles in English that mention Weleminsky's tuberculomucin but one, published in 1921 by another Czech Jewish physician, Karl Fischel, who had run a large sanatorium in Vienna before emigrating to California as a TB specialist,[23] classified tuberculomucin amongst the ''weakened tuberculins''. He admitted that even among the tuberculins it was a somewhat idiosyncratic preparation:

> ''Weleminsky's tuberculomucin (Prague), which is probably not known abroad, is a most interesting and rather odd preparation. Cultivated in special tubes, it is produced from degenerated cultures, which after a time secrete mucin. It provokes most violent local reactions, sometimes with swelling of the neighbouring glands and rise of temperature, which, however, lasts only three days (positive phase). On the fourth day, marked amelioration sets in [. . .] The preparation gives good results with active tuberculosis even in feverish cases of the fibrous-nodular, or nodous-pneumonic form. It is also of decidedly great prognostic value.''[24]

By the mid-1920s at least two companies seem to have been involved in producing and marketing the treatment – by now known as Tuberculomucin-Weleminsky. These were a German pharmaceutical company based in Dresden called the Helfenberg Chemical Company, and a Viennese company called Biopharma. The detail aid produced in 1927 by Biopharma specifically states that:

> Tuberculomucin Weleminsky IS NOT [a form of] TUBERCULIN but a METABOLIC PRODUCT of Tbc-bacilli, BELONGING TO THE PROTEIN FAMILY and specifically acting as antigen. It was produced by a unique and brand new culturing technique and has been tested in animal trials for its therapeutic effect against Tbc.[25]

By that time it had also been used fairly extensively on humans.

Weleminsky seems to have been well connected to the German biomedical institutions, as was his head of department Ferdinand Hueppe (1852–1938) who from 1879 to 1884 was on Koch's staff in Berlin.[26] The quality of the relationship between Hueppe and Weleminsky is not known but it was presumably supportive to enable Weleminsky's work on tuberculomucin and other projects over such a long period of time. The fact that both Weleminsky and his wife Jenny were secular Jews may have been significant[27] because Hueppe was an open advocate of racial hygiene, believing that the germ theory of infectious disease was too simplistic and that disposition and inherited constitution made people susceptible to infections. The historian, Paul Weindling explores this theme in Hueppe's *Handbuch der Hygiene* (1899) in which he characterized the Jews as a degenerate race in contrast to the Aryans who were a rural *Naturvolk*.[28] Although this type of racial rhetoric became increasingly common amongst western intellectuals during the last decades of the 19th century, it appears that Hueppe's radically nationalist views were something of an embarrassment to the German state and he was not recalled from Prague to a chair at a German university, despite some intercession on his behalf.[29] Whether Hueppe was responsible for blocking Weleminsky's promotion to associate professor (in 1906) is not known but in fact he may have been the person who recommended the promotion, which was turned down by the university council.[30]

Weleminsky's wife Jenny (née Elbogen, 1882–1957), whom he married in 1905, was from a wealthy Austrian banking family[31] with a large estate, Schloss Thalheim, in Lower Austria, which was renovated in 2013 and preserved as a cultural heritage monument.[32] It was here between 1910 and 1913 that Weleminsky tested tuberculo-

mucin on spontaneously diseased barn cows. Tuberculosis in dairy cows overwintered in barns was, according to Weleminsky, "extraordinarily high", with those at Thalheim usually surviving no more than two winters. Most of the 36 cows treated survived, were able to continue producing milk, and also produced healthy calves. When some of the cows were slaughtered the lung lesions were scarred but healed, proving the efficacy of the treatment.[33]

Weleminsky lectured at the German University Prague until the end of the summer semester of 1938 but he resigned from the university at the beginning of February the following year,[34] a couple of weeks before German troops invaded the city. Weleminsky and his family had arrived in London in the January but we know that Weleminsky briefly returned to Prague to ensure that his students were safely graduated, and perhaps to collect his tuberculomucin cultures before leaving for good on 6th March 1939.[35] Tuberculomucin continued to be produced in the kitchen of their West Hampstead home using broth from rationed beef mince boiled for hours; the by then tasteless mince being eaten by the family. Weleminsky's daughter, Marianne Hartstein (Fig 2), became a nurse at Prior Place Sanatorium, Surrey (a country branch of the London Chest Hospital), and used her stock of tuberculomucin to treat desperately ill patients. This was done quite illicitly, without the knowledge or permission of the medical staff.[36] Full treatment would have taken about six months beginning with weekly intradermal injections that left skin reactions of varying intensities.[37] Did anybody notice these? I have looked at what remains of the archive of the London Chest Hospital and certainly nothing is flagged up and Marianne's nursing records contain no evidence that she was "caught out". Indeed, she is praised in the Matron's Register as being "a highly intelligent nurse".[38]

Figure 2 Weleminsky's daughter, Marianne Hartstein (1906–1967) with her daughter, Charlotte (b. 1927). Courtesy Charlotte Jones

In London, in 1941, the TB death rate was one per 1,000 population, a 72% increase over 1938, and 4,500 people caught the infection that year.[39] Perhaps it is understandable that patients would jump at the chance of trying a new treatment when there were few alternatives before the antibiotic streptomycin became available at the end of that decade. Marianne's own daughter, Charlotte, who was 12 years old when the family came to London, was treated successfully with tuberculomucin, and according to Charlotte there was no evidence of antibacterial resistance to the drug.[40]

Laboratory findings during first phase of research, 2012–2013:

1. Addition of old tuberculin (OPD) to infected cultured cells (macrophages) results in greater clearance of the TB-like bacteria, BCG *M. bovis*, when compared to current substances that have replaced OPD.
2. Preliminary work suggests that the effect of OPD may occur via an increase in certain macrophage inflammatory proteins (e.g. MIP1á) responsible for controlling the cell's immune response

Current laboratory research (2014–2105):

3. (a) Further defining the effect of OPD on cellular responses;
   (b) repeating the cell culture experiments using aged *M. tuberculosis* culture ‡tuberculomucin¤ (in line with original Weleminsky work) using BCG *M. bovis* and *M. tuberculosis*;
   (c) adapting the protocol to enable simpler, large-scale production of old tuberculin or equivalent.

Acknowledgement is given to the following scientists and historians who have worked on the tuberculomucin project: Julio Ortiz Canseco, Stephanie Eichberg, Dimitri Evangelopoulos, Marc Lipman, Tim McHugh, Jennifer Willis. Special thanks to UCL donors, John and Ann-Margaret Walton for funding the laboratory and the historical research.

Notes

1 UCL-TB: Tuberculosis research at UCL: http://www.ucl.ac.uk/tb/tb-proj (accessed 29 August 2014).
2 Global Tuberculosis Report 2014 (Geneva: WHO, 2014): page xii. Downloaded from (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1 (14 March 2015).
3 Giovanni Battista Migliori, Giovanni Sotgiu, Neel R Gandhi *et al*., for the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB, ''Drug resistance beyond extensively drug resistant tuberculosis: individual patient data meta-analysis,'' *Eur Resp J* 42 (2013): 169–79.
4 Elize Pietersen, Elisa Ignatius, Elizabeth M Streicher *et al*, ''Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study,'' *Lancet* 2014; 383: 1230–39.
5 Max R O'Donnell, Julie Jarand, Marian Loveday *et al*, ''High incidence of hospital admissions with multi-drug resistant and extensively drug-resistant tuberculosis among South African health care workers,'' *Ann Intern Med* 2010; 153(8): 516–22.
6 M Worboys, *Spreading germs: disease theories and medical practice in Britain, 1865–1900* (Cambridge: Cambridge University Press): 232.
7 Keertan Dheda, Tawanda Gumbo, Neel R Gandhi *et al*, ''Global control of tuberculosis: from extensively drug resistant to untreatable tuberculosis,'' *The Lancet Infectious Diseases/Respiratory Medicine, Tuberculosis 2014*, March 2014: 31–48.
8 *Ibid.*
9 Also known as the Charles University.
10 Friedrich Weleminsky, ''Ueber die Bildung von Elweiss und Mucin durch Tuberkelbacillen,'' *Berliner klinische Wochenschr* 28 (1912): 1–8. Translated by Stephanie Eichberg (SE).
11 These were probably made by H Grünewald, glassblower of the German Chemical Institute, Prague, who had produced similar glassware for Weleminsky's earlier experiments cultivating microorganisms. See Friedrich Weleminsky, ''Ueber Züchtung von Mikroorganismen in strömenden Nährböden,'' *Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten* 42 (1906): 1–7. Translated by SE.
12 Friedrich Weleminsky, ''Tierversuche mit Tuberculomucin,'' *Berliner klinische Wochenschr* 18 (1914): 1–10. Translated by SE.
13 Christoph Gradmann, ''Robert Koch and the white death: from tuberculosis to tuberculin,'' *Microbes and Infection* 2006; 8: 294–301.
14 Christoph Gradmann, ''Locating therapeutic vaccines in nineteenth-century history,'' *Science in Context* 2008; 21(2): 145–60.
15 Christoph Gradmann, ''Money and microbes: Robert Koch, tuberculin and the foundation of the Institute for Infectious Diseases in Berlin in 1891,'' *History & Philosophy of the Life Sciences* 2000; 22: 59–79.
16 W.F. Bynum, *Science and the practice of medicine in the nineteenth century* (Cambridge: CUP, 1994), pp. 158–9. For an account of the national contexts (Paris and Berlin) of vaccine research and production see Christoph Gradmann, ''Locating therapeutic vaccines in nineteenth-century history,'' *Science in Context* 2008; 21(2): 145–60.
17 Entry for Weleminsky in the *Biographical Lexicon of the German Medical Faculty in Prague 1883-1945*, edited

by Ludmila Hlaváčková and Petr Svovodn (Karolinum: nakladatelstvi Univerzity Karlovy Praha, 1998): pp. 225–226. Jews in Prague rarely attained the rank of professor. Charlotte Jones, "My grandfather: a kind and modest man," *Association of Jewish Refugees Journal* 11.7 (2011): 5.

18 For an account of Koch's proposed profiteering from tuberculin see Christoph Gradmann, "Money and microbes."

19 Currently 23 pages of archive material relating to Weleminsky have been obtained from the Charles University, Prague, some of which has been cited in this article and some awaits translation. Acknowledgements are given to archivist, Jana Ratajová.

20 These were Biopharma in Vienna, which produced a detail aid in October 1927 inviting interested doctors to apply for samples (Wellcome Library, London, General Collections Ephemera Collection, Box 293), and Chemische Fabrik Helfenberg A.G, Dresden, which produced an undated promotional brochure, "Tuberculomucin Weleminsky", citing 59 publications from 1912 to 1925 lauding its therapeutic efficacy (purchased from Amazon Germany, January 2013). Translated by SE.

21 Microbiology notes, Tuberculin: http://www.microrao.com/micronotes/tuberculin.htm (accessed 25 August 2014).

22 Jennifer Willis, *Tuberculomucin: a forgotten treatment for TB* (unpublished BSc dissertation, University College London, 2013).

23 The White Plague in the City of Angels; website exploring the Jewish response to tuberculosis in Los Angeles: http://scalar.usc.edu/hc/tuberculosis-exhibit/key-people-practitioners?path=key-people-path (accessed 28 August 2014).

24 Karl Fischel, "The theory and practice of specific treatment of pulmonary tuberculosis," *Tubercle* 2.12 (1921): 529–37.

25 Biopharma detail aid, 1927.

26 It was Hueppe who showed that tuberculin was produced from tuberculosis pure cultures even whilst Koch was refusing to divulge the exact formula of his "secret remedy". Christoph Gradmann, "Robert Koch and the pressures of scientific research": note 151, p. 26.

27 Interview with Charlotte Jones, 2 January 2012.

28 Paul Weindling, *Health, race and German politics between national unification and Nazism 1870–1945* (Cambridge: CUP, 1989), pp. 170–173.

29 Paul Weindling, *Health, race and German politics*: p. 172.

30 Entry for Weleminsky in the *Biographical Lexicon of the German Medical Faculty in Prague 1883–1945:* pp. 225–226.

31 This was not a banking "dynasty". Jenny's father, Guido Elbogen (1845–1918), had become wealthy through his banking activities in Vienna. Judy Weleminsky, personal communication, 13 April 2015.

32 Modern photographs of the house and outbuildings can be seen at: http://www.geolocation.ws/v/W/File%3ASchloss%20Thalheim%2002.jpg/-/en (accessed 29 August 2014).

33 Friedrich Weleminsky, "Tierversuche mit tuberculomucin,"

34 Entry for Weleminsky in the *Biographical Lexicon of the German Medical Faculty in Prague 1883–1945*.

35 *Ibid.*

36 Interview with Charlotte Jones, 2 January 2012.

37 Tuberculomucin was injected *intradermally*, an injection procedure common to vaccines and to skin testing for tuberculosis.

38 Nurses Admission Book, London Chest Hospital archives, RLHLC/N/1/3 (Royal London Hospital Archives).

39 W. Allen Daley & B. Benjamin, "Tuberculosis in London in wartime," *British Medical Journal*, 10 October 1942: 417–420.

40 Interview with Charlotte Jones, 2 January 2012.