Waldemar Mordecai Haffkine, CIE (1860–1930): prophylactic vaccination against cholera and bubonic plague in British India

Barbara J Hawgood

Summary: Waldemar Mordecai Haffkine developed an anticholera vaccine at the Pasteur Institute, Paris, in 1892. From the results of field trials in India from 1893 to 1896, he has been credited as having carried out the first effective prophylactic vaccination for a bacterial disease in man. When the plague pandemic reached Bombay, Haffkine became bacteriologist to the Government of (British) India (1896–1915). He soon produced an effective antiplague vaccine and large inoculation schemes were commenced. In 1902 19 people in Mulkowal (Punjab) died from tetanus poisoning as a consequence of antiplague vaccination. Haffkine was blamed unjustly and exonerated only in 1907, following a campaign spear-headed by Ronald Ross. In India the stigma remained. In 1925 in tribute to the great bacteriologist, the Bombay Government renamed the laboratory as the Haffkine Institute. The Haffkine Biopharmaceutical Corporation Ltd and the Haffkine Institute for Training, Research and Testing in Mumbai continue to be important centres for public health.

Early years

Waldemar Mordecai Wolff Haffkine (Russian name Chavkin) was born in Odessa, Ukraine on 15 March 1860 to Aaron and Rosalie (born Landsberg) Chavkin (Figure 1). The Chavkin family were Jewish merchants, educated in Western culture. When Waldemar was young, his family moved to Berdiansk on the Sea of Azov where Aaron Chavkin became a schoolteacher. Waldemar received a classical education, then entered the University of Odessa in 1879 to study physics, mathematics and zoology. He came under the influence of Professor Elie Metchnikoff (1845–1916) and developed an interest in unicellular organisms. These were times of political unrest leading to repression and antisemitic pogroms. Haffkine became a political activist and member of the *Odessa League of Self Defence*. In one incident involving army cadets, he was wounded and imprisoned; fortunately, Metchnikoff was able to free his brilliant student and also saved him from persecution. In 1883 Haffkine was awarded the degree of Candidate of Natural Sciences and became an assistant to the Zoological Museum of Odessa with the use of a research laboratory. Here he studied the nutrition and hereditary characteristics of protozoans and, in 1884, he successfully defended his thesis for the degree of doctor of science. Debarred from a professorship because of

Figure 1 Dr Waldemar Mordecai Haffkine (by kind permission of the Royal Society of Medicine, London)

Barbara Hawgood, PhD, is a retired physiologist formerly of King's College, London. Since 1992 she has written several biographical articles on British and international medical scientists, published in *Toxicon* and the *Journal of Medical Biography*; she has a special interest in India. Correspondence: 26 Cloister Road, Acton, London W3 0DE, UK
(email: barbara@hawgood.com).

his religion, Haffkine decided to leave Russia for Geneva in 1888. He taught physiology at the university for a year but soon became dissatisfied and, in 1890, followed his former professor to Paris.[1] Metchnikoff had been invited by Louis Pasteur (1822–95) to be one of the heads of laboratory at the newly opened Pasteur Institute; his theory that phagocytosis was a means of protecting an organism against infection was groundbreaking. In Paris, Haffkine asked his old teacher for a position at the institute and Metchnikoff was able to find one as assistant librarian. In his ample spare time, Haffkine worked in Metchnikoff's laboratory on bacteria that attack *paramecium* and the adaptation of microrganisms to adverse conditions of growth. Pasteur looked favourably on his work.[2] After Alexandre Yersin (1863–1943) left for Saigon in French Indo-China, Pierre Roux (1853–1933) brought Haffkine into the laboratory of microbial technique where he took part in preparing the course in general bacteriology that Roux and Metchnikoff had initiated.[3] Haffkine began to study *Vibrio cholerae*, the microorganism which in 1883 Robert Koch (1843–1910) had shown to be the causative agent of Asiatic cholera.

Development of cholera vaccine at the Pasteur Institute in Paris

In 1880 Louis Pasteur made the landmark discovery that injection of a live culture of chicken cholera, in which the virulence of the bacilli had been reduced (attenuated) by ageing, protected chickens against a lethal attack of the disease. Haffkine became interested in developing an effective vaccine against Asiatic cholera in man. During the cholera epidemic in Spain in 1885, Jaime Ferrán y Clua (1849–1929) inoculated townsfolk in Barcelona with live vibrio bacilli collected from cholera patients. However, the efficacy was not established and the practice, criticized for the great variability in virulence of the inoculating agent, was discontinued. Haffkine stressed the importance of the discovery, first by Edward Jenner (1749–1823) and then by Louis Pasteur, of inoculating with microorganisms of an increased and fixed state of virulence obtained by passage through animals; Pasteur had shown this with the rabies virus in 1883.[4] After many false starts, Haffkine discovered that by repeated passages of Asiatic cholera bacilli through the peritoneal cavity of guinea pigs, he could obtain a culture of bacilli of an increased (exalted) virulence which on further passage did not alter; about 39 passages were required. An attenuated culture was produced by exposing the fixed exalted culture to conditions of aeration at a raised temperature. The potency of the attenuated culture remained stable but that of the exalted culture waned after about two weeks and required several passages through guinea pigs to restore full potency.[2,5] On 9 July 1892 Haffkine reported to the weekly meeting of the Society of Biology in Paris that an inoculation of attenuated cholera vibrios, followed later by exalted cholera vibrios, immunized guinea pigs against a lethal attack of Asiatic cholera.[6] A week later, a second note recorded that rabbits and pigeons were also immunized successfully.[7] The immunity acquired by animals of different genera and species gave Haffkine the reason to believe that his vaccines would be effective in man. He proceeded to be inoculated. The first vaccine did not produce any adverse reaction apart from light symptoms of fever (a small rise in body temperature and headache) and a local reaction of swelling and pain at the site of injection. These symptoms disappeared in a few days. Six days after the first injection, he was inoculated with the second cholera vaccine. Again the body temperature rose but returned to normal within 24 hours; local pain had disappeared by three days. With the safety of the vaccines demonstrated, Haffkine proceeded to vaccinate three Russian friends and other volunteers, one of whom was Mr EH Hankin, Fellow of St John's College, Cambridge and recently appointed as chemical examiner, analyst and bacteriologist to the Northwest Provinces in India; again, only mild adverse effects were observed. Haffkine concluded his third report within three weeks, expressing 'the hope that six days after vaccination, man would have acquired immunity against the cholera infection'.[8] Hankin, who was working at the Pasteur Institute at the time, sent to the *British Medical Journal* a detailed and favourable account of his experience and a description of the methods used to produce the vaccines;[9] Haffkine's published notes contained little detail.

Haffkine was anxious to test the value of his anticholera vaccine in the field. The word reached Lord Frederick Dufferin (1826–1902), British Ambassador in Paris and a former Viceroy of India (1884–88), who suggested the possibility of testing the vaccine in Bengal where cholera was rife. He arranged for Haffkine to meet Lord John Kimberley (1826–1902), Secretary of State for India, in London that year and explain his system to leaders of the medical profession. Haffkine was received very cordially and the Secretary of State granted facilities for him to visit every part of India to test the value of his anticholera vaccine with the stipulation that all inoculations were to be voluntary.[10] The enterprise was initiated privately with some or most of the funds supplied by Haffkine or his friends.[11] Before his departure for India in 1893, Haffkine made a second visit to London. In the pathological laboratory of Professor Almroth Edward Wright (1861–1947) at the Army Medical School at Netley, Haffkine gave a series of demonstrations of the techniques involved and the resulting immunity in animals. At the suggestion of the editor, Almroth Wright and David Bruce (1855–1931) wrote these up for the *British Medical Journal*.[12] Haffkine prepared a paper on injections

against cholera, which Dr Armand Ruffer read to an audience in the Laboratories of the Royal College of Physicians and Surgeons; interest was shown in the accompanying demonstrations.[4]

Prophylactic vaccination against cholera in India

Waldemar Haffkine arrived in India in March 1893. He had hoped to start his inoculations in Calcutta; cholera was not a problem at the time and he met local opposition to his plans. Apart from the fact that his vaccine required two painful injections and that its efficacy in man was not known, there was a body of medical opinion that believed it was impossible to obtain immunity to an intestinal-based disease by giving a subcutaneous injection of virulent microbes. Also Asiatic cholera bacilli induce a disease in guinea pigs with symptoms different from those produced in man. Nevertheless Hankin, now in charge of a newly established bacteriological laboratory, invited Haffkine to Agra to inoculate volunteers both military and civilian. Haffkine extended his inoculations to regiments serving in the northwest provinces, Oudh and the Punjab. By the end of the year, about 10,000 British and Indian troops and officers had been vaccinated with live bacilli, two-thirds with the second injection. Inoculation of civilians continued particularly in the agricultural villages that had a fixed population. Haffkine wrote of his work in his first year in India:

> Selection of the localities and groups of individuals was determined chiefly by the willingness of the people to undergo the preventive treatment; but, at the same time, in every place efforts were made to concentrate the operations on bodies of population living under similar conditions, and supervised by medical and sanitary authorities in order that, on the occasion of cholera outbreaks, a comparison could be made between the resistance of inoculated and uninoculated individuals.[13]

There was no cholera in Upper India that year. The problem of carrying out a trial of the anticholera vaccine in an endemic region remained. A start came in March 1894 through Dr William John Ritchie Simpson (1855–1931), Health Officer of Calcutta from 1886 to 1897. Simpson asked Haffkine for help in identifying cholera bacilli in a water tank in one of the *bustees* (suburban quarters) where cholera had broken out. Here, cholera was endemic and Haffkine realized that he had in each household a population living under identical conditions and that was exposed equally to the risk of infection. The local population was averse to being inoculated but, if some in each household could be persuaded to be vaccinated while others remained unvaccinated, he had a chance of making comparative observations.[14] Simpson agreed; he had been impressed by the observation of earlier army surgeons that troops attacked by cholera in one locality enjoyed a peculiar immunity when stationed in another. Haffkine and Simpson made the first inoculations at the Kattal Bagan *bustee* (Figure 2). After two months, the results were sufficiently encouraging to enable Simpson to convince the Calcutta authorities of the need for a prolonged trial of the vaccine, and a small grant for expenses was awarded.[15] A bacteriological laboratory was set up and Indian doctors from Simpson's department began administering 'middle' doses of vaccine to those volunteering in the *bustees*. Records of attacks and mortality were monitored carefully from March 1894 until the end of August 1895; Simpson and Haffkine revisited locations to ensure the accuracy of the records. The results revealed that cholera occurred in 36 houses containing inoculated persons: in 335 uninoculated there were 45 cases and 39 deaths; in 181 inoculated there were four cases and four deaths. The numbers were too small for any definite conclusion but the scheme continued into 1896. Results from inoculation of inmates in the Gya Jail during an epidemic in 1894 showed a reduced frequency of attacks in the inoculated when compared with the uninoculated; however, mortality was unchanged in those inoculated who suffered an attack.[13,15]

With word of the apparent success of the vaccine spreading, requests arrived from tea planters to vaccinate coolies contracted to work on the large tea plantations in Assam. Here Haffkine contracted malaria and in September 1895 he prepared to return to Europe to recuperate. The Government of Assam continued the anticholera inoculation scheme. Haffkine presented a report to the Government of India;[13] he requested and received permission to return to India the following year since much still needed to be done. A single injection of the exalted vaccine had been introduced recently;

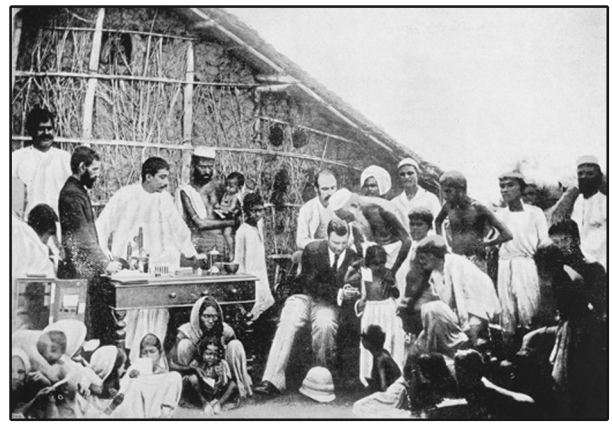

Figure 2 Introduction of anticholera inoculation in Calcutta in March 1894. Standing from left are Dr GN Mookerjee, Medical Inspector, Calcutta; Dr R Sen, Assistant Health Officer and Dr Jogendra Nath Dutt, Analyst to the Health Officer. Seated, injecting, is Mr WM Haffkine, and behind him is Dr WJR Simpson, Health Officer of Calcutta (From: Haffkine WM. Protective inoculation against cholera. Calcutta: Thacker, Spink & Co., 1913, facing p. 38. By kind permission of the Wellcome Library, London.)

this was to become the norm. Haffkine sent an inscribed copy of the report to Miss Florence Nightingale (Figure 3).

In England the cholera vaccine was perceived as a success. Almroth Wright discussed with Haffkine the possibility of producing a prophylactic vaccine against typhoid fever and, in a paper by Almroth Wright and Surgeon-Major David Semple on the development of an antityphoid vaccine, Wright acknowledged Haffkine's help.[16] On 18 December 1895, Haffkine delivered a lecture on vaccination against cholera in the examination hall of the Conjoint Board of the Royal College of Physicians of London and the Royal College of Surgeons of England.[17] He reported that from April 1893 to the end of July 1895 and with the assistance of officers of the Indian and Army Medical Staff in India, he had inoculated over 42,000 persons; detailed records had been made. Initially he had difficulty in establishing an acceptable but effective dose of vaccine and, in some cases, only the first injection had been given. All vaccinations were voluntary. He listed the trials, the results of which fell into three categories: those unsuccessful; those slightly favourable to the method; and those with satisfactory results. In his monograph of 1913, *Protective inoculation against cholera*,[18] Haffkine published figures of trials from 1894 to 1896. In 1915 the statisticians M Greenwood and GU Yule examined eight results.[19] They concluded that, in three results, the reduction in number of attacks in the inoculated relative to those in the uninoculated 'established a presumption in favour of Haffkine's inoculation'. These trials were in the Cachar tea estates in 1895–96, the trial encompassing 12,000 persons; in the Margherita tea estate during an epidemic in 1895, a trial in which Haffkine sought to randomize the selection of inoculated and uninoculated;[20] and in Calcutta in 1894–96, from the start of immunity at the fifth day to the 416th day. The reduction in the number of attacks in the inoculated in the other results could possibly arise by chance from errors in sampling.

Prophylactic vaccination against bubonic plague in India

In June 1894 bubonic plague reached Hong Kong, having spread from the endemic region of South China. Alexandre Yersin was dispatched from the Pasteur Institute in Saigon to investigate the outbreak and, on 21 June, he made the first identification of the Gram-negative bacillus *Yersinia pestis* (formerly *Pasteurella pestis*). In late September 1896, the plague reached Bombay. Haffkine was now back in Calcutta and the Government of India, impressed by the anticholera vaccine, requested Haffkine to go to Bombay to devise, if possible, a similar vaccine to combat the dreadful disease. On 8 October 1896 Haffkine entered the Indian Civil Service.[21] Major William Burney Bannerman, Indian Medical Service (IMS) (1859–1924), described the subsequent events:[22]

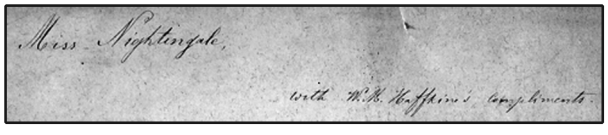

Figure 3 Inscription to Miss Nightingale on the cover of a copy of Anti-cholera inoculation: report to the Government of India by WM Haffkine Calcutta: Thacker, Spink & Co, 1895 (By kind permission of the Wellcome Library, London)

> [That day Haffkine] began work in a room in the Petit Laboratory of Grant Medical College. His laboratory consisted of one room and a corridor, and his staff of one native clerk and three peons or messengers. It was here that Mr Haffkine made the discovery of the stalactite growth assumed by the plague bacillus when grown in nutrient broth, which will ever be connected with his name as a reliable and easy means of diagnosing the organism. In December 1896 Mr Haffkine was successful in protecting rabbits against an inoculation of virulent plague microbes, by treating them previously with a subcutaneous injection of a culture in broth of these organisms sterilised by heat. The rabbits treated in this way became immune to plague. On the 10th January 1897 Mr Haffkine caused himself to be inoculated with 10c.c. of a similar preparation, thus proving in his own person the harmlessness of the fluid.

Haffkine chose to be inoculated with a much higher dose of the broth and sediment than the 3 cl^3 to be given to the public. Side-effects were restricted to pain at the seat of injection and an attack of fever that produced malaise for about two days.

Experience gained from testing the anticholera vaccine was now used to try and evaluate the effectiveness of the antiplague vaccine. At the end of January, an outbreak of plague occurred at Her Majesty's House of Correction at Bycullah, Bombay, and Haffkine arranged to inoculate 154 prisoners who volunteered. Three of the inoculated men died that day but in the following six days there were no deaths. Of the 191 untreated men, three died on the inoculation day and six in the following six days. When an apparent protection conferred by the vaccine became known, great demand for the prophylactic commenced. Over 11,000 individuals in the infected areas were inoculated in the next three months.[23] Twice that year the laboratory needed to move to bungalows owned by the Bombay Government as production of the vaccine expanded. In 1898 the laboratory moved to Khushru lodge owned by Sir Sultan Shah, Aga Khan III, KCIE (1877–1957), head of the Khoja Mussulman community. This bungalow was fitted up at the Aga Khan's expense for Haffkine's use and about half the Khoja Mussulman community of Bombay (10,000–12,000 persons) received prophylactic inoculations under the auspices of His Highness the Aga Khan.[24] The staff at the Plague Research Laboratory under Haffkine now consisted

of 'a commissioned officer of the Indian Medical Service [Major Bannerman], four medical men of those sent out by the Secretary of State for India for work there, four local medical men, three clerks and six servants'.[22]

In 1898 Haffkine was invited by the Baroda authorities to conduct a trial of the vaccine in the village of Undhera where plague was raging. A census had recently been taken of this agricultural village of 1031 persons, so the households were known. Haffkine organized a well-designed trial. On the day of inoculation, each household was called by name and, when collected in the street, half the members were inoculated and, as far as possible, a matching half left untreated to act as a control. There was no problem in inducing people to be vaccinated – rather the reverse. Haffkine inoculated one half of the village, Bannerman the other half. An Indian doctor with a small hospital remained in charge. Six weeks later Haffkine and Bannerman, together with the Director General of the IMS and others, returned to Undhera and visited each house where plague had occurred since the inoculation. In all, 28 families had been affected: 71 of the inoculated suffered eight attacks with three deaths, while 64 untreated persons suffered 27 attacks with 26 deaths.[24] Clearly the vaccine was providing considerable if not total protection against a plague attack. In 1899 the Plague Research Laboratory made a final move to the Old Government House at Parel, which provided space necessary for the manufacture of the hundreds of thousands of doses of antiplague vaccine that were required to meet the demand, both local and from abroad. The Plague Commission of 1898–99, sent from London to examine the undertaking, had certain criticisms of production in the previous laboratory[2] and Bannerman, in describing the new laboratory at Parel, was at pains to point out the checks and counterchecks that were now in place at each stage of production to ensure the presence of a pure strain of plague bacillus. In December 1901 Waldemar Haffkine was appointed Director-in-Chief with a staff of 53 persons.[22]

Haffkine had chosen a fluid medium for the growth of the plague bacilli to allow extracellular toxins to accumulate. He reasoned that a vaccine containing both killed bacilli and their extracellular toxin would be more effective both in protecting against infection and in combating the disease in those already infected, a result not observed with the anticholera vaccine. Early results from trials where accurate statistics had been kept showed that not only was the rate of attack diminished in the inoculated but also fewer of the attacks were fatal; the Commission accepted this. A beneficial effect of the vaccine was apparent within 24 hours of inoculation and the duration of the protection appeared to be one epidemic, that is 4–6 months.[24,22] Early results also suggested the vaccine reduced mortality in those incubating the disease at the time of inoculation. The Plague Commission and, particularly, Almroth Wright disputed this, although later results supported this finding.[25]

In 1899 Waldemar Haffkine went on leave to London where he received fulsome praise for his antiplague vaccine. In 1897, in the Birthday Honours List of Queen Victoria, he had been named Companion of the Order of the Indian Empire (CIE), an Order founded in 1877 on the assumption by Queen Victoria of the title of Empress of India. Now Waldemar Mordecai Haffkine applied and became a naturalized British citizen. In London he addressed The Royal Society on the subject of preventive inoculation against infectious diseases; both inoculation and general sanitation measures were required to combat these diseases and neither could ever be substituted for the other.[24] In 1900 the University of Edinburgh, in their award of the prestigious Cameron Prize in Practical Therapeutics, recognized Waldemar Haffkine's great achievement in saving many thousands of lives by prophylactic vaccination against cholera and against the plague.[26]

The Mulkowal disaster in Punjab

On 30 October 1902, 107 persons were inoculated against the plague at Mulkowal in the Punjab. Six days later symptoms of tetanus were observed in the first 19 inoculated; all died within the next few days. It was established quickly that all the dead had received vaccine from one bottle labelled 53N, issued from the Plague laboratory in Bombay 26 days previously, and that the other 88 people who had received vaccine from other bottles were unaffected. The Commission, appointed by the Government of India to enquire into the disaster, consisted of Sir Lawrence Jenkins (1857–1928), the Chief Justice of Bombay, Lieutenant-Colonel Bomford IMS, Principal of Medical College, Calcutta, and Major David Semple, RAMC, Director of the Pasteur Institute at Kasauli.[27] Incidentally, the Pasteur Institute at Kasauli had no connection with the Paris institute, being named in honour of the great man and, as mentioned previously, Semple had worked on typhoid vaccine with Wright at Netley. In the course of their enquiries, the Commission became aware that Haffkine had changed the production procedures that had been examined and approved by the Plague Commission of 1898–99. Haffkine was now using a water-agar medium sterilized by heat, a method in use at the Pasteur Institute in Paris since 1900. This allowed Haffkine to omit the addition of carbolic acid (final concentration 0.5%) and so speed up production time. There was a huge demand for antiplague vaccine in Punjab where the disease was raging and a large vaccination scheme was underway.[28] The Commission viewed the omission of carbolic acid with extreme gravity; army doctors,

trained in the procedure of antisepsis introduced by Lord Lister (1827–1912), had an exceptionally high regard for the efficacy of carbolic acid in controlling infection.

The Commission interviewed the inoculating officer, Dr AM Elliott, and his assistant or compounder Narindar Singh, and Semple carried out experiments under a great variety of conditions with tetanus bacilli, some from the Mulkowal bottle. On 16 April 1903 the Commission reported to the Indian Government that they considered tetanus organisms were present in the bottle containing the vaccine and that 'in our opinion the specific contamination was introduced before the bottle was opened at Mulkowal'; carelessness in the Bombay laboratory was blamed.[27,28] Haffkine was given a year's leave of absence and Bannerman was recalled from Madras to be the Director-in-Chief.[29] The Government of India sent the report and data to the Lister Institute of Preventive Medicine in London for a second independent investigation and, in addition, asked them to examine the efficacy of the new procedure and the role of carbolic solution. On 24 November 1904 Charles Martin (1866–1955), Director of the Lister Institute, sent a report to the Under-Secretary of State for India. In the section on the 'Probable Origin of the Tetanus Virus' he stated specifically that 'Colonel Semple's experiments cannot be held to exclude the possibility of contamination at the time of the opening of the bottle' in contradiction to the conclusion of the Commission. Unfortunately for Waldemar Haffkine, Martin did not include this in his final ambiguously worded statement:

> The conclusions of the Institute coincide with those of the Commission, that in all probability the tetanus was at the time of inoculation in the bottle, but that it is impossible to determine at what stage in its history or in what way bottle 53N became contaminated.[27]

As regards their other briefs, the Lister report found the new prophylactic 'no less efficacious than the old' but was of the opinion that it was easier to ensure freedom from contamination by Mr Haffkine's 'Standard Method' of manufacture. They agreed with the Commission on the value of 0.5% carbolic solution in restraining tetanus growth in the vaccine. By December 1904 the former method of production of antiplague vaccine had been reintroduced, a new method of bottling put in place and a Health Exhibition arranged to restore the confidence of the public in the plague vaccine.[27] The scale of the inoculation campaign in Punjab in the winter of 1902–03 was vast with over half a million people being inoculated. Of these, about one quarter received vaccine produced by the modified 'water-agar' method and the remainder a vaccine produced in the original manner.[30]

Unable to defend himself in India, Haffkine travelled to Europe, visiting Paris then taking up residence in London at St Ermin's Hotel.[31] With the completion of the enquiries, he was relieved of his post as director and remained unemployed. For two years Haffkine strenuously defended his laboratory through long letters to the India Office in which he argued that contamination of bottle 53N occurred at the injection site. He wrote two letters to the Lister Institute pointing out the contradiction in their statements. Eventually these letters resulted in the Governing Body informing the Under-Secretary of State on 5 May 1906 that they regretted 'they inadvertently referred to their conclusion as the same as that of the Commission'.[27] Throughout this difficult period, Haffkine was observed to bear himself with the greatest dignity.[32]

Finally, four years after the disaster, the official documents of the inquiry were published as a supplement to the *Gazette of India, Calcutta* on 1 December 1906. What became apparent was the failure of the Commission to take into account other important findings that had emerged from their inquiry. First, the inoculating officer Dr Elliott stated unequivocally that the bottle of vaccine in question did not smell on opening, a routine test he carried out: a tetanus culture growing in the rich medium of water-agar in a vaccine bottle more than 26 days old would produce a strong, offensive odour. Second, and this information was new to Haffkine, Narindar Singh, the assistant who opened the vaccine bottles, dropped the forceps on the ground as the stopper moved in the bottle. According to his testimony, then he 'swished the forceps in the [carbolic] lotion, and then pulled out the cork with it'. This was strictly against instructions from the Plague laboratory attached to each vaccine bottle that stated that sterilization of forceps, stoppers, etc. must be carried out by passage through the flame of a spirit lamp. This was an essential precaution since inoculation was usually carried out on open ground outside the village and the accidental dropping of instruments was known to occur. However, the assistant had followed the procedure given in the *Punjaub Plague Manual* (1902), issued to operators by the local authorities shortly before the vaccination campaign started. This had substituted a rinse in carbolic lotion for flaming; flaming was rapidly reintroduced after the disaster. Indicative of the closed mind of the investigators, in the report of the Commission and of the Lister Institute two other pointers to the accidental introduction of tetanus spores into the bottle at Mulkowal were either discarded or ignored: the onset of the disease was slow, consistent with the time needed for a few tetanus spores to multiply sufficiently in the body to produce a lethal dose of toxin; and the syringe used with bottle 53N was contaminated so slightly that after rinsing in carbolic acid it did not cause infection in the remainder of those inoculated.[27,28]

In England the part of the report relating to the Mulkowal disaster was published on 1 February

1907 in the *Journal of Tropical Medicine and Hygiene* accompanied by a detailed and highly critical editorial from James Cantlie.[27] The *Lancet*[30] published a shortened account with extracts from the report and concluded with a request for justice. A summary of the evidence was published in the *British Medical Journal*[33] but this time the editorial article agreed with the Commission. The writer congratulated Mr Haffkine on his prophylactic fluid, stating 'there are probably not many bacteriologists living whose discoveries have proved more effective in the service of humanity'. However, he concluded: 'it is difficult to conceive how the matter could have been investigated more thoroughly or impartially, and we think that Mr Haffkine would be well advised to allow the incident to be forgotten'.[34] This drew an immediate and succinctly argued rebuttal from WJ Simpson, CMG, now Professor of Hygiene at King's College, London. In a letter of 9 February Simpson stated

> the sole foundation for the conclusion arrived at as to the contamination having taken place in Bombay and not at Mulkowal was the assumption by the Commission that it was impossible for nineteen persons to have been infected so uniformly unless contamination had been in the fluid and the latter had been contaminated in Bombay.[35]

Simpson pointed out that this assumption had been negated by the very experiments carried out by the Indian Commission and the Lister Institute. He detailed evidence that showed it was impossible that contamination could have taken place in the Bombay laboratory and called for a redress of the 'grave injustice to Haffkine'.

In February 1907 Haffkine wrote to Ronald Ross (1857–1932) inquiring whether 'you care to contribute to the subject by making known the view which you may form [on this matter]'.[31] Ross, Nobel Laureate in 1902 for proving the role of the *Anopheles* mosquito in the transmission of malaria, was now Professor of Tropical Medicine at the University of Liverpool. Aware of the seriousness of the unfounded imputations being levelled against Haffkine, Ross, together with Simpson, commenced a campaign to exonerate Haffkine from blame for the disaster.

On 15 March 1907, in a letter to *The Times* on the need to bring more science into British administration, Ross cited the story of Dr Haffkine. After summarizing the evidence, Ross hit out at the Indian Government and the India Office:[36]

> The case as it stands does not convict him [Haffkine] of any fault whatever; but, unless the end of it is changed, it will convict India and her rulers of indifference to science, stupidity, injustice, and gross ingratitude to one of their greatest benefactors. Nor is this the only instance when these qualities, probably fostered by unseen spites and jealousies, have been displayed towards distinguished but defenceless workers in science. Unless the verdict is quickly amended, such men will hesitate before going to a country where the most meritorious services seem to lead only to neglect or censure

Ross wrote a letter to *Nature*[37] about the disaster. He pointed out that the public's perception in India that poisoning was due to carelessness at the laboratory, not to a local accident, was leading to rejection of the prophylactic vaccine. This was at a time when 20,000 deaths from plague were occurring in India every week. A critical editorial followed.[38]

A question was raised in the House of Commons and, in a written reply on 20 March, Mr John Morley (1838–1923), Secretary of State for India, agreed to lay before the House the papers containing the results of the inquiry into the origin of the accidental deaths from tetanus poisoning in Punjab as a consequence of the use of Dr Haffkine's prophylactic against plague. Also in a written reply, Mr Morley stated that the Government of India had offered Dr Haffkine employment on research work in India at his previous salary if he elected to return.[39] Two more letters from Ross to *The Times* followed. In June, copies of the Parliamentary *Return of Papers* reviewing the entire Mulkowal accident (108pp) reached Haffkine and Ross; the matter was now in the public domain. The climax of the campaign to exonerate Haffkine came in a letter to *The Times* published on 29 July 1907 that was signed by 10 distinguished bacteriologists:

> In conclusion, we should like to express our approval of the stand which Mr Haffkine is making to obtain justice in this affair. The baseless charge against him, widely published as it has been, amounts to a public accusation of having conducted his laboratory in such a manner as to cause the death of nineteen innocent persons – a most serious imputation. Moreover, it has tended to hamper the great cause of scientific hygiene in general, and of scientific hygiene against plague in particular, by encouraging popular prejudices against them. We sincerely trust, therefore, that the Government of India will see fit either to exonerate Mr Haffkine publicly from the imputations made against him, or, if they still remain unconvinced by the very decisive evidence which they themselves have collected, to order a new and more authoritative inquiry into the whole matter.
> RONALD ROSS (Professor of Tropical Medicine, University of Liverpool)
> R. TANNER HEWLETT (Professor of Pathology, King's College, London)
> ALBERT S. GRUNBAUM (Professor of Pathology, University of Leeds)
> W. J. SIMPSON (Professor of Hygiene, King's College, London)
> R. F. C. LEITH (Professor of Pathology, University of Birmingham)
> WILLIAM R. SMITH (President, Royal Institute of Public Health)
> G. SIMS WOODHEAD (Professor of Pathology, University of Cambridge)
> E. KLEIN (Lecturer on Advanced Bacteriology, St Bartholomew's Hospital London)
> SIMON FLEXNER (Director of the Laboratories,

Rockefeller Institute, New York)
CHARLES HUNTER STEWART (Professor of Public Health, University of Edinburgh)[40]

Exoneration came four months later. On 29 November 1907 *The Times* carried a news item that Mr Haffkine had received a letter from the India Office stating:

> The Secretary of State recognizes that, though the views on the matter are not unanimous, an important body of scientific opinion is favourable to him in the question of the origin of the Mulkowal disaster, and adding that the Secretary's own attitude is indicated by the offer of employment upon honourable terms.[41]

Mr Haffkine expressed gratitude for the expressions contained in the letter, accepted the offer and looked forward to returning to India as soon as possible. Haffkine received many congratulations upon the recognition he received finally from the India Office and his resolution to return to India.[32]

Haffkine was deeply grateful for the support and help of Ronald Ross. He had first met Ross in April 1899 at the opening of the Liverpool School of Tropical Medicine and, during 1907, had formed a warm personal relationship with Ross and his wife. The high respect accorded to Haffkine was evident in the award of the prestigious Mary Kingsley Medal[42] from the Liverpool School of Tropical Medicine and in election to the Council of the newly formed Society of Tropical Medicine and Hygiene. Both these honours in 1907 predated his exoneration.[31] Before his departure for India, Haffkine presented to the Epidemiological Section of the Royal Society of Medicine a paper entitled *On the Present Methods of Combating the Plague*.[43] He cited figures from India that suggested antiplague inoculation led to a reduction in mortality by some 85% when compared with the non-inoculated.

The question was raised as to whether being a Russian Jew (although naturalized British) played a part in the affair. Eli Chernin[31] studied the correspondence of Haffkine in the archives of the Jewish National and University Library in Jerusalem. He did not find evidence that Haffkine was 'overtly victimized by anti-Semitism' but added 'it would be naive to think that Edwardian bureaucracy was wholly uninfluenced by Haffkine being a Jew'. Haffkine, without a medical qualification, believed he was the victim of local political intrigues. His personal diaries for the years 1903–05 reflect his bitterness that 'he was dispossessed of the fruits of his labours by faithless assistants [British medical men]'.[44] The IMS must bear considerable responsibility; reparation was to come much later (see below).

Return to India

In 1908 Waldemar Haffkine took up the post of the Director-in-Chief of the Biological Laboratory in Calcutta,[45] a research laboratory without facilities for vaccine production; in fact his terms of employment stipulated that his work be restricted to research.[2] Sadly, the stigma of the Mulkowal disaster remained with Haffkine in India. Shortly after his return, in a letter to Ross, Haffkine wrote 'the whole of the unjust punishment for Mulkowal has been placed and remains on me quite as before'.[31] He apologized for mentioning the matter and then remarked that he was writing in the laboratory occupied by Ross during his work on mosquito-transmission of bird malaria. In 1909 the French Academy of Sciences awarded Waldemar Haffkine *le Prix Bréant* for his achievements in preventive vaccination against cholera and bubonic plague;[46] the prize carried an award of 4000 francs.

Haffkine became interested in developing for use in the field a killed or 'devitalized' anticholera vaccine. He had first prepared such a vaccine in 1892 and, in few experiments, shown it to remain efficacious in animals yet harmless to man. He had demonstrated its preparation to Wright at Netley in 1893 and mentioned it in his London lecture that year. Although a killed vaccine was very much easier to manage, at the time he preferred Pasteur's method of injecting living microbes which he believed would give stronger and longer-lasting immunity. Living microbes introduced under the skin posed no threat since these died after a time. Several times Haffkine wrote to the Secretary to the Government of India for permission to test his new, devitalized vaccine in humans; this would lay the ground for a large-scale field trial for which he had great experience. Repeatedly he was refused, although he was encouraged to continue his laboratory investigations.[2] A devitalized vaccine was used in Japan in 1904 with some success and by 1915 live vaccines were being given no longer.[19]

The Mulkowal disaster had virtually stopped Haffkine's career. By nature, Haffkine was introspective and he became more so over the years. His upbringing had been without much religious training but increasingly he became devoted to the Jewish religion.[1] Before his retirement, Haffkine described the history of anticholera vaccines (both living and devitalized) and subsequent testing in the field.[18] In a second monograph he detailed the history of his use of the antiplague vaccine during the incubation stage of the disease and its subsequent application to other infectious diseases.[47] In these monographs Haffkine sought to safeguard his right to be the first person to undertake prophylactic inoculation in man.

In March 1915, having reached the minimum retirement age of 55 years, Haffkine left the Indian Civil Service on a comfortable pension. He travelled to Europe, stopping off in London. During this stay he was asked by Sir Walter Morley Fletcher (1873–1933), the Secretary of the Medical Research Committee (later Council), to join a committee which was to decide whether the British Forces in Flanders and France should have

vaccination against paratyphoid A and paratyphoid B combined with typhoid vaccination. He was to act 'as a kind of neutral assessor'. The combined vaccine was opposed by Sir William B Leishman (1865–1926), the Director of Pathology to the Expeditionary Force, but was supported by other members of the committee. The committee met in November 1915 and in Fletcher's opinion the successful outcome was 'in great measure due to the quiet influence of Haffkine' who supported the use of a combined vaccine. This episode was recounted later by Fletcher who continued 'Haffkine had, of course, always been a great name to me, but I never met him except within the hour in which he gave this last service [to the country]'.[32]

The Haffkine Institute

In 1905 the *Plague Research Laboratory* was renamed the *Bombay Bacteriological Laboratory* due to its widened role in public health; vaccines for plague, typhoid and cholera were being manufactured and diagnostic and other services were provided. Training of personnel and research was being developed and in 1925 the Director of the laboratory, Lieutenant-Colonel Mackie FP, IMS, suggested to the Bombay Government that the laboratory be renamed the *Haffkine Institute*. This received universal approval. The change in name was 'a tardy but, nonetheless, wholehearted recognition of the great bacteriologist'.[48] When informed of the naming of the institute, Waldemar Haffkine replied:

> I am very greatly indebted to Col. Mackie for the name given to the Parel Laboratory and to you for the terms in which you have written to me. Very much do I appreciate also your mentioning of the friendly attitude towards me of the other members of the Institute's staff. The work at Bombay absorbed the best years of my life and I need not explain how much I feel everything connected therewith. I wish the Institute prosperity as an active centre of work on behalf of the health organisation of the country and I send blessings to the whole of its staff.

The staff that knew Haffkine remembered him as 'a generous, kind and sympathetic master and a good friend indeed'.[49]

From the opening of the laboratory up to the end of 1925, nearly 26 million doses of the antiplague vaccine were sent out. Successive attempts were made to improve upon the original method of manufacture but came to nought.[50] However, Lieutenant-Colonel Sahib Singh Sokhey, IMS, the Director of the Haffkine Institute (1932–49), undertook systematic studies of the vaccine shortly after becoming director. His development of a biological assay of the protective power of the antiplague vaccine helped solve several problems,[51] one of which was variability in quality.[20] An antiplague vaccine of high immunizing value and low toxicity was developed at the institute. In 1975 the Haffkine Institute was divided by the Government of Maharashtra into the Haffkine Biopharmaceutical Corporation Ltd (fully owned by the government) which dealt with production of vaccines, curative sera and other biochemicals, and the Haffkine Institute for Training, Research and Testing; both centres continue to the present day.

Later years

From 1915 until 1927 Waldemar Haffkine lived in France at Boulogne (Pas-de-Calais) with his sister. He was interested in cultural and theological aspects of the Jewish religion and supported the Jewish emancipation movement that followed the First World War. In 1926–27 he visited the Ukraine and the Crimea in order to inspect Jewish agricultural facilities on behalf of the Universal Israelite Alliance.[3] In 1927 he moved to Lausanne in Switzerland and in 1929 placed his considerable savings in a fund to support religious schools for the training of Jewish youth in eastern Europe. After his death the *Haffkine Foundation for the Benefit of Yeshivoth* was founded.[1]

Waldemar Haffkine died in Lausanne on 26 October 1930, aged 70 years. He had retained his interest in India and remained in communication with some of his Indian friends until his death. In Bombay the Haffkine Institute and Grant Medical College closed on 27 October to pay homage to his memory. He was remembered as a man 'full of modesty and very considerate to his adversaries'.[50] Professor Sir William Simpson wrote in his obituary of Waldemar Mordecai Haffkine:

> I knew him intimately. He stayed with us several times when in Calcutta, and on one occasion when he was ill with malaria, which he had contracted in Assam. Whether ill or well, he was very likeable and always the same: a courteous and amiable gentleman, even towards those who opposed him and attacked his views and work; very determined, remarkable for his powers of work, full of enthusiasm, and with a dauntless courage which was not to be damped by disappointments.[52]

Conclusion

Indisputably Haffkine's antiplague vaccine was saving tens of thousands of lives, even though its efficacy was probably less than the figures from India suggested. A review of cases in 1903 showed that proof of the identity of the condition of plague was not always forthcoming.[32] In 1921–22 a large scale, matched trial of Haffkine's antiplague vaccine in Java[53] showed a reduction of 50% in plague mortality. With the difficulty in making other antiplague measures effective, the vaccine remained the main line of defence for decades in India[48] and has always been an important adjunct to these measures.[54] Haffkine's anticholera vaccine produced protection in the field such that the

incidence of the disease was reduced but not the case mortality; the vaccine appeared to be 'anti-microbic rather than antitoxic'.[55] The prophylactic was an important public health measure in India at a time when sanitary reforms lagged far behind what was required.

The apparent success of the anticholera and antiplague vaccines led some of Haffkine's co-religionists to call him the 'Jewish Jenner',[56] a claim to which, unfortunately, the bacteriologist and medical historian William Bullock (1868–1941) took exception. In his obituary of Haffkine, Bullock criticized him as a scientist and even implied that the Mulkowal disaster was due to shortcomings in his laboratory.[57] Indeed, Haffkine had set up a full-scale field trial of the anticholera vaccine in man on the basis of relatively few experimental results in animals. However, such had been the success of Pasteur's protective inoculations against anthrax and rabies that, by preparing his vaccines according to the programme laid down by the great man, Haffkine believed these would be effective.[2] This possibility was accepted by the Secretary of State for India who, on the advice of the medical profession in 1892, welcomed a privately funded trial of the anticholera vaccine. In the field Haffkine sought to evaluate the efficacy of his vaccines in well-planned studies. In this he was a pioneer and he has been credited with being the first person 'to define the principles of controlled field trials and, moreover, to use them'.[20] Haffkine was to realize that numerical analysis was central to the evaluation of a vaccine.[2]

Dr Ferrán claimed priority for using the first anticholera vaccine for prophylactic inoculation in man. However, several investigating commissions failed to find evidence that his inoculations provided protection against cholera.[5] The contributions of Ferrán in demonstrating the pathogenicity of the cholera vibrio in animals and of immunizing animals against the disease were recognized by the French Academy of Science with the award of the Bréant Prize in 1907.[46] In 1970 the bacteriologist and medical historian Dr William Derek Foster (1925–81) cited Waldemar Mordecai Haffkine as the person to have made, in 1893 in India 'the first vaccinations for bacterial disease in man the utility of which seemed reasonably certain'.[58] In Mumbai the Haffkine Biopharmaceutical Corporation and the Haffkine Institute for Training, Research and Testing ensure that the beneficent work of Waldemar Haffkine for India is not forgotten.

References and notes

1 Waksman SA. *The Brilliant and Tragic Life of WMW Haffkine Bacteriologist*. New Brunswick, New Jersey: Rutgers University Press, 1964

2 Löwy I. From guinea pigs to man: the development of Haffkine's anticholera vaccine. *Journal of the History of Medicine and Allied Sciences* 1992;**47**:270–309. (This detailed article is based on archival material, including Haffkine's laboratory notebooks, correspondence and diaries, in the Jewish National and University Library, Givat Ram, Jerusalem)

3 Waldemar Haffkine. Repères chronologiques, 1860–1930; http://www.pasteur.fr/infosci/archives/haf0.html (consulted November 2004)

4 Haffkine WM. Injections against cholera, a lecture. *Lancet* 1893;**i**:316–18

5 Bornside GH. Waldemar Haffkine's cholera vaccines and the Ferran–Haffkine priority dispute. *Journal of the History of Medicine and Allied Sciences* 1982;**37**:399–422

6 Haffkine WM. Le choléra asiatique chez le cobaye. *Comptes Rendus Hebdomadaires des Séances et Mémoires de la Société de Biologie* 1892;**4**(Series 9):635–7

7 Haffkine WM. Le choléra asiatique chez le lapin et chez le pigeon. *Comptes Rendus Hebdomadaires des Séances et Mémoires de la Société de Biologie* 1892;**4**(Series 9):671

8 Haffkine WM. Inoculation de vaccins anticholériques à l'homme. *Comptes Rendus Hebdomadaires des Séances et Mémoires de la Société de Biologie* 1892;**4**(Series 9):740–1

9 Hankin EH. Remarks on Haffkine's method of protective inoculation against cholera. *British Medical Journal* 1892;**ii**:569–71

10 Simpson WJ. Memorandum on cholera and Professor Haffkine's anti-choleraic vaccination. *Indian Medical Gazette* 1894;**29**:235–8 (Simpson was editor of the journal at this time)

11 Protective inoculation against cholera. Editorial article. *Lancet* 1893;**i**:307–8

12 Wright AE, Bruce D. On Haffkine's method of vaccination against Asiatic cholera. *British Medical Journal* 1893;**i**:227–31

13 Haffkine WM. *Anti-cholera Inoculation: Report to the Government of India*. Calcutta: Thacker, Spink & Co., 1895

14 Haffkine WM. Anti-choleraic inoculations in India. *Indian Medical Gazette* 1895;**30**:35–41 (paper read at the First Indian Medical Congress held in Calcutta in December 1894)

15 Calcutta Medical Society Meeting on 14 August 1895: Farewell to M. Haffkine. Anti-choleraic inoculation. *Indian Medical Gazette* 1895;**30**:354–7. (Haffkine was too sick with malaria to attend but sent an account of his experience with the vaccine to be read to the society. A motion of praise for the work of M Haffkine was proposed and seconded by Dr Simpson who spoke of his part in the vaccination scheme in Calcutta)

16 Wright AE, Semple D. Remarks on vaccination against typhoid fever. *British Medical Journal* 1897;**i**:256–9

17 Haffkine WM. A lecture on vaccination against cholera. *British Medical Journal* 1895;**ii**:1541–4

18 Haffkine WM. *Protective Inoculation Against Cholera*. Calcutta: Thacker, Spink & Co, 1913

19 Greenwood Jr M, Yule GU. The statistics of anti-typhoid and anti-cholera inoculations, and the interpretation of such statistics in general. Section of Epidemiology and State Medicine. *Proceedings of the Royal Society of Medicine* 1914–15;**8**(Part 2):113–90

20 Cvjetanovi B. Contribution of Haffkine to the concept and practice of controlled field trials of vaccines. *Fortschritte der Arzneimittforschung* 1975;**19**:481–9

21 Haffkine WM, CIE Record of Services. Compiled from official records by direction of the Secretary of State for India in Council. *India Office List*. London: Harrison and Sons, 1916: p. 539

22 Bannerman WB. The Plague Research Laboratory of the Government of India, Parel, Bombay. *Proceedings of the Royal Society of Edinburgh* 1902;**24**:113–44

23 Haffkine WM. Remarks on the plague prophylactic fluid. *British Medical Journal* 1897;**i**:1461–2

24 Haffkine WM. A discourse on preventive inoculation. Delivered at the Royal Society, London, on 8 June 1899. *Lancet* 1899;**i**:1694–9

25 Bannerman WB. Inoculation and the incubation stage of plague. *British Medical Journal* 1901;**ii**:669–71

26 Lutzker E. Cameron Prizewinner: Waldemar M Haffkine, CIE. *Clio Medica* 1978;**13**:269–76. (Former prize winners included Louis Pasteur and Joseph Lister)
27 A study of the evidence as to the source of the infection which caused the cases of tetanus at Mulkowal, Punjab, India, during inoculation against plague in October, 1902. *Journal of Tropical Medicine and Hygiene* 1907;**10**:33–61
28 Simpson WJ. The evidence and conclusions relating to the Mulkowal tetanus case. *Practitioner* 1907;**78**:796–812
29 Bannerman William Burney, CSI. Record of Services. *India Office List*. London: Harrison and Sons, 1914, p. 437. (Bannerman became Superintendent of the Plague Research Laboratory in Bombay in June 1902. In December 1903 he was posted as Superintendent to the King's Institute of Preventive Medicine in Madras and, in April 1904, appointed Professor at the Medical College, Madras. In May 1904 he was recalled as Director to the Plague Research Laboratory in Bombay, a post he held until 1911 when he was appointed Surgeon-General with the Government of Madras)
30 The Mulkowal disaster. Editorial article. *Lancet* 1907;**i**: 299–302
31 Chernin E. Ross defends Haffkine: the aftermath of the vaccine-associated Mulkowal Disaster of 1902. *Journal of the History of Medicine and Allied Sciences* 1991;**46**:201–18. (The article draws on archival material in the Ross Institute in the London School of Hygiene and Tropical Medicine, the Jewish National and University Library, Givat Ram, Jerusalem, the India Office, London and the Liverpool School of Tropical Medicine)
32 Waldemar Haffkine, CIE Obituary. *Lancet* 1930;**ii**:995–6
33 Haffkine's antiplague prophylactic. *British Medical Journal* 1907;**i**:285–6
34 Haffkine's plague prophylactic. Editorial article. *British Medical Journal* 1907;**i**:277–8
35 Simpson WJ. Haffkine's antiplague prophylactic (Letter to the Editor). *British Medical Journal* 1907;**i**:343–4
36 Ross R. India and Mr Haffkine (Letters to the Editor). *The Times* Friday, 15 March 1907: (Issue 38281); p. 4
37 Ross R. The inoculation accident at Mulkowal (Letter to the Editor). *Nature* 1907;**75**:486–7
38 Notes. *Nature* 1907;**75**:588–9
39 Dr Haffkine's prophylactic. House of Commons. Wednesday, March 20. (Politics and Parliament) *The Times* Thursday, 21 March 1907: (Issue 38286); p. 6
40 Ross R, Hewlett RT, Grunbaum AS, *et al*. Mr Haffkine and the Mulkowal accident (Letters to the Editor). *The Times* Monday, 29 July 1907: (Issue 38397); p. 18
41 The India Office and Mr Haffkine. News. *The Times* Friday, 29 November 1907: (Issue 38503); p. 8
42 The study of tropical medicine: the Mary Kingsley Medal. Editorial article. *Lancet* 1907;**ii**:853–4. (The first two recipients of the medal, named in honour of the famous African traveller, were David Bruce and Robert Koch)
43 Haffkine WM. On the present methods of combating plague. Epidemiological Section. *Proceedings of the Royal Society of Medicine* 1908;**1**:71–81
44 Löwy I (op. cit. ref. 2): footnote p. 303
45 Haffkine WM CIE (op. cit. ref. 21): a date was not given for the Calcutta appointment; termination of the post of Director-in-Chief, Plague Research Laboratory, was not recorded
46 Bornside GH (op. cit. ref. 5): pp. 419–22. (In 1849 the industrial chemist Jean-Robert Bréant bequeathed in his will the sum of 100,000F to the French Academy of Sciences to be awarded to any person who discovered the means of curing Asiatic cholera or discovered its causes. The prize has never been awarded in full but, in the terms of the Will, interest on the capital has been given in prizes to those who have advanced science on cholera or any other epidemic disease)
47 Haffkine WM. *On Prophylactic Inoculation Against Plague and Pneumonia*. Calcutta: Superintendent Government Printing, India, 1914
48 Government Central Press. *Report of the Haffkine Institute for the year 1925*. Bombay: Government Central Press, 1926: p. 2
49 Jhala HI. Haffkine and the evolution of the Institute. *Haffkine Institute Diamond Jubilee 1899–1959*. Bombay: The Times of India Press, 1959: pp. 1–5
50 Naidu BPB. The late Professor WM. Haffkine, CIE, ScD (Odessa), the first Director of the Haffkine Institute. *Report of the Haffkine Institute for the year 1930*. Bombay: Government Central Press, 1932: pp. 3–8
51 Jhala HI. Department of Vaccine. *Haffkine Institute Diamond Jubilee 1899–1959*. Bombay: The Times of India Press, 1959: pp. 81–4
52 Simpson WJ, Waldemar H, CIE. Obituary. *British Medical Journal* 1930;**ii**:801–2. (Reprinted in *Journal of Tropical Medicine and Hygiene* 1930;**33**:346–8)
53 Hirst LF. *The Conquest of Plague*. Oxford: Clarendon Press, 1953: p. 444
54 Sokhey SS. The passing of the present plague pandemic and India. *Haffkine Institute Diamond Jubilee 1899–1959*. Bombay: The Times of India Press, 1959: pp. 6–11
55 MacLeod K. Anticholeraic vaccination. In: Allbutt TC, Rolleston HD, eds. *A System of Medicine*. London: MacMillan & Co, 1907: vol. 2 (part 2), p. 471
56 Chernin E (op. cit. ref. 31): footnote p. 215
57 Bulloch W. Waldemar Mordecai Wolff Haffkine. *Journal of Pathology and Bacteriology* 1931;**34**:125–9
58 Foster WD. *A History of Medical Bacteriology and Immunology*. London: William Heinemann, 1970: p. 130