Waldemar Haff kine: Pioneer of Cholera Vaccine

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Most Americans who could answer immediately if asked for the name of the scientists who defeated polio, rabies and smallpox, and who could retrieve within a few moments the name analogously linked with syphilis, yellow fever and malaria, would probably come to a complete halt if asked for the developer of the vaccines against two of the deadliest epidemic diseases of all—cholera and bubonic plague. The answer is Waldemar Mordecai Haffkine (1860–1930), a microbiologist who during his lifetime was made a Companion of the Indian Empire by Queen Victoria for his service to that country and was hailed by Lord Joseph Lister as "a savior of humanity." Writing in the 1920s and 1930s, Sinclair Lewis (in *Arrowsmith)* and A. J. Cronin (in *The Citadel*) mentioned his name as one with which their readers would be automatically familiar. It is hard today to find anyone in this country who has ever heard of him.

Haffkine was born in Odessa in 1860, the fourth of five surviving children in a petit bourgeois Jewish family. His years at Novorossisk University in that city were a melange of intellectual and political activity. Early interested in protozoology, he wrote an undergraduate paper for his teacher and mentor Elie Metchnikoff (1845-1916) on *Astasia ocellata* that was good enough to be published in the *Annales* of the Pasteur Institute 4 years later. Committed as well to Jewish and revolutionary causes, he helped to organize the Jewish self-defense which attempted to meet the bloody Odessa pogrom in 1881, an involvement that landed him in a Czarist prison from which he was rescued by Metchnikoff s intercession. Simultaneously, his work for the Narodnaya Volya (People's Will) and other underground organizations subjected him to continual police surveillance and periodic suspensions until his graduation in 1884.

Barred by his religion and political record from academic work in Russia, Haffkine went to Switzerland, where he worked under Moritz Schiff at the University of Geneva for 2 years. The work was agreeable but lacked intellectual stimulation, and Haffkine, looking for a way out, was rescued for a second time in 1889 by Metchnikoff, who invited him to come to the Pasteur Institute in Paris. (Like many other Russian scientists, Metchnikoff had left Russia after the wholesale academic repression of the 1880s, a government response to the assassination of Alexander II-the same event that had triggered the pogroms.) Beginning as a librarian, Haffkine soon graduated to full-time research.

The last and worst of the five great cholera pandemics of the nineteenth century was then threatening Europe, and it was to this question that Haffkine turned his energies. He faced a difficult situation. Despite Robert Koch's identification of *Vibrio cholerae* in 1883, most scientists of the day believed the microbe was not the sole cause of the disease, and therefore held that a preventive vaccine based on its cultures would be useless or impossible. In 1882, Max von Pettenkoffer of the University of Munich, who believed that the vibrio was powerless unless united with an element in the groundwater, swallowed 1 milliliter of broth culture of vibrios, suffered diarrhea but nothing worse (probably a subclinical case resulting from a weak strain of the microbe), and went to his grave (much later) believing that his theory had passed its ultimate test.

Furthermore, humans were the only animal known to be susceptible to the disease, rendering laboratory research impossible. For instance, Nikolai Gamaleia (1859–1949), who thought he had successfully passaged *Vibrio cholerae* through a series of pigeons in 1888, had been unwittingly working with a different microbe, one causing gastroenteritis in fowl.

Most ironically, the work of Jaime Ferran y Clua (1852-1929) in Spain had dealt a temporary blow to the respectability of the idea of an anticholera vaccine. In 1884, Ferran had grown a pure culture of cholera vibrios in nutrient broth and inoculated thousands of subjects in cholera-ravaged Spain with it. Of the inoculees, 1.3% came down with cholera, as opposed to 7.7% among the uninoculated; however, when Ferran refused to give key information to the Pasteur Institute's Brouardel Commission, which came to Spain in 1885 to question him, they wrote off his work as worthless. The resulting obloquy was such that Haffkine later dis-

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Haffkine prepares a rabbit for intraperitoneal injection of cholera culture, part of the passaging process- which resulted in the "exalted" preparation that formed his cholera vaccine.

missed Ferran's work as "mere pre-Jennerian variolization," although this was not the case.

Haffkine began by growing cultures of *Vibrio cholerae* in nutrient broth containing increasing amounts of rabbit serum until he had developed a strain resistant enough to survive in and infect laboratory animals. He then began a series of animal passages, injecting the culture into a guinea pig's peritoneum and extracting it when the animal died. This exudate, which would be either plentiful and diluted or scanty and concentrated, was then injected into a second animal whose size would have to be in direct proportion to the concentration of the sample. The second animal would die in a shorter time than the first, the third in still shorter time, and so on through 20 or 30 passages until the interval could be made no shorter. The culture at this point Haffkine called the "fixed" or "exalted virus," following Pasteur's terminology. The artificially enhanced strength of this culture, much greater than that of any strain occurring naturally, could be expected to immunize a human subject of any size and differentiated Haffkine's preparation qualitatively from Ferran's. When injected subcutaneously it would protect an animal from an intraperitoneal or intramuscular injection of "fixed virus" 20 times larger than one that would kill a control animal in 8 hours. However, it caused a large, granulating wound at the site of injection, something Haffkine felt he could not inflict on human subjects, so he devised a preliminary injection of "attenuated virus" by passing a current of air heated at 39°C over the brew. Injected 4 to 5 days before the enhanced culture, it immunized tissues against necrotization, causing the second injection to leave only a nodule. (In India in 1895, Haffkine began to suspect that human tissues were not subject to this necrotization, tested the question on himself, and found he was right. The first injection gradually fell into disuse thereafter.)

Haffkine climaxed his research with a pair of autoinoculations four times greater than the 2.5 milliliters he would come to use, experienced a slight rise in temperature, pain, and swelling but nothing more, and reported his findings on 30 July 1892 at the Biological Society of Paris, to wide acclaim. He found himself unable, however, to take his vaccine to Russia, as he wished, for political reasons (a Russian commission used Ferran's "failure" as an excuse); to Germany (where von Pettenkoffer's theories reigned supreme); to France (where Metchnikoff, who followed von Pettenkoffer's thinking, had come to regard Haffkine as an ungrateful upstart); or to Spain (obviously). Instead, through the good offices of Lord Dufferin, a former Viceroy, he went to India, whose Ganges-Brahmaputra delta was the immemorial incubator of the disease. He landed there in March 1893.

Haffkine went with the dream, never before put into practice, of transferring experimental laboratory procedures to a human population by selecting a trial village, inoculating half the inhabitants, and waiting for the next epidemic to collect his figures. This proved impossible; the advances of the disease were far more unpredictable than anyone in Paris had thought to tell him. As a matter of fact, 1893 was one of the quietest years India had had with regard to cholera for some time. Haffkine spent his first year in India travelling along the Ganges plain northwest of Delhi, attempting

The Jherria Coal Fields, Bengal, April 1908. Haffkine grimaces sympathetically at a victim of the worst cholera epidemic in the region in several years. The massive resurgence of the disease was partly the result of the government% suspension of inoculation regulations 3 years earlier.

to overcome native resistance through interpreters. He got over 22,000 volunteers, but in the total absence of epidemic cholera along his route was unable to formulate any scientific conclusions.

However, that opportunity came in Calcutta in 1894, when he inoculated 116 of 200 people in a stricken bustee, or suburb. All 116 escaped infection; there were 9 cases, several fatal, among the 84 controls. The vaccine continued to acquit itself similarly throughout the year that followed and on the tea gardens of Assam, where Haffkine spent the winter and spring of 1894-1895. He had tremendous difficulties there; the inoculation produced a 2-day reaction during which labor was impossible, and the growers were as reluctant to lose the work time as the coolies were to forfeit 2 days of pay, which meant 2 days of life at the subsistence level. In addition, the laborers formed a highly mobile population, unused to having their movements tracked, which made the collection of results extremely difficult. Nevertheless, Haffkine ultimately tested almost 20,000 subjects. A colleague's report on seven tea gardens showed that mortality among the uninoculated ranged from 22 to 45.4%, whereas the highest rate among the inoculated was about 2%.

Efforts to Combat Bubonic Plague

In 1896, Bombay was stricken by bubonic plague, and the second phase of Haffkine's career began. He crossed India by railroad and was promptly installed by the British in a makeshift laboratory in the only free space available, a corridor in the Grant Medical College. There, after isolating and identifying *Yersinia pestis*, he set up culture flasks of broth based on goat flesh (beef and pork being ruled out by the religious considerations of the Indian population) whose surfaces were dotted with *ghee* (clarified goat butter) inoculated with the plague bacillus. These sent down characteristic stalactite cultures for about 4 to 6 weeks, until the broth could no longer support microbial life. Haffkine then killed the microbes by heating the flask to 70°C for 1 hour. Unlike his cholera vaccine, the finished product contained not only the bacilli but also their metabolically produced toxins within the "supernatant fluid." Haffkine included this to have a therapeutic as well as a preventive element in his vaccine. His cholera preparation, which conferred immunity to the uninfected, had had no effect in an already infected inoculee.

On 10 January 1897, Haffkine subjected himself to another fourfold autoinoculation, experienced a painful week of febrile reaction, and announced his findings to the authorities. Two weeks later, when plague struck the Byculla Jail, he put his vaccine to a controlled test. (The British had originally regarded prison trials as morally impermissible, but had relented in the face of a virulent cholera epidemic in 1894.) There were 154 volunteers, 3 of whom were found to have been suffering from plague at the time of inoculation; those three died. Two more volunteers developed plague but recovered. Of the 170 controls, 12 caught plague; 6 of them died.

For the next 5 years, Haffkine worked on antiplague inoculation in and around Bombay, moving to ever larger quarters as the demand for his vaccine burgeoned. Nevertheless, he had an uphill fight. In northeastern India, where cholera was endemic, the authorities allowed him to experiment within certain limits. But the plague that sailed into Bombay in August 1896 was not a condition to be lived with but a crisis to be met, and it engendered a crisis mentality among the authorities, who clung to their own way of dealing with it. That way was the sanitarian approach, which consisted of scouring the city daily for plague cases, carting them off to hospitals, removing their families to contact camps outside the city, turning out their houses, and washing the walls and drainage gullies with lime.

There was no philosophical contradiction between sanitarianism and inoculation; both were based on the germ theory of disease. Whereas sanitarianism was an enormously influential social concept of the nineteenth century, immunology was still in its infancy. And upon this infant the British were not about to spend their prime monies and energy. Haffkine soon found that his desperate needs for manpower and facilities were regarded by his employers as something to be attended to after everything else was taken care of. Often, there was nothing left over.

Haffkine regarded the British attempts at disinfection as hopelessly inadequate to the epidemiological realities of plague, and therefore, ultimately futile. Beyond that, he was appalled by the misery and upheaval they caused in the lives of their intended beneficiaries, who were far more terrified of camps and hospitals than they were of plague. Again and again he begged the government to suspend segregation orders and travel restrictions for persons who had been inoculated, adducing ever more impressive inoculation statistics to buttress his case. This did not endear him to the authorities, who regarded him as something of a foreign upstart to begin with and who in addition had the nineteenth-century physicians' aversion and distrust of "merely scientific men."

In April of 1898, however, plague hit the three villages of the Dharwar township, about 300 miles southeast of Bombay, at the beginning of the monsoon season. The weather made wholesale sanitation measures physically impossible, and they were accordingly declared suspended for inoculees. To the government's amazement, the tens of thousands of voluntary inoculees remained calmly in the township while their unprotected fellows took to the hills, pursued by the double terror of plague and internment. After that Haffkine's proposal quietly became de facto policy.

But Haffkine's success was probably his undoing. The British, convinced now that inoculation would be a major weapon in any antiplague campaign they would mount, wanted it to be unequivocally in their own hands, and they began machinations to oust Haffkine from his laboratory and replace him with his second-in-command, a surgeon-major in the Indian Medical Service and one of their own.

In June of 1902 the Punjabi Provincial Government

announced a massive inoculation campaign for the following autumn, the first such government-sponsored event in-India. Haffkine, jubilant, submitted a requisition for the additional laboratory workers he would need to meet this unprecedented demand on his resources. Owing to a fantastic succession of governmental bungles, they failed to arrive until much too late, forcing Haffkine to fall back on an alternative method of manufacture.

Then, in October 1902, 17 persons in the Punjabi village inoculated from the same bottle of vaccine died of tetanus. The government convened a commission to investigate the incident and to bring evidence against Haffkine. The commission held an inquiry and found that a native compounder (assistant) had-dropped the forceps he was using to extract the stopper of the bottle in question to the ground and then had neglected to sterilize it by flame before reapplying it. (Nothing happened to anyone inoculated from "sister bottles" decanted from the same brew, and the bottle itself was odorless, and therefore nonputrescing, when opened for use that day.) The commissioners submitted a report which included the compounder's testimony in an appendix but in the body of which they claimed that, while such an accident "might have" occurred, they believed that the contamination had been introduced in the laboratory. Then, perhaps in an attempt to do injustice justly, they spent 10 of their 12 pages indicting the Indian Government for having failed to supply Haffkine with the qualified assistants he had requested. The government suppressed the report and suggested Haffkine take a European vacation.

Haffkine spent the next 4 years in England, taking his case to the India Office at Whitehall and the scientific community. The matter, which became known as a "little Dreyfus affair" (Haffkine's Jewishness, and his employers' reactions to it, had been an undercurrent in his professional life from the start), climaxed in July of 1907 with the publication of a letter in the *London Times* engineered by Ronald Ross, the Nobel laureate who had explicated the life cycle of the malarial mosquito. After recapitulating the facts, the letter declared that the case against Haffkine was "not only not proven, but distinctly disproven," and was signed by the most illustrious medical scientists of the day: Ross himself; Albert Grunbaum, Professor of Pathology at Leeds College and a pioneer in cancer research; R. F. C. Leith, the founder of Birmingham's Institute of Pathology; William R. Smith, President of the Council of the Royal Institute of Public Health; G. Sims Woodhead, the Professor of Pathology at Cambridge who had introduced serotherapy to England; Simon Flexner, Director of Laboratories at New York's Rockefeller Institute; and others.

The Indian government gave in, not because of the unanswerable credentials the letter presented, but because its desperate (and secret) attempts to get Haffkine permanently employed in London had failed. Haffkine went back to India, although at a humiliating level of status and salary. He spent the remaining 8 years of his professional life, from 1908 to 1915, in a three-room bungalow in Calcutta that also was his laboratory, as an independent researcher for the Indian government. He proposed several government 'projects, dealing with cholera inoculations (the government had allowed his original programs to lapse), the disinfection of wells, and the preservation of antirabies sera. All were quashed.

Haffkine left India at the mandatory age for pensionable retirement of 55, and spent most of the remaining 15 years of his life in France. When the British officially renamed his laboratory the Haffkine Institute in 1925, he learned about it through a newspaper clipping someone sent him. In 1926 he revisited his much-transformed native land for the first time in 38 years. He was warm toward the Bolsheviks from 1917 until the end of his life, on the grounds that they had eliminated the Jewish disabilities imposed by the Czars. He died quietly in his rented room in Lausanne, Switzerland, on the evening of 25 -October 1930, felled by the heart condition from which he had been suffering for 10 years.

"The journey we make here upon the earth is so short," he had written when he was 38 years old. "Before we know where we are, we are at the end, and called upon to answer an inner voice: 'Have you finished the work you had to do?' Happy are they who can think, yes, they have finished their work." ❑