A Rip van Winkle in an exploding field—the Haffkine Institute

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The Haffkine Institute in Bombay and the School of Tropical Medicine in Calcutta are two of India's oldest and most venerated institutions and pioneered medical research in the country. But now, even with much opportunity for fruitful biomedical research, Haffkine languishes from neglect.

Set up as a Plague Research Laboratory under Haffkine, the present lovely old mansion with beautiful gardens in a 29-acre prime site right in the middle of the city of Bombay—formerly the residence of British governors—was formally opened on 10 August 1899 by the then Governor of Bombay, Lord Sandhurst. It was renamed Bombay Bacteriological Laboratory in 1905 and rechristened 'Haffkine Institute' in 1925 in commemoration of the crusading work on plague and cholera by its founder and first director-in-chief Dr Waldemar Mordecai Haffkine (1860–1930)[1a].

Research is similar to trade, it should be learnt from a master. Haffkine, born in Odessa, Russia, studied zoology under Prof. Elie Metchnikoff, later a Nobel laureate, whom he followed to Paris to work under Louis Pasteur[1b]. He was then able to enter the mainstream of research in preventive medicine at a time when an entirely new dimension had been added to medicine by Pasteur's search for the causes, prevention and treatment of infectious diseases. Robert Koch in 1883 had demonstrated the causal relationship between cholera vibrio which he had isolated, and cholera, Haffkine prepared the first cholera vaccine and reported success in a presentation to the Biological Society in Paris on 18 July 1892. He arrived in Calcutta in March 1893, being persuaded by Lord Dufferin to go to India where cholera was raging. He worked without pay and his itinerant team inoculated over 42,000 people in Eastern India over two and a half years. He could not yet evaluate the degree of immunity or how long it was effective, but the death rate had been reduced by 70%.

Haffkine was reassigned to Bombay, where he arrived on 7 October 1896, to deal with the epidemic of bubonic plague and colossal death and destruction. He prepared an antiplague vaccine in an improvised one-room laboratory in a corridor at the Grant Medical College, Bombay. He urged inoculation of troops, prisoners, and coolies employed in the railways, tea plantations and coal mines. Germany, China, France and Russia sent their scientists to Haffkine's Laboratory in Bombay to study techniques in vaccine preparation, inoculation procedures and to observe and report results. In 1899 he became a British citizen.

However, in those days there was no limit to the indignities heaped on Haffkine, or the ordeals he had to undergo for doing medical research; being himself not a medical doctor, or in the civil service or in the army. His pioneering achievements often evoked doubt and derision about his techniques or successful results by many Indian medical service officers to whom he was an outsider. He had to pass through days of privation, anxiety, challenge and even ridicule. He was accused of carelessness and censured when a few people out of the thousands inoculated with his vaccine developed tetanus. It was subsequently proved beyond any doubt that he had scrupulously maintained high standards of production and the tragedy was due to negligence on the part of a junior medical officer who was in charge of the plague vaccine inoculation. Meanwhile he was suspended and later dismissed, while an enquiry committee was set up which lasted five years. Many scientists at the Lister Institute in London and the Pasteur Institute in Paris pleaded in vain that, at Malkowal (the village where death occurred), lack of adherence to proper sterilization techniques resulted in death owing to tetanus. Finally, Ronald Ross and leading bacteriologists took up

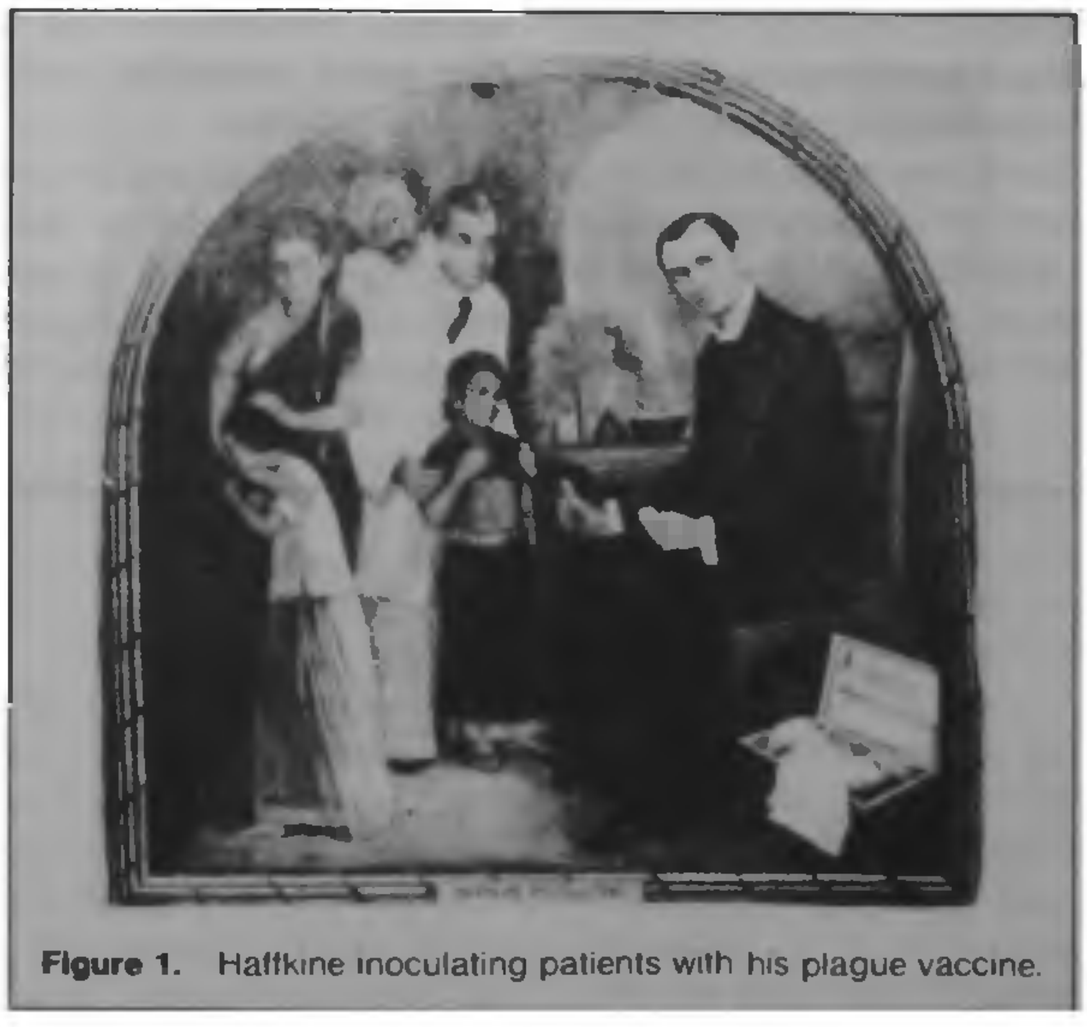

Figure 1. Haffkine inoculating patients with his plague vaccine.

cudgels on his behalf and Haffkine was ultimately exonerated by the British Government.

Haffkine's interest in the production of bacterial vaccines was continued by his successors W. G. Liston (1911–1923), F. P. Mackie (1923–1931) and J. Taylor (1931–1932). The institute also got involved in pioneering work in bovine tuberculosis, epidemiology of plague, vaccines for rabies, Kyasanur forest disease and typhoid in later years. But it was Sahib Singh Sokhey (1932–1949) who created a new agenda for science in the institute. There is a superb article on Sokhey by Ganapathi, who worked closely with him for many years at the Haffkine[1c].

When I joined the Haffkine in August 1947, Sokhey was already reaching the end of his innings and was due to retire shortly. For a man in his sixties, I was struck by his dynamism and drive, his zest and zeal, his ability to cut across adiposities and come straight to the point of the nerve, his great qualities of determination and goal-oriented direction of work. His courtesy was his frankness. Experimentation was his way of thinking as well as the practical expression of his thought. He came with a high pedigree in medical research. He did research in biochemistry with F. G. Hopkins at Cambridge and got the doctorate in Harvard under Folin. He worked with Macleod in Toronto. In those days, there was a need for curiosity and questioning of various aspects of avowed and attested observations and experience—this he freely allowed; there was also a need for creation of doubts about established versions of thoughts or facts—this he frequently encouraged; and the need for introducing statistical methods in the design and conduct of experiments and quantifying biological test data—this he insisted upon. His leadership at the institute was action and motivation, not position alone; and the institute attained lustre and international repute because he enabled people and things rather than enforced them.

Ganapathi writes[1c]: 'Strange as it may seem, he introduced micropipettes in bacteriological work, in place of the old primitive methods of delivering volumes by drops, introduced the measurement of pH in the place of litmus paper dips. Thermostats and other instruments which can control conditions within narrow limits all came into use. In his work on plague, he began from the very beginning, standardizing all the parameters involved in the experiments. He standardized the technique of counting the number of viable organisms in an inoculum to standardize the dose, instead of using, as before, a certain weight of infected liver, which gave very erratic results. He found the white mouse the ideal experimental animal rather than the field rat, and worked out all the practical details of breeding 'the standard white mouse'. The result was remarkable accuracy in and reproducibility of results which amazed counterpart workers in San Francisco. Anyone can see that the so-called biological variation is just another pedantic name for sloppiness in experimentation in clumsy hands'.

Figure 2. Sahib Singh Sokhey (right) with C. V. Raman

Sokhey conducted field trials with plague vaccine, sulpha drugs and antibiotics with meticulous care, accuracy and reproducibility. He established plasma freeze-drying and fractionation facilities in the early forties when these things were unknown in India. He set up a large department of organic chemistry (called Chemotherapy Department, cocking a snook at the flinty-eyed administrative surveillance of the government) and pioneered work on anti-TB and anti-malarial drugs. He played a prominent role in establishing facilities for the testing, standardization and quality-control systems in the assay of pharmaceuticals and biologicals. Indeed, he was primarily responsible (along with Ganapathi) for the initial planning and direction of work of Hindustan Antibiotics at Pimpri. His interest in Indian drugs and pharmaceuticals manufacture continued, even after his retirement from the Haffkine institute.

Sokhey was followed by P. M. Wagle (1949–1955) and D. W. Soman (1955–1957) who continued the bacteriological work tradition in Haffkine. H. J. Jhala (1957–1967) had a longer stint as director and, as an outsider with an academic background, for a time encouraged and fostered better interactions among the institute staff and the community of students and university professors. Yet, slowly but surely, many Haffkinites also started developing a sense of 'victimhood' *vis-à-vis* salary, facilities and working conditions in the institute. Though, during these years, many 'national' laboratories were being founded and provided for in terms of buildings, manpower and funds under the aegis of government science and technology agencies, the Haffkine remained unchosen for government benefaction and even for much-needed support. To this day, the Haffkine Institute does not have a conference hall to hold scientific meetings and seminars; such functions are even now held in the Durbar Hall, as the library is called, an unsuitable place causing a lot of inconvenience to readers and to those arranging these functions. It is astonishing that whereas large amounts of money is made available for newer and newer institutions of plausible benefit to the community, the government has been unwilling to spare even small funds for revamping old institutions or maintaining them properly.

N. K. Dutta became director (1967–1971) after a long innings as the head of pharmacology. Dutta got his spurs in pharmacology under Burn at Oxford University and has done some excellent work in developing an experimental model (infant rabbit) system for the studies on cholera. During the directorship of B. B. Gaitonde (1972–1979), a distinguished professor of pharmacology from the Grant Medical College (well known for his report on standard procedures and protocol for evaluation of pesticide toxicology), the institute was divided into two separate autonomous institutions, viz. Haffkine Institute for Training, Research and Testing (HITRT, a research society), and Haffkine Biopharmaceutical Corporation Limited (HBPCL, for manufacturing activities). As outlined in the Memorandum of Association of the research society, the important functions of HITRT are: (i) To conduct research in communicable diseases, especially those of public health importance and relevance to the problems of the state of Maharashtra and the rest of the country; (ii) To train medical and other scientific personnel in the microbiological, virological and other biomedical sciences, (iii) To render patient-oriented services to the public of Bombay, Maharashtra, Goa and other states of the country; (iv) To develop more potent biologicals, antiviral antibodies and chemotherapeutic agents which are safe, effective and economical, especially for the common man; and (v) To render reliable and accurate testing facilities to municipal, governmental and other agencies.

How far have the objectives of HITRT been fulfilled and Gaitonde's vision of bifurcating the research from the production activities and thus giving a thrust, identity and sense of purpose to medical research succeeded? It must be ackowledged that the attempt was largely a failure, due to two major reasons. Firstly, the erstwhile colleagues in Haffkine, now working in HBPCL got a better deal in terms of remuneration and other fringe benefits, were in a better bargaining position and were more visible in the power structure in dealings with the government. Secondly, the HITRT management, being a totally research outfit, had to fend for itself, particularly for its financial needs, which, though ultimately were provided by the state government on an year-to-year basis and sometimes even on a monthly basis, left little money for 'research' expenses. To complicate matters further, the existing skeleton staff in HITRT was burdened with mundane and routine testing activities (that are easily available elsewhere at probably a higher cost), with the sole object of generating income that was too meagre to justify such an activity. This further excerbated the demoralization of the scientific staff, leading to deficiencies in the functioning of the institute and the non-availability of suitable people to lead key departments.

K. D. Sharma (1979–1982) became director at this juncture. He was previously director of the Medical Education of the Government of Maharashtra. His short innings was followed by V. R. Deshpande (1982–86) and M. V. N. Shirodkar (1986–87) who held additional charge as directors. The present director, S. R. Sen Gupta, a microbiologist from Grant Medical College, has left no stone unturned to ensure that the finances of the institute are certain. Various interim steps are being taken to upgrade the infrastructure facilities of the institute such as by acquisition of modern scientific equipment, building a library and staff quarters, repairs to the main buildings, construction of a large laboratory building under the master plan, revision of pay scales of scientists according to ICMR pay scales, and the major task of recruiting young scientific staff.

Till the outbreak of World War II, we were entirely depending upon imports for various biologicals like tetanus, gas gangrene and diphtheria vaccines and antitoxins of all types. The manufacture and supply of antitoxins and toxoids commenced in the institute in 1940. The process for the manufacture of a polyvalent anti-snake venom serum in lyophilized form, effective against four most common poisonous snakes in India was developed and the serum is made available to rural areas where it is most needed.

The institute has made a significant contribution to the manufacture of basic chemotherapeutic drugs by developing a process for the manufacture of sulphathiazole, which was most needed for the treatment of plague. This further led to the establishment of a full-fledged chemotherapy department engaged in developing processes for the manufacture of antimalarials, CNS agents, and antiTB and antidiabetic drugs. Not only are the needs of the state health department with respect to these drugs met, but many other formulations and infusions to meet the needs of state health authorities without imposing undue burden on the state exchequer.

A unit for the preparation of freeze-dried plasma was established in the forties. This group has also undertaken preparation of blood products like gamma-globulin, fibrin foam, antihaemophilic factor, etc. as well as group sera and other reagents required by blood banks.

Some of the research projects on the anvil are cloning of *Vibrio cholerae* antigen genes, preparation of the hypoglycaemic factor from *Bordetella pertussis* and its mode of action, synthesis and study of antifungal and antitubercular agents, the role of antigen-presenting cells in the regulation of immune response against mycobacteria, investigation of indigenous plants for vector control, the role of various enteropathogens in the causation of acute sporadic diarrhoeas, and construction of DNA probes for the diagnosis of malaria and filariasis. A Centre for AIDS Research and Control under the ICMR with K. M. Pavri, formerly director of the National Institute of Virology in Pune, as project director, has been set up. This group is doing a great job in disseminating information about the prophylaxis and control of AIDS in India through their journal *CARC-Calling*.

Haffkine had a God-given chance to pioneer investigative medical research in this country; unfortunately it has forsaken much of that opportunity, role and responsibility. The causes are not far to seek:

Unnecessary caste difference has been created between medical and non-medical scientists which has led to serious deficiencies in the armamentarium of scientific research. It should be clearly understood that medical research is research in medicine and not research by medical men. Today's medical research involves a whole spectrum of sciences starting from taxonomy, anatomy, physiology, morphology, pathology, biochemistry, pharmacology, molecular biology and molecular genetics, apart from clinical medicine which itself involves various disciplines such as paediatrics, ophthalmology, cardiology, gynaecology, neurology, endocrinology, nephrology, gastroenterology, etc. It would require the concerted effort of

scientists in various disciplines, including chemistry and physics to conduct first rate medical research now-a-days. Indeed, some of the greatest medical scientists, e.g. Pasteur, Haffkine, Sayers, Lazarow, 'do not have medical degrees'. Conversely, though having formal medical degrees, many distinguished medical researchers such as Ochoa, Sutherland, Kornberg and Cori were essentially biochemists. Perhaps this argument is not so valid in Indian circumstances, where our molecular biologists have no concept of physiology and vice versa and most of our biochemists lack exposure to medical disciplines.

The institute's bureaucracy had more turf problems than elsewhere. This eventually lead to serious lack of interaction and communication at all levels in the scientific personnel, especially in national forums. Scientists attribute this to longstanding financial problems and consequent neglect of outside contacts; due to nonavailability of funds for participating in scientific meetings and conferences, let alone hosting them.

It is characteristic of bureaucracy that it often yields to pressure but never to logic; thus, over a period of time, many of the critical and crucial decisions, concerning even the internal management, were left to the officers of the state government, who had little empathy with the culture and working environment of the institute. In choosing between efforts to resuscitate the 'work hygiene' of the scientists and those to curry favour from the 'powers that be', the management never hesitated. At the same time, the government held on to the reins of management of the institute (as exemplified by the appointment of a succession of directors from the state medical service who had no experience in the practice or management of research) partly owing to reasons of prestige and partly for the sake of advantages and benefits accruing from the institute's activities. One cannot, however, question the good intentions of the state government, for they seriously sought out various ways and means to bolster the working of the institute and appointed a committee under Rajadhyaksha (and subcommittees with M. G. Deo and V. K. Iya) to make recommendations to promote 'quality' work. Recently an expert committee with Lovraj Kumar as chairman was appointed by the Government of India to investigate the problems of HITRT and make recommendations to the state. The Government of Maharashtra has already initiated steps to implement these recommendations and as an interim measure sanctioned funds for the urgent repairs to the buildings.

The institute has been too compliant with the undefined and undefinable inclinations of the sponsor. This has not only abridged its former style of striving for scientific excellence and panache for performance but has also greatly eroded the motivation of scientists' minds to watch themselves and strive for self-correction and self-accreditation amongst peer groups in India and abroad. Today the Haffkine has lost its *élan*.

AT present HITRT has the departments of virology, clinical pathology, zoonosis, toxicology, pharmacology, chemotherapy, biochemistry, radiation biology, immunology, immunohaematology, bacteriology, testing unit and library. For an institute with its wide spectrum of activities, the number of scientists is limited and of these, very few are engaged in research and academic activities. Scientists do not seem to be attracted to opportunities in the institute partly because the salaries remain woefully short in comparison with salaries in other research institutions like ICMR, CRI or CSIR laboratories or academic institutions such as colleges and universities, and partly because the institute has for some reasons or the other been kept out of funding from the main governmental science and technology agencies such as Department of Biotechnology, Department of Science and Technology, Council of Scientific and Industrial Research and others. For instance, in the programmes and plans of DBT on the manufacture of viral vaccines, Haffkine Institute is nowhere in the picture nor does it participate in any major medical biotechnology areas funded by DBT.

It is extremely rare to have an institute with such a wide variety of disciplines under one wing. The Haffkine campus is also ideally situated in Parel in the midst of a number of other medical research and teaching institutions and hospitals in the neighbourhood, such as the KEM Hospital, Seth G. S. Medical College, Institute for Research in Reproduction, Tata Memorial Centre, Cancer Research Institute, J. Wadia Childrens' Hospital, N. Wadia Maternity Hospital, Institute of Immunohaematology, ICMR Genetic Centre, MGM Hospital, Radiation Medicine Centre (BARC), Bombay Veterinary College, T. B. Hospital, Dinshaw Hospital for Animals, and Enterovirus Research Institute (ICMR). Obvious opportunities for fruitful cross fertilization of ideas, exchange of case materials and information abound and exist in this complex.

The lack of support from industries in a city such as Bombay, particularly from the pharmaceutical industry, is galling, specially in view of the contributions of the institute in the initiation and development of biologicals and pharmaceuticals in the late forties. Because of its Rip van Winkle status, most of the modern techniques and applications in biology are being sorely missed within its walls, e.g. molecular-biological techniques in microbiology, immunology and genetics, modern and up-do-date chemical tools such as MS, NMR and HPLC (even the routine use of rudimentary laboratory apparatus such as GLCs, liquid scintillation counters and ultracentrifuges is not widespread). Obviously, people are attracted to people, not to places with facilities alone, and the paramount need today is to flesh the organization with young scientists with innovative skills and ideas without getting enmeshed in the sinuous complexities of the institute's history.

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c. Sahib Singh Sokey as I know him, K. Ganapathi, p. 20 28.

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