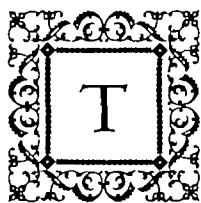


# Cholera and Plague in India: The Bacteriophage Inquiry of 1927–1936

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THE Bacteriophage Inquiry was the name given to a project, cooperatively organized by the government of British India, The Indian Research Fund Association, several hospitals in India, and several medical research institutes in India. The purpose of the project was to evaluate bacteriophage as treatment, and, to some extent, as prophylaxis, for cholera. The story of this project illuminates several interesting questions: How were medical and public health decisions made and implemented in colonial India? How was laboratory research translated into clinical application? And, how was a new therapy evaluated?

This account follows these three themes in parallel and interrelated fashion. It starts with an account describing a convoluted trail of communications between scientists, diplomats, and public health authorities and shows how, in this case, a few committed individuals were able to carry out their plans in spite of bureaucratic misgivings and the rather unsettled political conditions in India. The application of phage therapy and prophylaxis both in the hospital setting and in the field trials seem to have been possible because of the confidence inspired by the main proponent of these trials rather than by much experimental support for his program. Yet, after nearly ten years of study, the role of bacteriophages in the treatment and prevention of cholera was still debated. The account of the trials of phage therapy and prophylaxis shows the difficulties faced in complex field trials, the shifting standards by which success was judged, and the part played by alternate and possibly competing approaches to prevention.

It might be said that this story starts in 1921 on the fictional West Indian island of St. Hubert, when Dr. Martin Arrowsmith triumphantly pre-

sided over the suppression of an epidemic of bubonic plague by treating all comers with his newly discovered X principle or Bacteriophage. Sinclair Lewis's medical hero, *par excellence*, antedated the real-life version of this event by only two and a half years.<sup>1</sup>

Félix d'Herelle had discovered bacteriophages in 1917 while working at the Pasteur Institute in Paris during World War I. He was immediately impressed by the possibility for antibacterial therapy afforded by these lytic viral parasites of bacteria. Within months of his discovery he had started treating experimentally infected animals with bacteriophage preparations designed to cure a variety of infectious diseases. On a research trip to Indo-China in 1920 he had managed to isolate a phage active against a strain of the plague bacillus but it was not until the summer of 1924, however, that d'Herelle found the opportunity to test this phage against plague in patients.

At that time he was Director of the Bacteriology Laboratory of the Quarantine Station in Alexandria, Egypt, sponsored by the League of Nations. This station was set up to detect and prevent the spread of plague and cholera from Asia and the Middle East into Europe via traffic through the Suez Canal. The large population movements associated with the annual Moslem pilgrimages to Mecca (the *hajj* pilgrimage) were seen as particular problems in the control of these diseases. Given the historic and dreaded nature of bubonic plague, d'Herelle's claim of clear and dramatic cures was certain to attract wide attention. The following is his own description of one such case which did, indeed, attract the desired attention of the medical establishment. In July 1925 three individuals were diagnosed with bubonic plague on one ship in port in Alexandria and shortly thereafter a fourth patient was discovered on another ship. These four patients were taken to the Quarantine Station hospital. D'Herelle described his treatment of these patients with his anti-plague phage from Indo-China:

In each of the four cases the sole method of treatment was with injection of the bacteriophage, *given directly into the bubo*. The results are presented here in some detail.

Case 1. Georges Cap. . . . 18 years old. On July 10, 1925 he complained of fever, lassitude, vertigo, headache, and examination showed a bilateral tonsillitis. On the following day his condition became worse. During the night of the 11th and the 12th the crural gland on each side swelled. He was brought to the hospital on July 12th.

1. Although the fictional events were set in 1921, *Arrowsmith* was not published until January 1924.

[A diagnosis of *B. pestis* was made on material aspirated from one of the swellings by specific antiserum agglutination and guinea pig inoculation.]

On July 13th, at 2 p.m., the patient had a temperature of 40.3°C., the pulse was 130, the face was congested, the eyes were injected and drooping, and prostration was extreme. The two buboes were the size of nuts, and painful when pressed. I gave an injection of 0.5 cc. of Pestis-bacteriophage into each of the two buboes, the needle being introduced about the center of the bubo. Apparently the injection caused no pain, since the patient showed no reactions of defense.

At 8 p.m., of this same day there was some sweating of the axilla and the forearms.

On the morning of the 14th the condition of the patient was completely changed. He stated that he felt weak, but that he was not in pain and felt well. The buboes were somewhat painful and had slightly increased in volume.

On the 15th he sat up in bed; and on the 16th he begged for food.

On the 16th the buboes had increased in size to that of a small hen's egg, but they were not painful. Puncture of the left bubo with a syringe permitted the withdrawal of a few drops of bloody fluid. Direct examination showed nothing in the way of organisms, and the culture made from it failed to yield growth. Some of it was inoculated into a guinea pig and the guinea pig was still alive 10 days later. The aspirated material, examined for bacteriophage, showed that it was present, with a very high virulence for *B. pestis* (+ + + +).

On the 25th both of the buboes were incised very freely. Both contained some purulent material. By August 8th healing was complete . . .<sup>2</sup>

Figure 1 shows the temperature profile for this patient and indicates the course since receiving the single, bilateral injection of bacteriophage. D'Herelle's descriptions of the treatment and clinical courses of the other three plague patients are equally dramatic. These cases were first presented in the lead article in *La Press médicale* on 21 October 1925.<sup>3</sup>

#### BACTERIOPHAGES FOR INDIA

D'Herelle gave a copy of his report on treatment of plague to Dr. A. Morrison, the British representative on the Quarantine Board in Egypt, who immediately wrote to C. E. Heathcote-Smith, the British Consul General in Alexandria, as follows:

To my mind the article is very interesting and of intense importance, offering (as it appears to me to do) an almost certain cure for bubonic plague . . . [he

2. Félix d'Herelle, *The Bacteriophage and its Behavior* (Baltimore: Williams and Wilkins, 1926), pp. 567-76.

3. Félix d'Herelle, "Essai de traitement de la peste bubonique par le bactériophage," *La Press médicale*, 1925, 84, 1393-94.

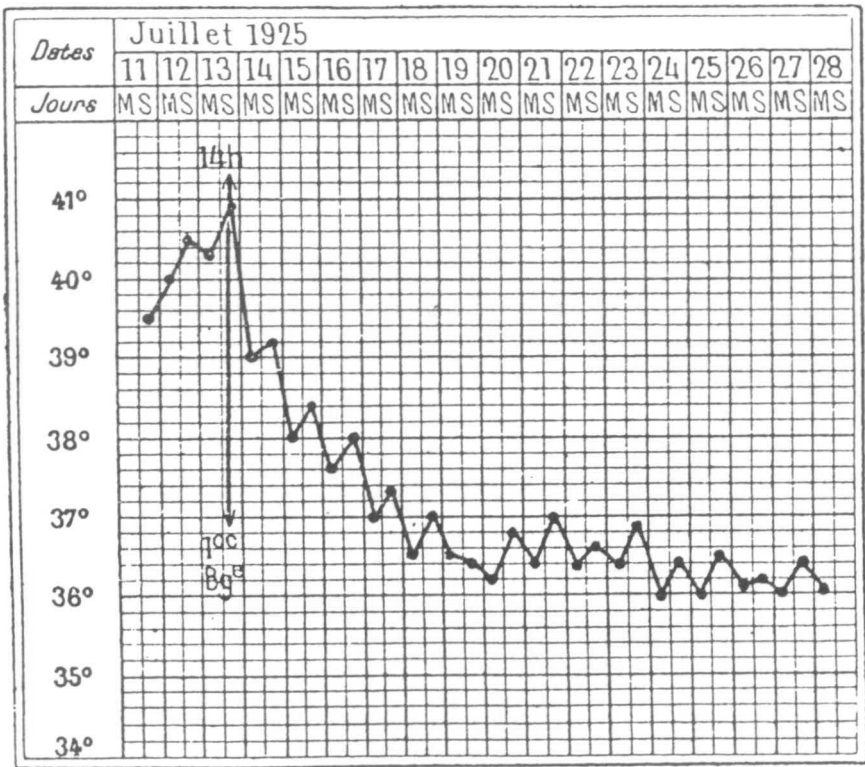


Figure 1. Temperature chart for patient Georges Cap . . . treated on 13 July 1925 for bubonic plague by injection of antiplague bacteriophage by Félix d'Herelle. Reprinted with permission of the publisher (see n. 3).

went on:] I see every reason to hope for a favorable result by this method of treatment even in pneumonic plague. If so, then the dread of plague is conjured [conquered]. Anti-plague serum is useless as a preventative. *The only true prophylaxis is deratization, and the only true treatment is bacteriophage.*

Dr. d'Herelle has supplied already the Sanitary Administration of Egypt with the necessary bacteriophage. I think India ought to arm itself. Also all countries where plague prevails. All honour to D'Herelle. I am proud of having introduced him to Egypt.<sup>4</sup>

This enthusiastic letter, together with the copy of d'Herelle's article, was forwarded by Heathcote-Smith that same day to London, addressed to

4. A. Morrison to C. E. Heathcote-Smith, 4 December 1925, pp. 118-19, I/E/7 #1425, File 7616, India Office Records, The British Museum, London.

His Majesty's Principal Secretary for Foreign Affairs, Sir Austen Chamberlain. The matter found its way to the India office where the *La Presse médicale* article was sent on to India to the Secretary of the Department of Education, Health, and Lands. In an internal memo, however, I. H. Smith, the medical advisor at the India Office, expressed caution. In a note dated 24 December 1925, he first pointed out that the only copy of d'Herelle's article had been dispatched to India, so he could not express an opinion without seeing the paper. Second, he was sceptical of Morrison's reaction to d'Herelle's article: "Dr. Morrison appears to have allowed his enthusiasm to run away with his judgement when he made, on the basis of only 4 consecutive cases of recovery, the assertion that 'the only true treatment is bacteriophage'." The medical advisor went on to suggest that a study of fifty cases with controls be carried out by a "laboratory of standing," for example, the Haffkine Institute in Bombay.<sup>5</sup>

On 6 January 1926, the Secretary of State for India, Frederick Edwin Smith, Lord Birkenhead, sent a coded telegram to the soon-to-depart Viceroy in India, Rufus Isaacs, Lord Reading, directed to the Department of Education, Health, and Lands in India, offering to act as intermediary in obtaining "a supply of remedy for trial in India under laboratory control."<sup>6</sup>

Not surprisingly, the Viceroy responded promptly with the request that the phage go directly to the Director of the Haffkine Institute in Bombay. The bureaucratic chain of communication then seemed to be as follows: the Medical Advisor to the India Office wrote to the Undersecretary of State for India, who in turn wrote to the Foreign Secretary, Sir Austen Chamberlain, whose deputy then wrote to Heathcote-Smith in Alexandria who, in turn, conveyed the request to d'Herelle that a supply of antiplague phage be dispatched to the Haffkine Institute for trial in India.<sup>7</sup> Finally, on 20 February 1926, Heathcote-Smith notified the Foreign Office that d'Herelle had agreed to provide the phage "at an early date."<sup>8</sup>

The phage arrived in March 1926 and very soon thereafter d'Herelle received word in Alexandria that the Haffkine Institute was having

5. Medical Advisor to P. J. Patrick, 24 December 1925, pp. 113-14, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

6. Secretary of State for India to Viceroy, 6 January 1926, p. 111, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

7. R. H. Campbell to Heathcote-Smith, 26 January 1926, p. 105, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

8. Heathcote-Smith to Foreign Office, 20 February 1926, p. 84, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

trouble with the phages.<sup>9</sup> Apparently, the phage grew very poorly at the Haffkine Institute and took twenty-four hours to lyse the cultures. Upon hearing this, d'Herelle immediately applied for an unpaid leave from the Quarantine Board in Egypt, and went to Bombay, at his own expense, to straighten things out.

He arrived in Bombay on 23 April 1926 and soon found the source of the problem in growing the phage. It seemed that the standard bacteriologic medium used for enteric organisms as well as plague bacillus was Martin's medium, developed for this purpose at the Pasteur Institute in Paris. This medium included a digest of macerated pig stomach and beef muscle. In India, however, this medium could not be used because it offended both Muslims and Hindus. The Haffkine Institute, therefore, routinely used a modified Martin's medium based on a hydrochloric acid digest of goat tissue. D'Herelle found that this medium was very poor for producing bacteriophages and developed a modification whereby the goat tissue was digested not by HCl, but by papaya juice (the commercially available source of papain). With this modification, as well as improved filtration to eliminate their prevalent contamination problems, d'Herelle managed to produce active anti-plague phage stocks in India.<sup>10</sup>

While d'Herelle was engaged in the laboratory study of plague bacilli, clinical studies were being attempted at Hyderabad and Agra. The protocol for these trials involved, first, the establishment of a definite diagnosis of plague and, then, treatment of alternate cases with bacteriophage.<sup>11</sup>

D'Herelle returned to Alexandria in the first week of June 1926, in time for *Hajj*, the annual pilgrimage to Mecca, and the possibility of a cholera or plague epidemic.<sup>12</sup> In India, the Acting Director of the Haffkine Institute, Lt. Col. J. Morison, had become a convert to bacteriophage therapy.<sup>13</sup> His report to Major General A. Hooten, the Surgeon General with the government of Bombay, noted that the trial had been unsuccessful, apparently because the phage isolated in Indo-China

9. *Haffkine Institute Annual Report for the Year 1927* (Bombay: n.p., 1928), "Visit of Professor d'Herelle," p. 5. "Bacteriophage treatment of plague," pp. 35-37.

10. John Morison and A. C. Vardon, "A cholera and dysentery bacteriophage," *Ind. J. Med. Res.*, 1929, 17, 48-54. John Morison, *Bacteriophage in the Treatment and Prevention of Cholera* (London: H. K. Lewis and Co., 1932), pp. 12-13.

11. J. Morison, "Report on a trial of d'Herelle's antiplague bacteriophage with a note by Dr. F. d'Herelle," 23 June 1926, pp. 68-81, 1/E/7 #1425, File 7616, India Office Records, The British Museum, London.

12. D'Herelle to George H. Smith, 4 June 1926, G. H. Smith file, Yale Medical Historical Library.

13. John Morison (b. 1879), MB ChB (Hon.) 1901 (Glasgow), DPH 1914 (Cantab.), Indian Medical Service 1906-34, Acting Director Haffkine Institute, Director Pasteur Institute of Rangoon, Director King Edward VII Pasteur Institute and Medical Research Institute, Shillong, Assam.



did not work in India. Morison was nevertheless still enthusiastic: "The possibilities are so great that I would urge the Government of India to invite Dr. F. d'Herelle to return to India to study further the bacteriophage in relation to plague and also to cholera for at least six months." In this report, too, was the mention of the first isolation of cholera phages from clinical cases. One of these isolates was considered "very active." Morison concluded his letter with the description of d'Herelle as "a consummate technician, and a most inspiring worker."<sup>14</sup>

Both d'Herelle and Morison seemed to attach significance to the isolation of cholera phages directly from the patient. Previously d'Herelle had isolated such phages, but only from animal sources. Given his deeply-held beliefs about the importance of study of diseases in their natural hosts, these new findings substantiated and reinforced his general view of the role of bacteriophages in natural immunity. From this point onward, the Bacteriophage Inquiry focussed more and more on cholera and less and less on plague and, by the time it was published, it had become known as "The Cholera Study."

#### D'HERELLE GOES TO INDIA

Even in 1926, over two decades before India's formal independence from Great Britain, the governing bureaucracy was under severe strain and was developing faults and fissures. The linkages between London, British India, and the Indian populace, never very certain, were loosening daily. In 1917 Edwin S. Montagu, Secretary of State for India,<sup>15</sup> set out British policy toward India as aiming toward ". . . the increasing association of Indians in every branch of the administration and the gradual development of self-governing institutions with a view to the progressive realisation of responsible government of India as an integral part of the British Empire."<sup>16</sup>

14. Morison to Surgeon General, 21-23 June 1926, pp. 61-62, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

15. The Secretary of State for India was a Cabinet member with equivalent rank to the Foreign Secretary. The senior British official in India was the Governor-General, who reported to the Secretary of State for India on one hand, and at the same time represented the Crown as Viceroy. The Governor-General, together with a council, made up the central government of British India who governed with administrative help of the Indian Civil Service made up almost entirely of European British subjects. Provincial governments in British India were headed by Lieutenant Governors and their legislative councils. Not all of present-day India and Pakistan was in British India; the nominally independent "Native States" were ruled by Indian princes in an essentially feudal relationship to British India.

16. *Report on Indian Constitutional Reforms* (London: His Majesty's Stationery Office, 1918), Publication Cd 9109, p. 5.

The form in which this policy was realized was the Government of India Act of 1919. Under increasing pressure from Indian nationalists, both Hindu and Muslim, Britain agreed to divide the provincial government into “transferred” and “reserved” subjects. They would turn over to local, i.e., Indian, control certain administrative departments in the provincial governments. These so-called “transferred” departments included those dealing with education, public works, and public health. The “reserved” subjects included justice, police, and land-revenue functions. This partial concession was inadequate and insufficient for the nationalists of the Congress party such as Gandhi and Jinnah, but, in a spirit of pragmatic compromise, they agreed to this system of “dyarchy” as a way to get full government by Indians as soon as possible.

One consequence of this arrangement was to politicize the transferred departments. They became, willing or not, drawn into Indian political struggles as the dominant Congress party launched repeated campaigns of non-cooperation to put further pressure on their British rulers. As a result of a Congress boycott between 1920 and 1937, the transferred departments were staffed almost entirely by Indians belonging to minor communal (religious and ethnic) organizations rather than to the secular Congress party representing the majority of Indians.<sup>17</sup>

At the same time, communal tensions were on the increase, often encouraged by one group or another for political advantage. Both the secular Congress party, with Hindu and Muslim supporters, and the Muslim League seemed in basic agreement that the goal of Indian independence rested on communal cooperation. The minor communal organizations, however, were frequently involved in civil strife and communal rioting.<sup>18</sup> Provincial administration in the transferred departments, such as public health, thus became even more disconnected from the central government in British India and the policy makers at the India Office in far away London.

Against this background of political instability in provincial governments and administration, British medicine and medical research seemed oblivious to the turmoil in the streets. The Indian Medical Service (IMS) was open, de facto, only to British-trained physicians and was being limited to the needs of the British Army and the Europeans and their families in the Indian Civil Service. Morale was declining and recruitment

17. B. N. Pandey, *The Breakup of British India* (London: Macmillan, 1969), p. 123.

18. Pandey, (n. 17) *Breakup*, pp. 118–21.



into the IMS was becoming difficult.<sup>19</sup> The main source of support for medical research, the Indian Research Fund Association, also was firmly under the control of the British establishment in India.

These circumstances of communal unrest in the populace with a politicized provincial administration, together with a conservative, entrenched British medical establishment, were the limits and constraints under which the Bacteriophage Inquiry would operate.

In response to Lt. Col. Morison's enthusiasm and Major General Hooten's support in early summer, by mid-September 1926 the Government of Bombay approached the Secretary of Education, Health, and Lands of the Indian Government. By December 1926 the Indian Research Fund Association had committed funds to support the project, so the Government of India requested the India Office to contact the Secretary to the Ministry of Health (Sir Neville Chamberlain) to ask the Foreign Secretary (Sir Austen Chamberlain) to approach the Quarantine Board in Egypt to ask for a "loan of d'Herelle's services."<sup>20</sup>

The British Consul-General in Alexandria, Heathcote-Smith, finally approached the Quarantine Board. While the Board agreed to grant d'Herelle unpaid leave, there was yet another snag: the Government of Egypt still had to be approached; when they were, they raised the problem of credit for discoveries or publicity that might come out of d'Herelle's work in India. Finally, the India Office mediated an acceptable solution: simultaneous publication in India and in Egypt of the report of d'Herelle's study yet to be even started in India.<sup>21</sup> By this time the correspondence mentioned only cholera as an object of study.

By the time d'Herelle arrived in India in late February or early March 1927 the effect of nearly a decade of nationalist agitation was being felt in India. Gandhi's policy of *satyagraha* ("holding fast to the truth") translated into a policy of non-cooperation and boycott of British goods, activities, and institutions. The Indian economy was suffering from depressed agricultural prices, increased rural poverty, and accelerating urbanization. In the wake of strikes, protests, and boycotts, the British had responded with repression and retaliation. In such a social and political

19. *Report of the Indian Statutory Commission. Volume I: Survey* (London: His Majesty's Stationery Office, 1930), Publication Cmd 3568, pp. 278–79.

20. Austen Chamberlain (Foreign Secretary) and Neville Chamberlain (Secretary of Health) were half brothers.

21. F. d'Herelle, R. H. Malone and M. N. Lahiri, *Études sur le Choléra* (Alexandria: Arturo Serafini, 1929); F. d'Herelle, R. H. Malone and M. N. Lahiri, *Studies on Asiatic Cholera* (*Indian Med. Res. Memoirs. No. 14.*) (Calcutta: Thacker, Spink and Co., 1930).

climate, the success of any broadly based population study would have been problematic, yet d'Herelle seemed undaunted. He immediately embarked on two studies, one aimed at treatment of individual cases of cholera and the second aimed at study of phage and cholera in natural populations. For the former, he arranged to work at the Campbell Hospital in Calcutta. This hospital was a large public hospital which had a rather low mortality rate for cholera. D'Herelle may have thought that his chances of finding cholera phages would be higher in an environment with more recovering patients. For the field studies, he selected two regions in the Punjab where cholera was endemic.

By this time the entire project was focussed on cholera, but d'Herelle still exploited plague for its publicity value. Thus, he discussed plague at length, together with cholera, in an interview published in the *Times of India* of 21 May 1927 under the headline: "TREATMENT OF PLAGUE: Results of research work."<sup>22</sup>

D'Herelle was joined by two physicians. Major Reginald Malone was the assistant director of the Haffkine Institute and a member of the Indian Medical Service. He organized the field tests of phage in the villages of the Punjab. Dr. M. N. Lahiri was an Indian physician (and hence, essentially ineligible for the Indian Medical Service) who carried out the studies with patients in the Campbell Hospital in Calcutta. Their first work was to study both the cholera vibrio and the bacteriophages present in their patients in India. All in all, they studied 361 vibrio isolates in some detail. To understand the natural history of the disease and the possible role of bacteriophages, they examined 23 hospitalized patients in Calcutta and 10 more in Lahore. Of these 33 patients, treated with the conventional injections of fluids and salts as recommended by Rogers, 13 died (mortality rate = 40%). The Campbell Hospital group had a mortality rate ( $7/23 = 30\%$ ) which was comparable to the overall 1926 cholera mortality rate of 27% at the Campbell Hospital. Against this control group, over the same period, Lahiri treated 16 patients with d'Herelle's most active phage preparation. The usual practice was to give two ounces of a phage lysate by mouth as early as possible in the course of the disease. There were no deaths in the group of 16 treated patients [Table 1]. These hospital studies lasted until the end of June 1927.

By mid-July 1927 d'Herelle was in the Punjab with Major Malone with the plan to distribute phage ampoules in the villages for use by the

22. Press clipping from *Times of India*, 21 May 1927, p. 38, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

TABLE I  
Mortality Rates for Cholera Patients  
Treated or Untreated with Anticholera Bacteriophage

Author	Deaths/Total number of patients [%]	
	Untreated	Bacteriophage
Lahiri [ref 21]	13/33 [39]	0/16 [0]
Malone [ref 22]	78/124 [63]	6/74 [8]
Pasricha [ref 54]	All cases	114/685 [16.6]
	Vibrio +	79/443 [17.8]
	Agg + /Vib +	49/244 [20.1]

local dispensary doctors at the first sign of cholera. He was the guest of the Central Research Institute in Kasouli where he was given a laboratory and help in preparation of the necessary phage stocks for distribution in the villages. The selection of cases to be treated was poorly controlled, perhaps reflecting some aspects of Gandhian non-cooperation, but after six weeks they had collected information on 198 cases of cholera in the villages under surveillance. Of these cases, 124 had not received bacteriophage treatment and 74 cases had been given the anti-vibrio phages. The mortality rate in the untreated group was 63 percent while that in phage-treated group was 8 percent [Table I].<sup>23</sup>

By the end of August 1927 d'Herelle felt he had completed his test and had demonstrated the utility of anti-vibrio phages in both individual therapy and in epidemic control and prophylaxis, and he concluded his laboratory and field work in India. After a few days of vacation in the mountain resort town of Simla, he indulged his life-long wanderlust and visited Agra, Peshawar, and the Khyber Pass. Since he planned to remain in India to attend the 7th Congress of the Far Eastern Association of Tropical Medicine to be held in Calcutta in December 1927, he accepted an invitation to spend six weeks in Kuala Lumpur at the Pasteur Institute in that city where he collected even more isolates of cholera vibrios.

In November 1927 an account of the cholera work appeared in a brief note in the *Indian Medical Gazette*.<sup>24</sup> At the 7th Far Eastern Association of Tropical Medicine (FEATM) Congress in Calcutta in December 1927,

23. D'Herelle, Malone and Lahiri, (n. 21) *Études*, pp. 88-121.

24. Félix d'Herelle and Reginald H. Malone, "A preliminary report of work carried out by the Cholera Bacteriophage Enquiry," *Ind. Med. Gaz.*, 1927, 62, 614-16.

d'Herelle presented a brief report on his work on cholera along with a general talk on bacteriophage,<sup>25</sup> and he then returned to Alexandria about mid-January 1928.<sup>26</sup>

Results such as d'Herelle had reported for the dreaded disease cholera could not be ignored, and, indeed, there was much discussion of his work. Even while he was still working in India, he was attracting attention:

A new light has appeared on the horizon in D'Herelle who has been working in the province [the Punjab]—and whose *bacteriophage appears likely to revolutionize both the prevention and treatment of cholera*. This is apparently a really good thing and the tests he is now carrying out are *most encouraging*. It is promised that all vaccines will go by the board in a few years. I have not read much of his work at present, but [Sir Rickard] *Christophers considers that he is on to the biggest thing in bacteriology since Pasteur*.

So wrote Lt. Col. C. A. Gill, former Director of Public Health in the Punjab, to Sir Leonard Rogers, the great cholera authority, in August 1927.<sup>27</sup> In his presidential address to the FEATM Congress, T. H. Symons singled out Shiga and d'Herelle for special mention.<sup>28</sup> Meeting conjointly with the FEATM, the Expert Plague Committee of the League of Nations Health Organization called d'Herelle's work on plague an item of "particular importance" and recommended "further studies on antiplague bacteriophage and its practical application."<sup>29</sup> Five months later at the May 1928 meeting of the Permanent Committee of the Office for International Public Health of the League of Nations, it was noted that, with regard to cholera, the discussion turned mainly on J. D. Graham's report of the work of d'Herelle, Malone, and Lahiri.<sup>30</sup>

25. F. d'Herelle, "Bacteriophagy and bacteriophage," in J. Cunningham, ed., *Transactions of the 7th Congress held in British India, December 1927, Far Eastern Association of Tropical Medicine* (Calcutta: Thacker, Spink and Co., 1929), II, 278–83. F. d'Herelle, R. H. Malone, and M. N. Lahiri, "The pathology and epidemiology of infectious diseases of the intestinal tract and of cholera in particular," in Cunningham, (n. 25), II, 284–87. F. d'Herelle, R. H. Malone, and M. N. Lahiri, "The treatment and prophylaxis of infectious diseases of the intestinal tract and of cholera in particular," in Cunningham, (n. 25), II, 288–93.

26. Félix d'Herelle, *Les Pérégrinations d'un Microbiologiste* (n.p., 1947), p. 707. D'Herelle to Smith, 14 January 1927, G. H. Smith file, Yale Medical Historical Library.

27. C. A. Gill to L. Rogers, 18 August 1927, Item 58, Box C10, Leonard Rogers Correspondence, Wellcome Institute, London. In a footnote added later, Rogers commented: "I was also very hopeful that bacteriophage would prove to be valuable, but now (1949) it has proved to be a failure in cholera. LR."

28. *Far Eastern Association for Tropical Medicine. Report of the 7th Congress in British India* (Calcutta: Government of India Press, 1929), Dec. 5, 10, 24th, 1927. Part 2.

29. *Ibid.*, Part 2, p. 71.

30. *Office International d'Hygiène Publique, Comité Permanent, Procès-verbaux*, Meeting of May 1928, p. 15.

Although many Indian cities had been beset with mass demonstrations against the visit of the Simon Commission,<sup>31</sup> and nationalist fervor was increasing daily, the Government of India remained interested in continued field trials of bacteriophage. By the end of February 1928, the Secretary of State for India received a telegram from the Viceroy, Edward Wood, Lord Irwin, on behalf of the Department of Education, Health, and Lands, requesting that d'Herelle be engaged for another six months on the same terms as his previous visit.<sup>32</sup> Again the bureaucratic channels were put to work: E. J. Turner, the medical advisor at the India Office, wrote to the Under Secretary at the Foreign Office asking that the Consul-General in Alexandria (Heathcote-Smith) again be requested to approach the Quarantine Board and ask for d'Herelle's services.

By this time, however, d'Herelle had been in correspondence with Milton Winternitz, Dean at the Yale Medical School, and, anticipating an offer to join his faculty, d'Herelle declined the invitation to return to India in 1928–29. He did, however, desire to see the Bacteriophage Inquiry go forward in trusted hands. For this, he recommended that the Government of India secure the services of a Yugoslavian bacteriologist, Igor Asheshov. With d'Herelle's assurances that he would still participate in an advisory role to Asheshov, the Government of India through the India office in London offered Asheshov a three-year contract to conduct phage research in India.

#### THE BACTERIOPHAGE INQUIRY

From this point forward, the Bacteriophage Inquiry followed three lines. Starting in January 1929, Asheshov and his group worked at a newly established bacteriophage laboratory in Patna, with the responsibility for providing phage for use in the province of Bihar and Orissa, a region of high epidemic cholera. Asheshov had a contract for five years of employment as chief of this laboratory. This work was supported by the Indian Research Fund Association (IRFA) and was reviewed annually. In October 1927, after a year in Rangoon as director of the Pasteur Institute in Burma, Lt. Col. Morison moved to be the director of the King Edward

31. The Simon Commission was the seven-man Indian Statutory Committee of Parliament, led by Sir John Simon, empowered by the Government of India Act of 1919 to review, within ten years, the government functions in India and recommend changes, if needed. Since, as a committee of Parliament, it had no Indian members, it was viewed with offense by the Indian population. Mass demonstrations against the commission took place in Bombay, Delhi, Calcutta, Lucknow, Lahore, Patna, and Madras.

32. Viceroy to Secretary of State for India, 29 February 1928, p. 31, L/E/7 #1425, File 7616, India Office Records, The British Museum, London.

VII Pasteur Institute and Medical Research Institute in Shillong in Assam Province where he initiated a large-scale field trial of phage prophylaxis. His work was supported in part by the IRFA and in part from his Institute resources. Cholera phage studies at Campbell Hospital in Calcutta were continued under the direction of Captain C. L. Pasricha, Professor of Bacteriology and Pathology at the Calcutta School of Tropical Medicine.

Asheshov and his group contributed to the classification of cholera vibrios and their phages. They seemed to be interested in laboratory bacteriology and lacked d'Herelle's vision and drive to practical applications. Prior to Asheshov's arrival, at the December 1928 Conference of the IRFA, a plan for the Bacteriophage Inquiry was outlined and a Resolution was voted: "This conference of medical research workers recommends that the whole question of the epidemiology of cholera should be the subject of enquiry under the direction of a first-class expert."<sup>33</sup> The first goal would be to classify both the phages and the vibrios found in Indian cholera patients with the aim of finding phages of highest virulence. In his first progress report to the IRFA, Asheshov noted that, in addition to the diagnostic and taxonomic work, they had attempted trials of cholera prevention as well as cholera treatment. In an area where many pilgrims took up temporary lodging during a summer pilgrimage, they added anti-cholera phage to each of fifteen wells from which drinking water was drawn. This addition was repeated a week later. The incidence of cholera that summer in the region treated was 4 cases in about 10,000 pilgrims lodged there. In the entire region (untreated), the cholera incidence was about ten-fold higher with 231 cases in about 70,000 people. The trial of bacteriophage in hospitalized cases at the Puri Cholera Hospital was unsuccessful, however. They cited the usual problems of hospital staff cooperation and compliance, inaccuracies of diagnoses, and another problem that would make it harder and harder to evaluate the effectiveness of phage therapy: the mortality rate in the control population was very low, about five percent. Against this low background, dramatic results are hard to observe and statistically significant results require very large sample sizes.<sup>34</sup>

Perhaps to work in a more cooperative environment, their next clinical

33. Editorial. "The cholera bacteriophage," *Ind. Med. Gaz.*, 1930, 65, 91.

34. Igor N. Asheshov, Inna Asheshov, S. Khan, and M. N. Lahiri, "Bacteriophage Inquiry. Report on the work during the period from 1st January to 1st September 1929," in *Annual Report of the Scientific Advisory Board, Indian Research Fund Association for the Year 1928-1929* (Calcutta: n.p., 1929), p. 54.

trial was conducted in the hospital of the Patna Medical College. All patients were given alkaline intravenous fluid therapy following the method advocated by Rogers. In addition, patients were given bacteriophage preparations by mouth in small sips so as not to induce vomiting. The authors noted that they reduced the incidence of mortality “almost to nil,” even in cases where the patient was “pulseless and severely collapsed.”<sup>35</sup>

At the Annual All-India Conference of Medical Research Workers held in December 1929 and sponsored by the IRFA, the most important topic was the Bacteriophage Inquiry, according to an editorial in the *Indian Medical Gazette*. The Conference heard reports from Asheshov, Morison, Malone, and Lt. Col. J. Taylor of Rangoon. The Association voted to continue funding the three projects of Asheshov, Morison, and Malone. They noted that “Dr. Asheshov’s investigation was of fundamental importance.”<sup>36</sup>

After these reports of work carried out in 1929, Asheshov published no more work involving clinical trials or population-based studies. This direction to his research was in response to the advice of the IRFA Scientific Board: “The decision of the S.A.B., IRFA, limited the activity of this enquiry to pure basic research. In interpreting this decision the problems chosen were studied in such a way that the results obtained might directly help the practical application of bacteriophage.”<sup>37</sup> The IRFA seemed less than happy with Asheshov and, as early as 1932, started reducing his grant funds in anticipation of the end of his contract in 1934: for 1932 he received Rs. 64,260; for 1933 he received Rs. 43,550 with the explicit notation that the budget reduction was because of his activities being confined to basic research only. For 1934 he was awarded only Rs. 8,500 to suffice until his contract expired.<sup>38</sup>

In 1933 Asheshov and his group published three long articles in the *Indian Journal of Medical Research* in which they summarized their work over the previous four years. These articles appeared back-to-back and seem to represent a final report of their work. In addition to detailed description of the laboratory methods used to study cholera phages, they

35. Igor N. Asheshov, Inna Asheshov, Saranjan Khan, and M. N. Lahiri, “The treatment of cholera with bacteriophage,” *Ind. Med. Gaz.*, 1931, 66, 179–84.

36. Editorial, (n. 33).

37. Igor N. Asheshov, *Annual Report of the Scientific Advisory Board, Indian Research Fund Association for 1933–1934* (Calcutta: n.p., 1934), p. 41.

38. *Annual Reports of the Scientific Advisory Board, Indian Research Fund Association* (Calcutta: n.p.), 1931–1932, p. 107; 1932–1933, p. 122; 1933–1934, p. 94.



presented extensive studies of the classification of cholera phages based on their host range specificity for various vibrio isolates. The final part of this report described biological studies on the various properties, such as agglutinability, of the different strains they had studied. While Asheshov determined the requirements needed to make good therapeutic strains and investigated the pitfalls involved in their use, he had not addressed the issue that seemed critical to the Bacteriophage Inquiry, namely, is bacteriophage therapy useful in treatment or prevention of cholera?

The Eleventh All-India Research Worker's Conference met in December 1933 and seemed frustrated by the lack of results of the Inquiry: "The subcommittee on cholera considered experiments in connection with the use of *bacteriophage* for the prevention and treatment of cholera, and came to the conclusion that, on the evidence available, it was not possible to express any definite opinion on the subject and recommended the appointment of an *ad hoc* committee to go into the data available."<sup>39</sup> The Scientific Advisory Board of the IRFA appointed an "*ad hoc* Bacteriophage Committee" and charged it "to examine all available Indian data in regard to researches on bacteriophage carried out during the last six years and, in the light of this examination, to evaluate its use in the prevention and treatment of cholera and dysentery."<sup>40</sup> Members of this Committee included A. J. H. Russell, A. D. Stewart, and H. H. King, all members of the Indian Medical Service.<sup>41</sup>

Their report, dated 27 April 1934, was adopted by the Scientific Advisory Board in December 1934 and was also transmitted to the Comité Permanent de l'Office International d'Hygiène Publique of the League of Nations on which Russell represented British India.<sup>42</sup>

This special IRFA committee noted the deficiencies of previous work and reviewed the extensive data presented by Morison from his studies

39. "Annual Report, Eleventh All-India Research Worker's Conference, December 1933," *Ind. Med. Gaz.*, 1934, 69, 40.

40. A. J. H. Russell, A. D. Stewart, and H. H. King, "Report of the *ad hoc* Bacteriophage Committee," *Report of the Scientific Advisory Board for 1933-1934* (n. 37), Appendix III, p. 103.

41. A. J. H. Russell, CBE, Lt. Col. IMS, Director of Public Health for Madras, Chairman of the Scientific Advisory Board, I.R.F.A., and delegate from British India to the Comité Permanent de l'Office International d'Hygiène Publique of the League of Nations. A. D. Stewart, Lt. Col. IMS, Professor of Hygiene at the Calcutta School of Tropical Medicine, Director of All-India Institute of Hygiene and Public Health. H. H. King, Lt. Col. IMS.

42. Russell, Stewart and King, "Report," (n. 40), pp. 103-10. This report or its conclusions were included several times in the publications of the Office International d'Hygiène Publique: *Comité Permanent de l'Office International d'Hygiène Publique. Procès-verbaux des Séances*, Extraordinary session, April-May 1934, pp. 57-61. Ordinary session, October 1935, pp. 42-45.

in Assam<sup>43</sup> and the preliminary alternate case trial of phage treatment by Pasricha in Calcutta. The uncertainties in the field tests frustrated the committee, and they noted, "It is practically impossible to obtain reliable figures for comparable treated and untreated cases under field conditions." They then recommended continued support for the case-control study just started at the Campbell Hospital. They also observed: "There is so far practically no conclusive evidence from Assam or elsewhere on the most important question of all, namely, should epidemics of cholera be treated by bacteriophage rather than by the accepted methods of disinfection and vaccination." They concluded their report with the statement:

The necessity for the appointment of this Committee shows the need for the presence of a statistician in the Medical Research Department whose duty it would be not only to examine collected figures but, even more important, to advise all enquiries before hand as to the figures which should be collected and the methods of collection which should be adopted.<sup>44</sup>

While Asheshov's laboratory classification and bacteriophage collection would continue to be used by cholera workers, he did not continue with the Bacteriophage Inquiry. He published no more papers in India and left there in 1935.<sup>45</sup>

Morison, on the other hand, used his position as Director of the King Edward VII Pasteur Institute in Assam to organize hundreds of villages in endemic cholera regions to assess the effectiveness of anti-vibrio phage in controlling cholera outbreaks. He selected two widely separated, but rather comparable, regions in Assam for the test of phage prophylaxis. Both had histories of serious and repeated cholera outbreaks all through the 1920s. In 1928 and 1929 Morison issued phage to "Tea Garden doctors [physicians employed to care for the workers on tea plantations], Civil Surgeons and Assistant and Sub-assistant surgeons of rural dispensaries," but he got poor usage and little cooperation, perhaps reflecting

43. J. Morison, E. Milford Rice and B. K. Pal Choudhury, "Bacteriophage in the treatment and prevention of cholera. A statistical examination," *Ind. J. Med. Res.*, 1934, 21, 790-907

44. Russell, Stewart, and King, (n. 40), p. 106.

45. A short biographical summary for Igor Nicholas Asheshov is in *J. New York Botanical Garden*, 1948, 49, 173-74. After leaving India he spent two years in London as a Research Officer at the National Institute for Medical Research and collaborated with W. C. Topley at the London School of Tropical Medicine. In 1937 he went to the University of Western Ontario where he became chairman of bacteriology in 1942. In 1948 he was recruited to the New York Botanical Garden to work in a newly-established laboratory on antiviral antibiotics using bacteriophage as a model. This work was funded by a five-year grant from the National Foundation for Infantile Paralysis. At the end of this period, he moved to the Lister Institute in London, from which he retired in 1959.

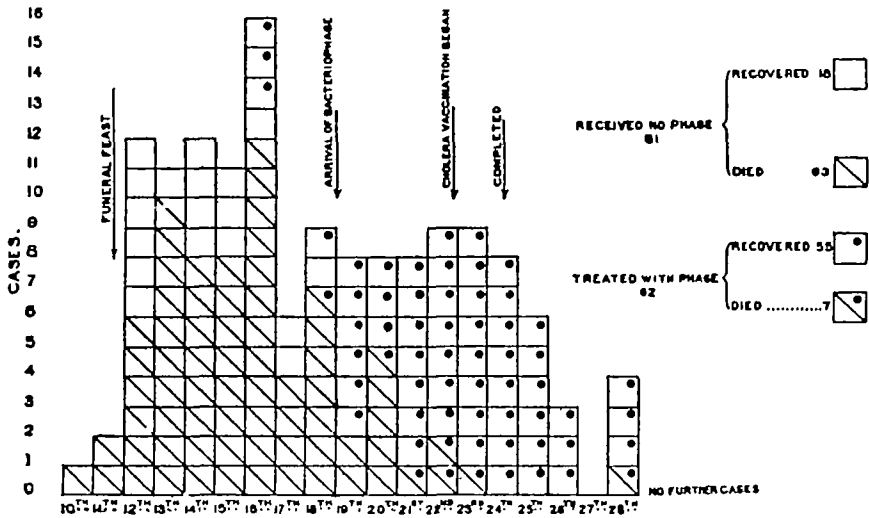


Figure 2. Daily case incidence and mortality during an epidemic of cholera in Jakrem village in Assam. Cases treated with anticholera bacteriophage are indicated. Reprinted with permission of the publisher from J. Morison, (n. 10) *Bacteriophage in the Treatment and Prevention of Cholera*, p. 26.

the general attitudes fostered toward centralized authority by the past *satyagraha* campaigns. His next approach was to bypass the trained medical personnel and make the phage available directly to the village leaders, the headmen. The project worked as planned in the Naogaon region, but the District Official in the Habiganj region objected for unknown reasons and so this region became the control group in Morison's study.

In December 1929 phage was issued along with instructions for its use to every village headman along ninety miles of the Kalang river. In the first six months sixty-three scattered cases of suspected cholera were treated this way. No epidemics occurred in 1930–35, the duration of the study.<sup>46</sup> In contrast, in the Habiganj region, in both 1930 and 1931 there were spring and fall epidemics of cholera. In the first half of 1932 there were 474 deaths at which time the Government ordered the use of bacteriophage in the district. For the next three years the two districts had similar low death rates from cholera, that is, about ten per year. In the

46. Morison, (n. 10) *Bacteriophage*, p. 28; d'Herelle, (n. 26) *Les Pérégrinations*, p. 652. See also: J. Morison, "Bacteriophage in Cholera," *Transactions of the Royal Soc. Trop. Med. and Hyg.*, 1935, 28, 563–70.

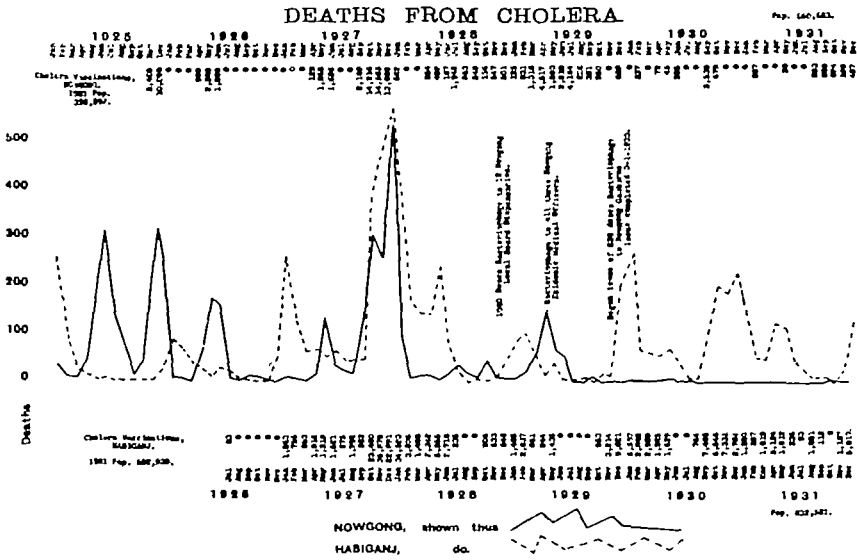


Figure 3. Monthly mortality from cholera in two districts in Assam between 1925 and 1932. In Nowgong district anticholera bacteriophage was widely distributed while in Habiganj it was not generally available. Reprinted with permission of the publisher from J. Morison, (n. 10) *Bacteriophage in the Treatment and Prevention of Cholera*, p. 28.

nearby district of Sunanganj, for example, where no phages were used, the cholera mortality in 1933 was 1505 people dead.

Figure 2 shows the mortality data for one village for patients given bacteriophage and those who did not receive it. Figure 3 shows the cholera mortality in the two districts for the period during which phage was available in only one of the two areas.

The Annual Reports from the King Edward VII Memorial Pasteur Institute and Medical Research Institute give some indication as to the extent of Morison's bacteriophage trials. For the year 1928, over 36,000 doses of cholera phage were produced.<sup>47</sup> In 1929 they made 130,823 doses of cholera phage; for 1931 they indicated they purchased the phage from the Laboratoire du Bactériophage in Paris, and for 1934 they distributed 871,316 doses, presumably made in Shillong.<sup>48</sup>

47. John Morison, "Twelfth Annual Report for 1928. King Edward VII Pasteur Institute and Medical Research Institute, Shillong," *Ind. Med. Gaz.*, 1930, 60, 472-74.

48. *Annual Reports of the King Edward VII Memorial Pasteur Institute and Medical Research Institute, Shillong, Assam for the Years 1928, 1929, 1930, 1934* (Shillong: n.p., 1929-35).

While Morison seemed to have had more success in his field trials than Asheshov, perhaps because Assam province is somewhat culturally and ethnically distinct from the rest of India and hence less nationalistic in its fervor to go along with Gandhi's second *satyagraha* of 1930–31, nevertheless Morison was still troubled by the lack of cooperation from the recipients of this material:

In spite of the wide and extending use of bacteriophage in Assam, few medical officers return the case sheets enclosed in every box [of bacteriophage]. It is not realized that though in Assam the bacteriophage has established itself through experiences not often possible in other places, others without such facilities await controlled figures capable of statistical examination. . . . On the other hand, numerous appreciative letters come to the Institute of which no statistical use can be made.<sup>49</sup>

Later he conceded:

Phage is not a remedy in a city like Calcutta, nor is it a remedy where the source of infection can be traced and dealt with. It may have little interest for us as we push on with sanitary reforms. Indeed, very distinguished Directors of Public Health have done all they could to prevent its use in their provinces. But the widespread epidemic of cholera in various provinces of India compared with its control, where this has been attempted with phage in Assam, shows it is a weapon we cannot yet afford to discard.<sup>50</sup>

Although in 1934 Morison reached retirement age and returned to Great Britain, and a new director, L. A. P. Anderson, was brought in from the Haffkine Institute, the Annual Report for 1935 from the King Edward VII Institute indicated the Bacteriophage Inquiry was still in progress. Indeed, the annual grants from the IRFA continued to increase from Rs. 9,800 for 1932 to Rs. 14,500 (1933), Rs. 14,958 (1934), Rs. 17,870 (1935), and Rs. 18,130 (1936). Finally, the Bacteriophage Inquiry was being phased out and for 1937 the grant for Assam was reduced to Rs. 6,084.<sup>51</sup>

Bacteriophage was employed as an agent against cholera in three ways: *treatment* of active cases; *prophylaxis* during epidemics; *prevention* in potentially epidemic areas. The initial studies of treating active cases by d'Herelle, Malone, and Lahiri suggested that phages were useful and effective when compared against no treatment or rather ineffective conventional

49. John Morison, "Annual Report for the year 1931. King Edward VII Memorial Pasteur Institute and Medical Research Institute," *Ind. Med. Gaz.*, 1932, 67, 53–54.

50. Morison, (n. 46), p. 569.

51. *Annual Reports of the Scientific Advisory Board for 1931–1936* (n. 38).

treatment. The Bacteriophage Inquiry itself was directed at the larger and more difficult problem of the utility of phage in prophylaxis and prevention. In these studies, the comparisons were more difficult. The “control” groups were difficult to define, and probably most importantly, the results obtained with phage were to be compared with other approaches toward cholera control, that is, vaccination and sanitary reforms.

Vaccination in India had a long history, and the popularity and acceptance of Haffkine’s antiplague vaccine prepared the populace for the introduction of an anticholera vaccine for prevention of cholera in potentially epidemic areas.<sup>52</sup>

The general value of sanitary reforms for public health, so successful in Western countries, was more problematic in India,<sup>53</sup> but, for some public health authorities in India, any new approach to cholera prevention that reduced the apparent critical need for better water and sewer systems seemed threatening.

At least four factors can be noted that likely contributed to the ending of the field studies of the Bacteriophage Inquiry: increasing political unrest in India and the attendant difficulties in provincial administration made large-scale field studies increasingly problematic; economic conditions seemed to constrain the budget of the IRFA; sanitary reforms in the major cities promised not only to reduce cholera but other diseases as well; the field trials were disappointing and the statistical results uncertain because of flaws in the design of the studies.

With regard to treatment of cholera patients with bacteriophages, C. L. Pasricha and his colleagues at the Campbell Hospital in Calcutta noted the deficiencies in the past clinical tests of cholera phages in the treatment of hospitalized cholera patients. These deficiencies included the use of historical controls and the lack of randomization of the cases to be treated. They undertook a more controlled test of cholera phage therapy in the hospital.

Two wards were set apart in the Campbell Hospital for cholera cases, and the admission of cases was alternately into the two wards. The treatment in the two wards was identical except that in one bacteriophage was used in addition to the usual treatment of cholera. Bacteriophage used was constantly “refreshed” by passage with vibrios isolated during the different phases of the epidemic and

52. Radhika Ramasubban. “Imperial health in British India 1857–1900,” in Roy McLeod and Milton Lewis, eds., *Disease, Medicine and Empire: Perspectives on Western Medicine and the Experience of European Expansion* (London: Routledge, 1988), p. 55.

53. *Ibid.*

was given mainly by the mouth. In 50 cases cholera phage was given intravenously and gave us satisfactory results.<sup>54</sup>

Pasricha's studies of the clinical use of phage and his laboratory investigation of the vibrio itself continued to be supported as part of the Bacteriophage Inquiry by the IRFA.

In his study of epidemic cholera for the years 1933–35 they admitted a total of 1,369 cases; 684 were treated with cholera phages and 685 were not treated with cholera phage. All together, the mortality rate was 13.5 percent for the phage-treated group and 16.6 percent for the control group [Table 1]. Pasricha noted that the control group was not "untreated," otherwise the mortality rate might well have been significantly higher. Thus, the comparison was phage along with conventional treatment tested against conventional treatment alone. At this time conventional treatments, which were not specified in Pasricha's paper because "the usual hospital treatment is so well known that it is not necessary to give details here," consisted of oral calomel, potassium permanganate, and essential oils, as well as injections of salt, water, and bicarbonate. Thus, the two wards were treated the same, with the addition that patients in the phage ward received two ml. doses of phage every four hours.

The results of overall mortality were not considered very significant. However, two other results of this study were emphasized both by Pasricha and others. First, when the results were confined only to patients with a bacteriologic diagnosis of cholera, that is, patients from whom vibrios had been isolated, 841 in all, the addition of phage treatment offered significant improvement: 8.3 percent mortality *versus* 17.8 percent mortality [Table 1]. For the patients who were infected with "agglutinable," that is, the "standard" cholera vibrios, the survival with phage treatment was a little better, 6.8 percent *versus* 20 percent [Table 1]. The very low mortality rates (3–8 percent) among patients from whom no vibrios could be isolated suggested that this group of patients were already on their way to recovery regardless of treatment, or else they had some other, less virulent, illness; the very high mortality rates (60–75 percent) among patients for whom no samples were examined suggested that patients in this group were too moribund for treatment. Thus, exclusion of these two groups of patients from the analysis of phage treatment seemed justified to these authors.

54. C. L. Pasricha, A. J. H. de Monte and E. G. O'Flynn, "Bacteriophage in the treatment of cholera," *Ind. Med. Gaz.*, 1936, 71, 61–68.



The second conclusion of this careful study was that phage offered significant reduction in morbidity, that is, the course of the illness was less severe among those patients who did survive.

We have analyzed various other clinical data. We find that there is an appreciable difference in the phage-treated and control series of cases. The patients are less toxic, there is less dehydration and fewer "salines" are required in the phage series than in the control series. Cases receiving phage are discharged sooner from the hospital, they secrete vibrios for a smaller number of days and in general run a clinically milder course. There is less tendency to develop pneumonia but these and other clinical conditions are not suitable for statistical analysis. The general impression of experienced workers in clinical charge of cases is that uraemia and other deadly complications are often averted, or, if they supervene, are milder in the phage-treated series.<sup>55</sup>

Pasricha and his colleagues found that the incidence of uremia was 11 percent for the phage group and 23 percent for the control group.

This study from Campbell Hospital, along with the epidemiological statistics from Assam, formed the basis for the 1936 report of the Cholera Advisory Committee of the IRFA. Item II in their report was entitled: "To consider the present position in regards to the bacteriophage treatment and prophylaxis of cholera in light of recent report." With regard to the Bacteriophage Inquiry, this committee noted that the "Cholera Clinical Enquiry" at Campbell Hospital was "brought to a close in June 1936" with the conclusion that, for patients with bacteriologically confirmed cholera, phage therapy appeared to reduce mortality by about two and one-half fold. This committee stated: "It is recommended that this enquiry be now discontinued, a sufficiently extended series of cases of cholera having been treated with bacteriophage under controlled hospital conditions to provide information as to the value of the method."<sup>56</sup> They reproduced in their report a note from Col. L.A.P. Anderson, the Director of the King Edward VII Pasteur Institute in Assam, about the state of the field studies of phage in Assam.

During the past year in which there was relatively little cholera in Assam, the results of bacteriophage control, taken as a whole, have not been sufficiently striking to permit us to modify the rather noncommittal attitude we adopted at this time last year.

[ . . . ]

55. *Ibid.*, p. 67.

56. *Annual Report of the Scientific Advisory Board for 1936* (n. 38), p. 128.

One factor has seriously militated against the success of this experiment and is probably mainly responsible for the absence of conclusive results one way or the other. This is the failure to confine the use of bacteriophage strictly, to the experimental areas. Although inoculation and other special measures were entirely stopped from the outset in the experimental areas, the use of bacteriophage was unfortunately permitted elsewhere when cholera was prevalent and this measure has become so popular in recent years that a very considerable quantity is used in every district in Assam during the cholera season. This can only be described as disastrous from the point of view of the experiment.

The original intention to make the rest of Assam as control for the bacteriophage-controlled areas was not carried through. Had the use of bacteriophage been strictly confined to the experimental area, we should, I believe, by now have reached a conclusive result. As it is, it appears unlikely that we shall ever do so by an experiment on these lines in Assam. It is now too late to withdraw bacteriophage from the other districts.<sup>57</sup>

The Committee on Cholera noted with some regret that they regarded it as "most unfortunate that this trial was not carried out as a strictly controlled experiment and that the issue of bacteriophage was not confined to the experimental areas only." Further, they concluded that "the balance of available evidence taken as a whole indicates that the widespread use of bacteriophage for the control of cholera and its treatment under village conditions has a certain value the precise degree of which they are not in a position to assess." At that point the IRFA stopped support for field bacteriophage work in Assam. They did, however, provide a reduced budget for continued work on cholera in Assam aimed at laboratory characterization of vibrio strains from various sources.<sup>58</sup>

With the departure of the phage partisans, d'Herelle, Asheshov, and Morison, the rising nationalism in the struggle for Indian independence, and the beginnings of World War II, the conditions for renewal and reinvigoration of the Bacteriophage Inquiry diminished in India after 1935. The original dramatic claims gave way to more muted hopes. At the same time, as Morison noted, advocates of broad public health measures such as improved sanitation and vaccination programs possibly saw phage prophylaxis as undercutting their goals. Still, the massive focus on the phages of cholera called attention to several problems that were later to provide important new insights. First was the question of phage-bacterium specificity. The detailed study of various cholera isolates in

57. *Ibid.*, pp. 126–27.

58. *Ibid.*, pp. 127–29.

terms of their ability to act as hosts for given strains of cholera phages was originally seen by Asheshov and Pasricha as important in the development of more effective and virulent phages for therapy. This information, however, turned out to be used later in almost a reciprocal way, as a method of wide utility for the identification and “typing” of bacteria. The second new impetus was the role of phage in altering bacterial phenotypes upon entering into a symbiotic relationship, later identified as the lysogenic state. This phenomenon appeared to be like mutagenesis and was of interest to the early cholera phage workers such as d’Herelle and Pasricha because they were seeking explanations of the variation in clinical behavior of cholera strains and non-pathogenic vibrios, the problem of reactivation of carriers, and the origin of the famous hemolytic cholera variant called the El Tor vibrio. The acquisition of new properties following phage infection and lysogenization subsequently provided explanations for conversion of some benign bacteria into toxin-producing strains as well as for the expression of new surface antigens.

D’Herelle’s work during his five years at Yale focused on the role of bacteriophages in generation of bacterial diversity and mutations. This work was a direct outgrowth of his experience with cholera: he was puzzled by the variability of the cholera vibrio with respect to pathogenicity as well as agglutinability by specific sera. His first love, however, seemed to be field work, and in 1934 he left Yale for a position in Tbilisi with the expressed desire to be able to do more applied work on infectious diseases such as cholera. Although his tenure in the USSR ended with the Stalin purges in 1936, his interest in cholera persisted. His final published book, “Cholera, Disease of Paradoxes,” was devoted to the subject and was published in 1946.<sup>59</sup>

From this brief account of the Bacteriophage Inquiry, I would like to emphasize three themes: first is the formal and procedural structures that seemed to exist for even the simplest interactions, such as requesting a phage sample, within the British colonial bureaucracy. The activities of the India Office, considered as a domestic service and under the Secretary of State for India, were so organizationally distinct from the Foreign Office that even simple matters had to be “passed up and down the ladder” for transfer from one bureaucracy to the other at a fairly high, often ministerial, level. Even the expert medical and public health advisors on the international boards were compartmentalized. A generation

59. Félix d’Herelle, *L’étude d’une maladie: le choléra, maladie à paradoxes* (Lausanne: Rouge, 1946).

earlier the “machine” of the Indian Civil Service was described in terms still applicable:

In Calcutta and Simla, the machine achieved the ultimate in complexity and self-perpetuation, for there each member of the [Legislative] Council was backed by his own secretary and department within which the clerks had clerks. As George [Lord] Curzon [Viceroy, 1899–1905] so aptly put it, “Round and round like the diurnal revolutions of the earth” went file after file in the bureaucratic daily dance, “stately, solemn, sure and slow.”<sup>60</sup>

The second theme is that determined and inspired scientists were able to bring recent laboratory-based ideas and materials to clinical and public health application rapidly and effectively. The relatively low level of regulatory activity certainly facilitated these applications in places such as Suez and India. While the Bacteriophage Inquiry was in progress, India was in the midst of full-scale nationalistic struggle for independence from Britain, yet these major political and social upheavals seem to have had little outward impact on the course of the Inquiry as seen in the published record or in the diplomatic correspondence related to this project. Only by inference, might we conclude that these events were to shape the final nature of the Inquiry.

The third theme, and perhaps most interesting, which may be illuminated by study of the Bacteriophage Inquiry is the question of the ways in which new therapies are tested, evaluated, and accepted or rejected as useful. In spite of what seems to be convincing results, endorsed by august committees, there were many sceptics of bacteriophage therapy. The competition between the “treatment” approach and the “public health” approach appeared to play a role in this assessment. The medical literature is full of reports, pro and con, as to the “real” efficacy of bacteriophage therapy. The advocates often advanced very plausible explanations for the failures; d’Herelle, himself, repeatedly emphasized the need to use a very active phage preparation specific for the particular strain being treated. Commercial polyvalent phage preparations often were found to be inactive because of the presence of preservatives such as merthiolate. Pre-war reviews of phage therapy usually concluded that the value of phage therapy in experimental conditions seemed demonstrated, but that the clinical and public health uses were still speculative. Common wisdom today is that phage therapy is not used because it

60. Stanley Wolpert, *A New History of India*, 3rd ed. (New York: Oxford University Press, 1989), p. 265.

“doesn’t work.” The origin of that wisdom is still unclear. While antibiotic therapy, vaccines, and other types of specific treatment have made the notion of bacteriophage therapy seem outmoded, as late as 1971 large-scale international trials of anti-cholera phages were being reported in the literature.<sup>61</sup> Why is it so hard to decide? While this case study suggests some answers, such as technical errors, uncertainties associated with field trials on actual populations, and lack of consensus over what is a good outcome, additional studies along these lines will certainly be needed to make clear additional complexities involved in this important question.

61. L. M. Marcuk, V. N. Nikiforov, Ja. F. Scerbak, T. A. Levitov, R. I. Kotjarova, M. S. Naumsina, S. U. Davydov, K. A. Monsur, M. A. Rahman, M. A. Latif, R. S. Northrup, R. A. Cash, I. Huq, C. R. Dey, and R. A. Phillips, “Clinical studies of the use of bacteriophage in the treatment of cholera,” *Bull. World Health Org.*, 1971, 45, 77–83.