Medical History, 1990, **34**: 144–163.

YELLOW FEVER IN RIO DE JANEIRO AND THE PASTEUR INSTITUTE MISSION (1901–1905): THE TRANSFER OF SCIENCE TO THE PERIPHERY

by

ILANA LÖWY *

Science, a purely European enterprise, began to be exported to peripheral countries in the nineteenth century. The rapid expansion of bacteriology is a striking example of this. But at the same time, the transformation of bacteriology into a well-established and codified scientific discipline hampered the diffusion of bacteriological knowledge, because the laboratory practice that developed in peripheral countries in the first wave of enthusiasm for the "miracle-making" science often failed to conform to the discipline's new, more stringent professional standards. The problem was of particular importance in bacteriology, in whose birth the techniques which allowed appropriate visualization, isolation, and characterization of micro-organisms played a crucial role. Indeed, debates on technical aspects of bacteriological investigation were at the heart of early controversies in this field.

The story of the search for the agent of yellow fever in Rio de Janeiro illustrates this evolution of bacteriology. In the 1880s and 90s numerous enthusiastic Latin American adepts of the new science started to look for the aetiological agents of tropical diseases. In Brazil, a favourite target of bacteriological studies was yellow fever. However, the efforts of many bacteriologists notwithstanding, both the epidemiology of the disease and the nature of its aetiological agent remained for long mysterious. There were a dozen or so triumphant announcements of the isolation of the "yellow fever germ" in the 1880s and 90s. Many of them came from physicians working in Rio de Janeiro, a city which suffered from regular outbreaks. But although some of those early announcements were at first received with interest by bacteriologists in Europe, they were ultimately rejected because they no longer conformed to the new, rapidly changing standards of bacteriological investigation. Investigators who had no direct contact with the few centres in which these international standards were elaborated had, even in Europe, difficulty in achieving the proper (i.e., recognized) technical level. The achievement of such standards in a peripheral country was even more difficult.

The mystery of yellow fever was finally solved by the American military delegation to Cuba, led by Major Walter Reed. The Reed Mission (1900–1) got the credit for the discovery, based on the epidemiological observations of a Cuban physician, Carlos

*Ilana Löwy, Ph.D., Unit 158 INSERM, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75015 Paris, France.

A short version of this paper was presented at the HSS/BSSS meeting, Manchester, 14 July 1988.

Finlay, that yellow fever is transmitted by the *Stegomyia* mosquito, and for the observation that the aetiological agent of this disease is a filterable virus. The conclusions of the Reed Mission were confirmed by, among others, the members of the Pasteur Institute Mission working in Rio de Janeiro from 1901 to 1905. This article will deal with the story of the French mission, the opposition it met in Rio de Janeiro, and its possible impact on the evolution of tropical medicine in Brazil. My thesis is that the investigations of the Pasteur Mission helped to establish a high degree of professionalism in bacteriology and in tropical medicine in Rio de Janeiro. The temporary transfer of a "model" European laboratory to a developing country may be related to the fact, unusual in a peripheral country, that a Brazilian scientific institution, the Instituto Sôrothérapico de Manguinhos (later, Instituto Oswaldo Cruz), was able to attain an international reputation as an important centre of research in tropical medicine between 1910 and 1930.

BACTERIOLOGY, TROPICAL MEDICINE, AND YELLOW FEVER

The late 1870s and the 1880s were years of triumph for the "microbe hunters". In a short period bacteriologists successfully isolated and cultivated a great number of pathogenic bacteria: bacilli that induced typhus (1879), leprosy (1880), pneumonia (1882), tuberculosis (1882), cholera (1883), diphtheria (1883–84), tetanus (1884), Malta fever (1886), and meningitis (1887). The isolation of aetiological agents of infectious diseases was followed by attempts to prepare protective vaccines and specific therapeutic antisera.

These discoveries and their practical consequences stimulated interest in the new science of bacteriology. Bacteriological and immunological knowledge became synonymous with medical progress. It also became the object of vigorous interpersonal and international competition. The rapid elaboration and codification of professional standards in bacteriology was stimulated not only by the obvious need to facilitate communication between specialists from different countries and to compare the results of different laboratories, but also by the existence of numerous controversies concerning the priority of bacteriological discoveries.[1] The new professional standards were rapidly propagated by various means: a dense network of personal contacts among the investigators, publications in specialized journals (e.g., the *Zeitschrift für Bacteriologie und Immunologie*, the *Annales de l'Institut Pasteur*), international meetings such as the International Congresses of Medicine and of Hygiene, and specialized teaching (e.g., the 'Cours de Microbie Téchnique' of the Pasteur Institute, founded by Emile Roux in 1889). The latter was particularly important, because the acquisition of bacteriological knowledge depended largely on the ability to master specific techniques, and because tacit knowledge played an important part in the transmission of these techniques. A prolonged training in the few leading European centres, and later training with bacteriologists that had studied in these centres, were viewed as crucial steps in the proper transmission of bacteriological knowledge.

[1] W. Bulloch, *The history of bacteriology*, London, Oxford University Press, 1938; H. A. Lechevalier and M. Solotorowski, *Three centuries of bacteriology*, New York, San Francisco, and Toronto, McGraw Hill, 1965; P. Collard, *The development of microbiology*, Cambridge University Press, 1976; G. L'E. Turner,

Competition for priority in bacteriological discoveries rapidly moved from Europe to the developing countries. Those countries offered particularly favourable conditions for "microbe hunting": on the one hand a high incidence of epidemic and endemic infectious diseases, and on the other, the active co-operation of local administrations. Tropical diseases, which often attacked newcomers preferentially, made the settlement of white colonies difficult, while epidemics which ravaged the native population disorganized work in the colonies. Tropical diseases were thus viewed as one of the principal obstacles to colonization. The collaboration of the colonial administrations in large-scale trials of new vaccines and sera often transformed developing countries into large laboratories in which the new advances of bacteriology were tested. At first well-known bacteriologists often either travelled themselves to the tropics or sent their collaborators there.[2] Later, institutes of tropical medicine were created in several European cities (London, 1899; Liverpool, 1899; Hamburg, 1900; Brussels, 1906).[3] The French chose a different strategy: they decentralized their research in tropical medicine and opened in their colonies "Instituts Pasteur d'outre-mer". These "Overseas Pasteur Institutes" were directed by French scientists in close collaboration with the Pasteur Institute in Paris.[4]

Although much of the French, English, and German research on tropical diseases developed in the colonies, studies on this subject were also made in independent countries, mainly in Latin America. In the late nineteenth century there was a rapid development of bacteriology and of tropical medicine in Latin American countries. This development was rendered possible by the importation of European scientists, who were offered the directorships of Latin American bacteriological laboratories; the training of local scientists in international scientific centres;[5] and by the appearance of self-taught or semi-autodidact bacteriologists: some Latin American physicians, e.g. the Cuban Carlos Finlay and the Brazilians Domingos Freire and João Batista de Lacerda, fascinated by the new science, attempted to learn bacteriology by themselves, mostly through the reading of books and of professional journals.

Essays on the history of microscope, Oxford, Science Publishing, 1980; W. D. Foster, *History of medical bacteriology and immunology*, London, William Heinemann Medical Books, 1979.

[2] H. Mollaret, *Alexandre Yersin, le vainqueur de la peste*, Paris, Fayard, 1985; Foster, op. cit., note 1 above.

[3] During the first period of development of bacteriology many European bacteriologists too were self-taught. See, e.g., G. H. Bornside, 'Jaime Ferran and preventive inoculation against cholera', *Bull. Hist. Med.*, 1981, **55**: 516–32. On the importance of personal contacts in the diffusion of scientific innovations, see Steven Shapin and Simon Schaffer, *Leviathan and the air pump: Hobbes, Boyle and the experimental life*, Princeton University Press, 1985, pp. 227–30.

[4] A. Calmette, 'Les missions scientifiques de l'Institut Pasteur et l'expression coloniale de la France', *Rev. scient.*, 1912, **89**: 129; *idem*, 'Pasteur et les Instituts Pasteur', *Rev. Hyg.*, 1923, **45**: 385; Pasteur Valery-Radot, 'Les Instituts Pasteur d'outre-mer', *Presse méd.*, 1939, **21**: 410–13; M. Worboys, 'The emergence of tropical medicine: a study of establishment of a scientific speciality', in G. Lemaine et al. (eds.), *Perspectives on the emergence of scientific disciplines*, The Hague and Paris, Mouton, 1976, pp. 75–98. The English too founded institutes in the colonies, such as the Kuala Lumpur Institute of Medical Research and the Bombay Bacteriological Institute.

[5] As early as 1886, the year after Pasteur had described his successful anti-rabies vaccination, Pedro II, the Emperor of Brazil, sent a young Brazilian physician, Augusto Ferreira dos Santos, to Paris "to study the methods of inoculation elaborated by Pasteur", and, later, to open an institute for the treatment of rabies in Rio de Janeiro. G. Raeders, *Pedro II e os sábios franceses*, Rio de Janeiro, Atlântica Editôra, 1944.

The bacteriologists working in Latin America often chose to study yellow fever. Other infectious diseases, such as tuberculosis, pneumonia, and childhood diseases, had more victims. However, these diseases were endemic, and were often perceived as part of "normal" life conditions. In contrast, yellow fever was a mysterious, epidemic disease with very deadly outbreaks. Its dramatic course ("black fomites", convulsions, and rapid death) struck the popular imagination. In addition, this disease specifically attacked the new immigrants, usually in the first year following their arrival. For this reason yellow fever became the symbol of the "scourge of the tropics".

THE "BACILLUS OF THE YELLOW FEVER" IN RIO, 1880–1900

We know today that yellow fever is a viral disease. But the nineteenth-century investigators who looked for its aetiological agent thought that this was a micro-organism that could be isolated and cultivated on a solid medium. At first, fungi which multiply in a warm and humid atmosphere were considered as the most probable candidates for this role. Later, the practical triumphs of bacteriology directed the attention of the scientists to pathogenic bacteria.

Rio de Janeiro was an ideal place for the hunt for "yellow fever germs". Yellow fever was endemic there, with regular epidemic outbreaks. The city also had a medical faculty, an impressive number of practising physicians, and several hospitals which treated yellow fever cases. It is not surprising that one of the first announcements of a discovery of the "yellow fever germ" came from a Rio de Janeiro scientist. In 1883 João Batista de Lacerda, an anthropologist and physiologist from the National Museum in Rio de Janeiro, declared that he had discovered the cause of the "yellow poisoning"—a "polymorphic fungus" that could be found in the intestines and the secretions of yellow fever patients, and which secreted a "zymotic toxin" that accumulated in the liver.[6]

Lacerda's ideas had only a limited audience outside Brazil. His colleague Domingos Freire was luckier. Freire, who was the president of the Federal Health Council of Rio de Janeiro, described in 1885 a "bacillus of the yellow fever", present in the blood, internal organs, and in the secretions of yellow fever patients. Freire named his newly discovered "bacillus" *Cryptococcus xantogenicus*, and concluded that this bacillus multiplies through the formation of spores growing within the bacterial cell. He explained that this micro-organism produced toxins ("black ptomaines") that were responsible for black vomiting, and a yellow pigment responsible for jaundice.[7] Freire, who viewed himself as Pasteur's follower, attempted in his studies to employ the most recent discoveries in bacteriology. He based his claim that the *Cryptococcus* is the aetiological agent of yellow fever on the observation that this bacillus could induce typical symptoms of yellow fever in rabbits and guinea pigs, in accord with the newly-published "Koch's postulates" on the nature of aetiological proof in infectious diseases.[8] Faithful to Pasteur's teachings,

[6] J. B. Lacerda, *Gazetta de Noticias* de Rio de Janeiro, 1883; *idem*, *Gazette des Hôpitaux*, 1883, p. 831; *João Batista de Lacerda: comemoração do centenário de nascimento 1846–1946*, Rio de Janeiro, Museu Nacional, Publicações Avulsas 6, 1951.

[7] D. Freire, *La doctrine microbienne de la fièvre jaune*, Rio de Janeiro, Imprensa Nacional, 1885.

[8] Koch stated that a micro-organism could be recognized as an aetiological agent of a given disease, only if this micro-organism, isolated from confirmed cases of the disease, could induce a similar disease in an experimental animal. R. Koch, 'Die Aetiologie der Tuberkulose', *Mitt. k. Gesundheitsamte*, 1884, **2**: 1–88. On Koch's postulates and the difficulties in their application see, e.g., C. Codell Carter, 'Koch's postulates

Freire also attempted to attenuate experimentally the virulence of the *Cryptococcus*, and affirmed that he had been successful in producing a weakened strain of his bacillus which could be used for vaccination. Freire made large-scale vaccination attempts (he stated that in 1884 and 1885 he vaccinated more than 3,000 persons per year) and claimed that a statistical analysis of the results of these attempts clearly demonstrated the protective value of his vaccine.[9]

Freire's observations were rapidly confirmed by another Latin American bacteriologist, Manuel Carmona y Valle, from the Medical School of the University of Mexico. In his first publications Carmona y Valle explained that the aetiological agent of yellow fever was a fungus of the Oöspore family, but later he accepted Freire's conclusions, affirming that the agent he had isolated was identical with Freire's *Cryptococcus xantogenicus*.[10] Freire's work was, however, severely criticized by other investigators. The British bacteriologists Sutton and Harrison stated that the so-called "yellow fever" that Freire induced in rabbits and guinea-pigs, was in fact a non-specific toxic reaction to the injection of a great number of bacteria. Freire's conclusions were also refuted by the French bacteriologist Félix Le Dantec, from the Pasteur Institute in Paris. Le Dantec, who studied yellow fever on the island of Cayenne in 1884–5, claimed that no micro-organism could be isolated from the blood of yellow fever patients. He strongly criticized Freire's bacteriological techniques, in particular his methods of isolation and cultivation of the "yellow fever germ".[11]

North Americans had a particular interest in yellow fever studies, because this disease was present in the southern United States. The US government named a special commission, headed by the bacteriologist George Sternberg, to investigate the discoveries of Freire and of Carmona y Valle. The commission was very severe on both Latin American bacteriologists. Sternberg reported that both Freire and Carmona y Valle had made technical errors at all stages of their investigations. Concentrating his attack on Freire, Sternberg stressed (as Le Dantec had), that Freire's bacteriological techniques were highly inadequate and his sterility measures almost nonexistent. He added that Freire had drawn many mistaken conclusions: e.g., crediting the *Cryptococcus* with such bizarre properties as the capacity to survive purification in ether suspension, and attributing the black colour of the patients' vomit to the "black ptomaines" supposedly secreted by the *Cryptococcus* (almost all pathologists agreed that the black colour of the "fomites" was due to their

---

in relation to the work of Jacob Henle and Edwin Klebs', *Med. Hist.*, 1985, **29**: 353–74; and W. Coleman, 'Koch's comma bacillus: the first year', *Bull. Hist. Med.*, 1987, **61**: 315–42.

[9] Freire, op. cit., note 7 above. Freire's was probably among the earlier attempts at using a laboratory-made vaccine in man. Another, strongly criticized later, was Ferran's anti-cholera vaccination campaign in Spain (1885). See, e.g., J. Ferran, 'A propos de la communication de M. Haffkine de 9 juillet', *C.r. Soc. Biol.*, 1892, **4**: 771–3; P. Bruardel, M. Charrin, and L. Albarran, 'Rapport sur les essais de vaccination cholérique entrepris en Espagne par M. le Docteur Ferran', *Annls Hyg. publ. Méd. leg.*, August 1885, vol. 14.

[10] M. Carmona y Valle, *Leçons sur l'étiologie et la prophylaxie de la fièvre jaune*, Mexico D.F., Imprimerie du Ministère des Travaux publics, 1885.

[11] J. H. Sutton and J. B. Harrison, 'The micro-organism of yellow fever', *Lancet*, 1885, **i**: 405–6; J. B. Béranger-Féraud, *Traité théorique et clinique de la fièvre jaune*, Paris, Octave Doin, 1890, pp. 704–48.

haemorragic nature). Finally, Sternberg examined the proofs of the efficacy of Freire's vaccine, and found that they had no statistical significance whatsoever.[12]

After the publication of Le Dantec's and Sternberg's criticisms, *Cryptococcus xantogenicus* disappeared from professional literature. But new pretenders to the title of "yellow fever germ" soon occupied its place. In 1897 the *Annales de l'Institut Pasteur* simultaneously published two articles announcing the isolation of the aetiological agent of yellow fever, one by Wolff Havelburg from Rio de Janeiro, and the other by Giuseppe Sanarelli, an Italian bacteriologist who was then the director of the Institute of Experimental Hygiene at the University of Montevideo. Havelburg's candidate for the role of aetiological agent of yellow fever was quickly dismissed. His description of the "agent"—a bacterium, akin to the bacillus of typhoid fever, and probably belonging to the family of Enterobacteriae—poorly fitted the epidemiological and clinical characteristics of yellow fever. This description suggests that Havelburg had studied an intestinal bacillus, which contaminated either his test-tubes, or, secondarily, his yellow fever patients.[13]

Sanarelli's discovery met a different fate. At first it was received with interest by his colleagues, because Sanarelli was viewed as a serious and competent investigator, known to have studied bacteriology in leading French and German laboratories and to use the latest methods and techniques. Moreover, the characteristics of Sanarelli's *Bacillus icteriodes* fitted well the clinical and the epidemiological data on yellow fever.[14] Sanarelli made most of his observations at the São Sebastião hospital in Rio de Janeiro, where he collaborated with the hospital's director, Dr Seidl. In 1898 Sanarelli developed a specific antiserum against *Bacillus icteroides*, and experimented with it first in Rio de Janeiro,[15] then in the state of São Paulo. The latter work was in collaboration with Adolfo Lutz, the director of the Bacteriological Institute of São Paulo and one of the pioneers of bacteriology in Brazil. During an outbreak of yellow fever in the city of São Carlos de Pinhal, a commission of the state of São Paulo studied there the therapeutic effects of Sanarelli's serum. The results were, at best, difficult to interpret. The bacteriologists on the commission affirmed, however, that they had isolated *Bacillus icteroides* from typical cases of yellow fever.[16]

[12] G. Sternberg, *Report on the etiology and prevention of yellow fever*, Washington, Government Printing Office, 1890, pp. 12–35. Freire refuted Sternberg's criticism, and in the pamphlet *La mission du Dr. Sternberg au Brésil* (first published in an abbreviated form in the *Medical News* of Philadelphia, 1889) he accused the latter of incompetence, myopia, and improper professional behaviour.

[13] W. Havelburg, 'Recherches expérimentales et anatomiques sur la fièvre jaune', *Anns Inst. Pasteur*, 1897, **11** (6): 512–22. A longer account was published in German: 'Experimentalle und anatomische Untersuchungen über der Wesen und die Ursachen des gelbens Fiebers', *Berl. klin. Wschr.*, 1887, **34**: 493–6.

[14] G. Sanarelli, 'Etiologie et pathogenèse de la fièvre jaune', *Annls Inst. Pasteur*, 1897, **11** (6): 433–512, 673–98, 753–66. Theoretically, Sanarelli could have been aware of the possibility that yellow fever was induced by an ultramicroscopic virus. He was one of the first investigators to describe, in 1898, a filterable agent of an animal disease—the myxomatosis of the rabbit. S. Smith Hughes, *The virus: a history of a concept*, London, Heinemann Educational Books, 1977, pp. 67–8. But this discovery came one year after (June 1898) his "discovery" of *Bacillus icteroides*, and by then he was already deeply involved in the controversy about his bacillus.

[15] G. Sanarelli, 'Premières expériences sur l'emploi du sérum curatif et préventif de la fièvre jaune', *Annls Inst. Pasteur*, 1898, **12**: 348–60.

[16] A. Lutz, 'Relatório dos trabalhos do Instituto Bacteriológico de São Paulo', *Rev. méd.* (São Paulo), no. 1, 1898, and no. 2, 1899.

Lutz and his collaborators were not the only ones to confirm Sanarelli's findings. In the meantime, Lacerda had abandoned his "polymorphic fungus" and adopted Sanarelli's ideas. In the years 1897 to 1899 *Bacillus icteroides* was also isolated from confirmed cases of yellow fever in Argentina, Mexico, New Orleans, and by the members of the US Navy commission sent to Cuba in 1899. It is not surprising that in their book on yellow fever, published in 1901, Drs Azevedo Sodré and Couto from the Medical School of Rio de Janeiro University explained that the proof of Sanarelli's bacillus being indeed the agent of yellow fever, was as perfect an aetiological proof as could be.[17]

Some problems remained, however. One was the curious epidemiology of the disease. In many cases, during a primary outbreak of yellow fever the disease was transferred to distant places, while the members of the infected household remained healthy. Such a form of epidemic propagation did not accord with the hypothesis of a contamination by bacteria or their spores. Another important obstacle to the acceptance of Sanarelli's ideas was the ineffectiveness of his anti-yellow fever serum. In addition, several bacteriologists repeatedly failed to cultivate a bacterium from the blood of yellow fever patients.[18] Sternberg's collaborator Aristides Agramonte, who went to Cuba to check the results obtained by the US Navy commission, observed that when the rules of sterility were strictly observed Sanarelli's bacillus was seldom found in the blood of yellow fever patients. In addition, the bacillus could be found in the blood of patients suffering from other diseases too, and thus its presence in some of the yellow fever cases could have resulted from secondary contamination.[19] Worse, in 1900 Walter Reed and James Carroll, who also worked with Sternberg, argued that *Bacillus icteroides* was in fact identical with a well-known bacterium: the aetiological agent of hog cholera (*Bacillus cholera suis*). In response to these accusations Sanarelli published a series of virulently polemical articles, in which he challenged the professional competence of Reed, Carroll, and Agramonte. Thus, in 1900 Sanarelli's discovery became the focus of a heated bacteriological controversy, one which dealt mainly with details of techniques and the nature of proof in bacteriology.[20] The final (or rather the nearly final) blow to the credibility of *Bacillus icteroides* did not come, however, from more advanced bacteriological studies, but from the experiments on human beings conducted in Cuba in 1900 by the Reed Mission.

THE "MOSQUITO THEORY" AND ITS EARLY RECEPTION IN BRAZIL

There is no need to repeat here the dramatic story of the Reed Mission, discussed and

[17] A. A. Azevedo Sodré and M. Couto, *Das Gelbfieber*, Vienna, Alfred Holder, 1901. Later Azevedo Sodré supported Oswaldo Cruz and the "mosquito hypothesis".

[18] A North American bacteriologist, Frederick Novy, who worked in 1898 at the Pasteur Institute, was asked by Roux to verify Sanarelli's findings. He reached similar conclusions. F. Novy, 'The etiology of yellow fever', *Med. News*, 1898, **73**: 326–31, 360–9.

[19] A. Agramonte, 'La relación del bacillo ictéroide con la fievre amarilla', *Prog. méd.* (Havana), 1900, no. 3.

[20] W. Reed and J. Carroll, 'A comparative study of the biological character and pathogenesis of Bacillus X (Sternberg), Bacillus icteroides (Sanarelli) and the hog-cholera bacillus (Salomon and Smith)', *J. exp. Med.* (Baltimore), 1900, **5**(3): 215–70. The controversy about Sanarelli's finding in the United States was studied by Margaret Warner in her article 'Hunting the yellow fever germ. The principle and the practice of etiological proof in late nineteenth-century America', *Bull. Hist. Med.*, 1985, **59**: 361–82.

analysed many times before.[21] It is worth noting, however, that one of the principal (and controversial) roles in the discovery of the transmission of yellow fever by the mosquito *Stegomyia faciens* (today *Aedes aegypti*) was played by a Cuban physician and self-taught bacteriologist, Carlos Finlay. As early as 1881 Finlay published a series of careful observations indicating a close correlation between the epidemiology of yellow fever in urban areas and the diffusion of the *Stegomyia* mosquito, and pointing to this mosquito's possible role in the transmission of the disease. Finlay repeatedly presented this hypothesis in international journals and congresses, but little attention was paid to it. Nowhere were concrete steps taken in order to eradicate the mosquito or to isolate the yellow fever patient from flying insects.[22] Only in 1900 did Reed and his colleagues, influenced by Finlay's ideas, by independent epidemiological observations made by British and American physicians,[23] and by the recent discovery of the role of mosquito in the transmission of malaria, decide to test the mosquito hypothesis. The positive results of their experimentation on human beings convinced the American governor of Havana to start a campaign of mosquito extermination. This campaign drastically diminished the number of yellow fever cases in the city, and thus furnished the most convincing proof of the truth of Finlay's hypothesis.[24]

Why did Finlay fail to reach a wider audience in the 1880s and 90s? His failure was in all probability related to the usual difficulties faced by an outsider working alone in a country lacking a recognized scientific tradition. But there was another problem as well. Finlay first published his epidemiological findings in a period in which research in tropical diseases was becoming more and more identified with bacteriological studies. It was also the period which saw the elaboration of international standards of bacteriological research. Studies in tropical medicine were often judged according to the technical quality of the laboratory investigation, as Sternberg's and Le Dantec's criticisms of Freire and Carmona y Valle show.

[21] W. Reed, A. Agramonte, and J. Lazear, 'The etiology of yellow fever—a preliminary note', *Philadelphia med. J.*, 27 October 1900, **148**(6): 101; W. Reed and J. Carroll, 'The etiology of yellow fever—a supplementary note', *Am. Med.* (Philadelphia), 22 February 1902, pp. 301–5. For discussion of the studies of the Reed Mission see, e.g., W. D. McCaw, 'Walter Reed—a memoir', in *Yellow fever: a compilation of various publications (presented by Mr. Owen)*, Washington, Government Printing Office, 1911, pp. 7–13; A. Agramonte, 'The inside story of a great medical discovery' (1915), repr. in S. Rappoport and H. Wright (eds.), *Great adventures in medicine*, New York, Dial Press, 1952, pp. 562–85; M. D. Gorgas and B. J. Hendrick, *William Crawford Gorgas—his life and work*, New York, Doubleday, Page & Co., 1924, pp. 92–110; A. McGehee Harvey, *Research and discovery in medicine*, Baltimore and London, The Johns Hopkins University Press, 1976; W. B. Bean, 'Walter Reed and the ordeal of human experiments', *Bull. Hist. Med.*, 1977, **51**: 75–92.

[22] C. Finlay, 'El mosquito hipotéticamente considerado como agente de transmisión de la fiebre amarilla', in C. Finlay, *Trabajos selectos*, Havana, Secretaria de Sanidad y Beneficiencia, 1912, pp. 28–9. Finlay presented his ideas before the International Sanitary Conference, Washington, 18 February 1881.

[23] Letter of Reed to Finlay, 7 October 1900, quoted in the biography written by Finlay's son: C. E. Finlay, *Carlos Finlay and the yellow fever*, Oxford University Press, 1940, pp. 98–9; C. Durham and J. Meyers, *Br. med. J.*, 1900, **ii**: 656–7; H. C. Carter, *New Orleans med. J.*, May 1900. Finlay may have known Manson's study (1879) on the role of the mosquito in the transmission of filariasis. He did not, however, quote Manson in his early articles on the "mosquito hypothesis". However, Manson's biographer stated that Finlay's work "had a very distinct influence on the malaria story". Sir Philip Manson-Bahr, *Patrick Manson, the father of tropical medicine*, London, Thomas Nelson and Sons, 1962, p. 161.

[24] For an evaluation of the contributions of Finlay and of Reed and his colleagues see S. Peller, 'Walter Reed, Carlos Finlay and their predecessors around 1800', *Bull. Hist. Med.*, 1959, **33**: 195–211. The socio-political background of the early refusal of Finlay's hypothesis has been investigated by Nancy

Finlay was undoubtedly a gifted and imaginative epidemiologist. He was unable, however, to prove the truth of his claims in the laboratory. His bacteriological studies, and his attempts at vaccination against yellow fever, might even have discredited his earlier epidemiological observations. In the years between 1882 and 1900 Finlay published numerous articles aiming at reinforcing his mosquito theory. About twenty of them described in detail a new candidate for the role of the "yellow fever germ", a bacterium he named *Micrococcus tetragenus febris flavae*. Finlay was unable, however, to provide convincing proof of the aetiological link between this bacillus and yellow fever.[25] In addition, Finlay saw the mosquito solely as a mechanical means of transfer of his germ from one person to another. He claimed that a mosquito which had recently fed on a sick person was particularly apt to transfer the disease. Finlay published several articles in which, on the basis of rather questionable results, he claimed that he had been able to induce a mild but immunizing form of the disease in 90 non-immune individuals bitten by a small number of mosquitoes that had shortly before been allowed to feed on yellow fever patients.[26] Thus in the 1880s and 90s Finlay's experimental data might have contributed to the delay in recognition of his mosquito theory.

The situation was quite different by 1900, when it was already known that the tropical diseases filariosis, Texas fever, nagana, and in particular avian and human malaria were transmitted by insects. It was also known that in many cases the parasite had to go through a stage of development in an insect host before it became contagious to humans. It had become clear that it was not enough to "isolate the microbe". The isolation and the *in vitro* culture of the aetiological agents of many tropical diseases were not possible, and even when they were, active steps against the disease did not automatically follow. Specialists in tropical medicine became interested in the complex problems of life-cycles of disease-inducing micro-organisms and parasites, the biology of their vectors, and the epidemiology of tropical diseases. The new cognitive context

---

Stepan in her article 'The interplay between socio-economical factors and medical science: yellow fever research, Cuba and the United States', *Soc. Stud. Sci.*, 1978, **8**: 397–423.

[25] At first Sternberg supported, albeit with caution, Finlay's claims concerning his micrococcus. Sternberg, op. cit., note 12 above, pp. 164–6. Shortly after however, he decided that the micrococcus was a saprophyte. 'Resultato de los experimentos comparticos hechos sobre el Micrococo Tetragenus versatilis para los doctores Finlay y Delgado', *An. R. Acad. Cienc. méd. fis. nat.* (Havana), 1889, **26**: 739–53.

[26] Finlay claimed that volunteers bitten by a freshly infected mosquito developed a mild form of yellow fever and became immunized. However he explained that 11 of the immunized volunteers (according to him those who had too mild a form of experimental yellow fever) later contracted yellow fever and three died from the disease. C. Finlay, 'Estatistica de los inoculaciónes con mosquitos contaminados en enfermos de la fiebre amarilla', ibid., 1890, **27**: 459–69; *idem*, 'Inoculation of yellow fever by means of contaminated mosquitos', *Am. J. med. Sci.*, Philadelphia, 1891, pp. 264–8. C. Finlay, 'Yellow fever: immunity, modes of propagation, mosquito theory' *Comptes rendus du Huitième Congrès International d'Hygiène et de Démographie*, Budapest, 1894, in Finlay, *Trabajos selectos*, op. cit., note 22 above. The members of the Reed Mission later found that a mosquito that had fed on a yellow fever patient was able to transfer the disease only after a lag period of 10–14 days, thus invalidating Finlay's claim that he had induced experimental yellow fever. Moreover, after the lag time, the bite of even a single experimentally-infected mosquito was extremely dangerous. It could (and, unfortunately, in some cases did) induce a lethal case of yellow fever. For the controversy between Finlay and Carroll on the priority of the discovery of the role of the mosquito in the transmission of yellow fever, see J. Carroll, 'The transmission of yellow fever', *J. Am. Med. Ass.*, 23 May 1903, reprinted in *Yellow fever*, op. cit. note 21 above, pp. 175–81.

allowed a more encouraging reception for Finlay's early epidemiological observations. It also led to the experimental verification of this hypothesis by the Reed Mission.[27]

Finlay himself later recognized the superiority of the experimental approach of the Reed Mission, acknowledging implicitly the methodological weakness of his own experiments. He pleaded, however, for adequate recognition of the practitioner's point of view:

> The scientist's point of view, in these matters, is quite different from that of the sanitarian. Science is insatiable, and will go to very great lengths in the hope of clearing up a doubt which seems to lie within its grasp; while the sanitarian's ideal is satisfied when his main object has been attained, namely, the protection of human life and health against disease.[28]

The results of the Reed Mission were received with great interest in Brazil. One of the most fervent supporters of the "mosquito hypothesis" (or, as it was often called in Latin American countries, "Finlay's hypothesis")[29] was the director of the Sanitary Services of São Paulo State, Emílio Ribas. During the 1895–8 outbreak of yellow fever in the city of Campinas, Ribas stopped the epidemic by taking sanitary measures. But he was unable to understand why these worked in Campinas, while similar measures were much less successful elsewhere. The publication of the first results of the Reed Mission gave him a key to this mystery: the sanitary operations in Campinas had included the draining of mosquito-breeding sites. In January 1901 Ribas published a highly enthusiastic account of the work of the Reed Mission. At that time Adolfo Lutz also became very interested in "Finlay's hypothesis", which well fitted his own epidemiological observations. As early as 1901 he asked and received the authorization of the Governor of São Paulo State, Rodrigues Alves, to repeat the experiments on human beings first performed by the Reed Mission.

In 1902–3 Lutz and his collaborators started their experiments in the Isolation Hospital in São Paulo. They were successful in inducing yellow fever in three healthy volunteers by the bites of infected *Stegomyia* mosquitoes, and showed, using other volunteers, that this disease could not be transmitted by direct contact with soiled clothing or bedding. Clearly the practical success of Gorgas's anti-mosquito campaign in Havana was not a sufficient argument to introduce similar sanitary policies elsewhere. The fact that in 1902 and 1903 dangerous experiments on human

[27] Jesse W. Lazear, who was the first member of the Reed Mission to become interested in Finlay's hypothesis, studied malaria prior to his stay in Cuba (1897–1900), and was among the first North American investigators (together with Wooley and Thayer) to confirm Ross's and Grassi's results on the cycle of life of the malaria parasite in the mosquitoes. A. McGehee Harvey, *Research and discovery in medicine, contributions from Johns Hopkins*, Baltimore and London, The Johns Hopkins University Press, 1976, pp. 34–48.

[28] C. Finlay, 'Methods of stamping out yellow fever suggested since 1899', In C. Finlay, *Trabajos Selectos*, op. cit., note 22 above, pp. 421–7. The switch of emphasis from broad measures of public health to more specific measures of individual protection and the application of bacteriological ("scientific") rather than epidemiological ("sanitarian") criteria in decisions concerning public health measures in the late nineteenth century was not limited to tropical medicine. See Worboys, op. cit., note 4 above, p. 93; Claire Salomon-Bayet, *Pasteur et la révolution pastorienne*, Paris, Payot, 1986.

[29] For example, in his book *Febre amarella* (Rio de Janeiro, H. Garnier, 1907) Z. Meirelles did not mention the Reed Mission, and attributed to Finlay alone the glory of replacing metaphysical ideas on the origin of yellow fever with a truly scientific view (p. 7).

beings were repeated several times (by the North American mission in Vera Cruz, by the Brazilian investigators in São Paulo, and by the Pasteur Institute Mission in Rio de Janeiro), points up the importance attributed to experimental, as opposed to epidemiological proof. The São Paulo commission defined its goal as the "use of rigorous scientific method in order to determine whether yellow fever is transmitted by mosquitoes", and later concluded that mosquito transmission had become "a positively acquired scientific fact".[30] This scientific fact was the basis of the urgent campaign of mosquito extermination initiated in 1903 by the Sanitary Services of São Paulo State.[31]

THE PASTEUR INSTITUTE MISSION TO RIO DE JANEIRO

In 1900 there was an outbreak of yellow fever in the colony of Senegal. The French merchants there were strongly opposed to the traditional means of fighting the disease, because the long quarantines imposed on ships from infected ports were harmful to their trade. They had heard about the "mosquito theory", and asked the French government to appoint a special commission to evaluate the utility of the practical recommendations issued by the Reed Mission: the replacement of quarantine by the isolation of the sick, and the extermination of mosquitoes. They also offered to contribute to the funding of such a commission. The French government accepted their suggestion. A commission of specialists was created by a special law, adopted in July 1901, which defined the goal of the future mission as the

> perfecting of our knowledge of the nature of the infectious agent of yellow fever, its usual means of transmission, and the prevention and cure of this disease. The elucidation of these points, which for the moment remain obscure, could help to save the life of Europeans who are an easy prey to yellow typhus.

The collaboration of the Pasteur Institute was requested.[32] The Chamber of Deputies voted a special budget of 150,000 francs for the commission, to be supplemented later, if necessary, with additional funds from the Ministry for the Colonies. The Reed Mission, the mosquito hypothesis, and the problem of quarantine were not mentioned in official documents, although—as later accounts attest—they were very much present in everyone's mind.[33]

Rio de Janeiro was selected as an ideal place to study yellow fever. The three investigators chosen by the Pasteur Institute's director Emile Roux to participate in the mission were Drs Paul Simond, A. Taurelli Salimbeni, and Emile Marchoux. All three were competent bacteriologists, and had previous field experience of

[30] Service Sanitaire de l'Etat de São Paulo, *Le moustique considéré comme agent de propagation de la fièvre jaune*, São Paulo, Diário Official, 1904, pp. 38, 44.

[31] E. Ribas, L. P. Barreto, A. G. da Silva Rodriguez, and A. de Barros, *Travaux touchant la prophylaxie de la fièvre jaune, 1901–1903*, São Paulo, Diário Official, 1904; E. Ribas, 'Rapport sur l'état sanitaire des ports du Brésil', 1904, (manuscript), Pasteur Institute Archives, Paris.

[32] Law no. 2240, proposed by M. Décrais, the Minister of the Colonies, 7 March, and adopted by 12 July 1901. Chambre des Députés: septième législature, session de 1901. Archives Nationales, Paris, document no. F-17-13052.

[33] E. Roux, 'Introduction au rapport de Mrs. Marchoux, Salimbeni et Simond', *Annls Inst. Pasteur*, 1903, **17**: 665.

epidemiology. Marchoux, a physician (2nd class) in the colonial army, had been sent in 1897 to Senegal to study malaria and sleeping sickness. Salimbeni, who specialized in immunology (he collaborated with Roux and Elie Metchnikoff) had participated in the elaboration of an anti-cholera antiserum, and had tested its curative and preventive value during a cholera epidemic in Oporto. Simond, the best-known of the three, was also a physician in the colonial army (1st class). In 1898 he had studied the plague epidemic in China and Indochina, and was the first to point to the role of the rat flea in the propagation of this disease.[34]

The Pasteur Institute delegation arrived in Rio de Janeiro in November 1901. It brought from Paris everything required by a modern bacteriological laboratory, from microscopes to glassware and culture media.[35] The French scientists set up their headquarters in the São Sebastião Hospital, and established their laboratory in a special building allocated to them by the hospital. The hospital's director, Carlos Seidl, and his colleagues, Drs Leão de Aquino, Antonio Ferraro, and Zepherin Mereilles, participated in the commission's studies, mainly by furnishing clinical cases, soiled bedding, and laboratory animals.[36] Ill-health forced Salimbeni to leave Rio de Janeiro early, but Simond and Marchoux stayed in Brazil until 1905, with a single interruption of several months in 1903. As well as yellow fever, they investigated two veterinary diseases: fowl spirilosis and "garotilha".[37]

The studies of the French mission fully vindicated the conclusions of the Reed Mission. First they confirmed Le Dantec's, Sternberg's, and Novy's conclusions that no bacterium could be cultivated from the yellow fever patient's blood. In the second stage of their investigation they repeated Reed's and Carroll's experiments with human beings. They used 27 healthy volunteers, who signed a paper stating that they were aware of the danger to which they exposed themselves: luckily, there were no fatal cases of experimental yellow fever in Rio de Janeiro. The French scientists were able to confirm that even prolonged contact with the secretions of the sick was not dangerous, and that the only way experimentally to induce yellow fever was either through the bite of an infected *Stegomyia* mosquito, or through the injection of infected blood. They also found, as Reed and Carroll had earlier, that even filtered serum could convey the disease, which suggested that the agent of yellow fever was an ultramicroscopic "filterable virus". The Pasteur Institute scientists concluded that the destruction of *Stegomyia* mosquitoes and their larvae, and the isolation of the sick

[34] E. Marchaux, 'Le rôle du pneumocoque dans la pathologie de la maladie du sommeil', ibid., 1899, **13**: 193–298; A. Calmette and A. T. Salimbeni, 'La peste d'Oporto', ibid., pp. 865–936; P. L. Simond, 'La propagation de la peste', ibid., 1898, **12**: 625–62; P. L. Simond, 'Comment fut mis en évidence le rôle de la puce dans la transmission de la peste', *Rev. Hyg.*, 1936, **58**(1): 517–28; J. Woeckel, 'La vie et l'oeuvre de P. L. Simond, 1858–1947', *Méd. trop.*, 1969, **23**: 429–41; P. Pluchon, *Histoire des médecins et des pharmaciens de la marine et des colonies*, Paris, Privat, 1985, pp. 386–8.

[35] In all probability they were not over-cautious. In 1903 the newly appointed Professor of Microbiology at the Medical School of Rio de Janeiro University complained that he had only one microscope to teach 150 students. P. Moyacyr, *A instruçao e a República*, vol. 3, Rio de Janeiro, 1942, p. 201, quoted by Nancy Stepan, 'Initiation and survival of biomedical research in a developing country: the Oswaldo Cruz Institute of Brazil 1900–1920', *J. Hist. Med.*, 1975, **8**: 303–25, on p. 309.

[36] C. Seidl, *Resnascenca: A Missão Pasteur*, Rio de Janeiro, 1905.

[37] A. Marchoux and A. T. Salimbeni, 'La Garotilha', *Annls Inst. Pasteur*, 1903, **17**: 564–8; *ibidem*, 'La spirilose des poules', ibid., pp. 569–80.

from the mosquitoes, were the only efficient ways to fight yellow fever. The commission also discussed the sanitary rules needed to prevent the spread of yellow fever through infected ships and goods. It strongly recommended the abolition of unnecessary quarantines and their replacement by strict sanitary measures aimed at preventing the transmission of contaminated mosquitoes or their eggs and larvae from port to port.[38]

Faithful to the new "global" approach to tropical medicine, the French scientist did not stop at the laboratory but made numerous epidemiological studies as well, arriving at the conclusion that natives of areas in which yellow fever was endemic were not "naturally" immune to this disease but were actively immunized in the early years of their life. In endemic areas, they claimed, yellow fever was a common childhood disease although it was often not recognized as such, because it was confused with other childhood "fevers." In such zones, little children could serve as a natural reservoir of the disease agent. Together with their colleagues in Paris, the French mission also studied the life cycle and natural ecology of the mosquito *Stegomyia*, in order to increase the efficiency of the sanitary campaigns designed to exterminate the yellow fever vector.[39]

OSWALDO CRUZ AND THE CONTROVERSY OVER THE ANTI-MOSQUITO CAMPAIGN IN RIO DE JANEIRO

The departure, in 1903, of the members of the Pasteur Mission for a short stay in France was the occasion for official ceremonies at the highest level. These ceremonies were not solely the expression of politeness, or of the desire to honour an official mission of the French Government. They were above all political demonstrations, a move in a complex struggle over the control of health services in Rio de Janeiro, itself part of a larger fight for political control of the Brazilian capital.

In 1902 a new president came to power in Brazil: the governor of São Paulo, Francisco Rodrigues Alves. Alves had always been interested in public health issues, and strongly supported the reform of health services in the state of São Paulo. He closely followed the conclusions of the Reed Mission, and personally allowed Lutz and his collaborators to experiment on human beings in order to confirm the results obtained by the Americans in Cuba. On moving to the federal capital, Rio de Janeiro, Alves became concerned about the poor state of sanitation in the city, and about the negative image of the country that this projected. In particular, the persistence of yellow fever, and the resultant avoidance of Rio de Janeiro harbour by foreign ships, became for Alves the symbol of Brazil's backwardness and under-development; and the struggle against this disease became the symbol of his own fight for the modernization of Brazil.[40]

Taking advantage of a law that forbade the accumulation of government jobs, President Alves dismissed the former director of the Federal Department of Public

[38] E. Marchoux, A. T. Salimbeni and P. L. Simond, 'La fièvre jaune: rapport de la mission française', ibid., pp. 665–731. In São Paulo, too, volunteers signed a paper confirming that they had been informed about deaths in Cuba during similar experiments. *Le moustique*, op. cit., note 30 above, p. 46.

[39] E. Marchoux and P. L. Simond, 'Etudes sur la fièvre jaune: deuxième mémoire', *Annls Inst. Pasteur*, 1906, **20**: 16–40; *ibidem*, 'Etudes sur la fièvre jaune: troisième mémoire', ibid., pp. 104–48; *ibidem*, 'Etudes sur la fièvre jaune: quatrième mémoire', ibid., pp. 161–205.

[40] S. Schwartzman, *A formação da communidade cientifica no Brasil*, Editora Nacional, São Paulo, 1979, pp. 119–37; S. Schwartzman, 'Struggling to be born: the scientific community in Brazil', *Minerva*, 1978, **4**: 545–80; José Maria Bello, *A history of modern Brazil, 1889–1964*, Stanford University Press, 1966.

Health in Rio, Nuno de Andrade, and appointed to this office a young and relatively unknown professional bacteriologist, Oswaldo Cruz. Cruz (1872–1917) had studied medicine at Rio de Janeiro University, then gone to France (1896–1899) for training in bacteriology. In 1896 he was a student in Roux's 'Cours de Microbie Téchnique' at the Pasteur Institute and from this time on he considered himself Roux's disciple. Cruz stayed in Paris a year and a half longer, working in the Paris Municipal Laboratory. Back in Brazil, in 1900 he was appointed, on Roux's recommendation, as the technical director of the Instituto Sôrothérapico de Manguinhos. The Manguinhos Institute had been created in order to produce antisera for medical use, and had at that time purely practical goals. Its later transformation into a leading research institution in tropical medicine was closely related to Cruz's career as a public-health administrator. This career, which started in 1902 when he was appointed head of the Federal Department of Public Health of Rio de Janeiro, was mostly identified with Cruz's campaign for the eradication of major infectious diseases—yellow fever, smallpox, and plague—from the Brazilian capital.[41]

The sanitary campaign started in January 1903. From its very beginning the campaign, and in particular the introduction of compulsory smallpox vaccination, the strict isolation of the sick, and the destruction of mosquitoes, aimed at the elimination of yellow fever, met strong resistance, not devoid of political undertones. It was perceived as the personal enterprise of President Alves, and as a means for him to control the city of Rio de Janeiro. Cruz, a research worker who had neither administrative experience nor the support of the city's medical establishment, was viewed as an outsider, and was attacked by the press and by some of his colleagues. Resistance to Cruz's sanitary measures culminated in the organized refusal of smallpox vaccination in 1904 (which included, in November 1904, street riots and a revolt in the Military Academy of Praia Vermelha) and the consequent revocation of the compulsory vaccination law by President Alves. Anti-vaccinationism diminished only in 1908, during one of the worst smallpox epidemics ever known in Rio de Janeiro. Cruz was, however, more successful in his attempts to control the other two diseases that were the objects of his sanitary campaign. The elimination of rats greatly reduced the number of deaths from plague, while the isolation of the sick from insects and the fight against the mosquito greatly diminished the number of yellow fever cases in Rio de Janeiro.[42]

[41] A detailed analysis of the social and political background of Cruz's sanitary campaign, of its institutional consequences for Brazilian medical science and of the events leading to the foundation of the Instituto Oswaldo Cruz, can be found in Nancy Stepan's book, *The beginnings of Brazilian science: Oswaldo Cruz, medical research and policy, 1890–1920*, New York: Science History Publications, 1976, in particular on pp. 69–104. See also O. G. Cruz, *Opera omnia*, Rio de Janeiro, Impressora Brasileira, 1972 pp. vi–x; E. Sales Guerra, *Oswaldo Cruz*, Rio de Janeiro, Vecchi, 1940; Clementino Fraga, *Vida e obra de Oswaldo Cruz*, Rio de Janeiro, José Olympio, 1972.

[42] Placido Barbosa and Casio Barbosa de Rezende (eds.), *O servicios de saúde pública no Brasil, especialemente na cidade do Rio de Janeiro, de 1808 a 1907*, Rio de Janeiro, Imprensa Nacional, 1909; Octavio G. de Oliveira, *Oswaldo Cruz e suas atividades na direção da saúde pública brasileira*, Rio de Janeiro, Serviço Gráfico do Instituto Brasileiro de Geografia e Estatística, 1955. On the resistance to compulsory smallpox vaccination in Europe, see Genevieve Miller, *The adoption of inoculation for smallpox in England and France*, Philadelphia, University of Pennsylvania Press, 1957; John Z. Bowers, 'The odyssey of smallpox vaccination', *Bull. Hist. Med.*, 1981, **55**: 17–33.

The Pasteur Institute Mission was in Rio at the height of the controversy over the sanitary campaign. Cruz, a fervent admirer of the Pasteur Institute, utilized the prestige of the French scientists in order to gain support for his anti-yellow fever measures. In a letter to Roux from August 1903, shortly after the beginning of the sanitary campaign, Cruz warmly thanked his former teacher for the "moral and scientific support given by the 'Pasteur Mission' for the sanitary measures that we have started to apply here".[43] The esteem was mutual. In 1905 Marchoux of the Pasteur Mission explained that the results obtained in Rio de Janeiro (a ten-fold decrease in the number of yellow fever cases in 1904)

> are so clear-cut . . . that they definitely establish the mosquito theory. Today nobody can contest the culidian origin of yellow fever. The honour for this important achievement should be attributed to President Rodrigues Alves. Alves, who aimed at the improvement of sanitary conditions in Brazil's capital, did not weaken under the attacks of his opponents, and chose and maintained an enthusiastic and convinced scientist, Mr Oswaldo Cruz, as the director of the hygienic services of the city.[44]

Cruz's opponents were indeed harsh. In addition to political opposition to the obligatory sanitary measures, there was scientific resistance to the "mosquito hypothesis". Some of Cruz's opponents tried to revive Sanarelli's *Bacillus icteroides*. In 1901 Sanarelli published a booklet in which he brought together new refutations of the theory of exclusive transmission of yellow fever by the mosquito. Lacerda, a former supporter of Sanarelli, wrote in 1902 that discussions with the scientists of the Pasteur Mission had persuaded him that the mosquito frequently transmitted yellow fever, but not that it was the *only* means of transmission. He also doubted that it had been conclusively proved that the disease was introduced by an ultramicroscopic virus, as opposed to a bacterium.[45]

A similar argument, albeit in a less crude form, was developed by Cruz's principal scientific opponent, the previous Director of the Department of Public Health in Rio de Janeiro, Nuno de Andrade. In a series of articles first published in 1903 in *Journal do Commercio*, and later collected in a booklet entitled *Yellow fever and the mosquito*, Nuno de Andrade denounced the behaviour of the scientists who followed the new doctrine "with the enthusiasm of apostles and the intolerance of sectarians" and sometimes, as in the case of Adolfo Lutz, a former supporter of Sanarelli's ideas, "with the zeal of new converts".[46] He stated that mosquitoes were responsible for most, but in all probability not all cases of yellow fever. He claimed that in several well-documented cases (e.g., the transmission of yellow fever by clothes that had been

[43] Letter of Oswaldo Cruz to Emile Roux, 9 August 1903, Archives of Casa de Oswaldo Cruz, Manguinhos, Rio de Janeiro. In this letter, headed "Monsieur et cher maître" and signed "votre élève très dévoue", Cruz reaffirmed his devotion to the Pasteur Institute: "Je profite de cette occasion pour vous assurer une fois de plus de notre reconnaissance à l'Institut Pasteur, dont j'ai l'honneur d'être le plus humble des élèves".

[44] E. Marchoux, 'La fièvre jaune á Rio de Janeiro', *Annls Hyg. Méd. trop.*, 1905, **8**: 304–8. See also E. Marchoux and P. L. Simond, 'Etudes sur la fièvre jaune: quatrième mémoire', op. cit., note 34 above.

[45] J. B. Lacerda, *Recherches sur la cause et la prophylaxie de la fièvre jaune*, Rio de Janeiro, Imprensa Nacional, 1902.

[46] Nuno de Andrade, *Febre amarrella e o mosquito*, Rio de Janeiro, Jornal do Commercio, 1903, pp. 54, 34.

stored for years in closed trunks and thus kept in conditions which made the survival of mosquito eggs highly improbable), yellow fever was shown to have been transmitted in a different manner; and thus concluded that the complete abandonment of traditional means of disinfection during epidemics, such as quarantines and the burning of infected clothing and bedding, constituted a serious danger for public health.[47] The Reed Mission, according to Andrade, was not able to prove that the agent of yellow fever was indeed a filterable virus; one could not exclude the possibility that the disease was induced by a bacterial toxin.[48] He pointed to the variability of clinical symptoms observed in cases of experimentally-induced yellow fever, and to the lack of attention paid by investigators to climatic conditions during the experiments. Moreover, Andrade claimed that the proof of lack of transmission of yellow fever by contaminated clothing was not conclusive, because this had been investigated in localities where yellow fever was non-existent or weak at the time of the experiment.[49]

Put in a nutshell, Nuno de Andrade's protest was against the "tyranny of the new scientific doctrines". Indeed, for the supporters of the mosquito theory, "science is nothing else but the sum of human knowledge in a given period. If some minds obstinately refuse to line up in a disciplined fashion and embrace the present scientific achievements, we may only feel sorry for them, and view them as holding themselves outside their times".[50] Andrade, however, strongly contested the claim that the new views "are the only ones that should be taken into consideration, because they are based on methods of investigation that correspond to the present state of development of science". He was also very critical of the process by which the new ideas rapidly gained institutional support and became the only accepted point of view. He thus expressed his indignation against the way the 5th Congress of Medicine "had enthroned the invisible germ as the aetiological agent of the disease", and therefore given an official stamp of approval to the results of Reed's Mission.[51]

Nuno de Andrade's views, published in the spring of 1903, were at hand during the wave of criticism of the activities of the Pasteur Mission in the Brazilian press, which took place on the occasion of the departure of the French scientists for a short stay in Europe in July 1903. At that time, French scientists were received by President Alves,

[47] Ibid., pp. 9–13, 20–8.

[48] Ibid., pp. 14–16. Indeed, the Reed Mission supplied no definitive experimental proof that yellow fever was induced by a "filterable virus" and not by a filterable bacterial toxin. Such a proof, a serial transmission of the disease by filtered serum, was never made by the US army scientists, due to the obvious difficulties of human experimentation. Reed and Carrol did claim that they were able to obtain a serial transmission of the disease, but their argument was based on a single and rather doubtful case (a volunteer, who was bitten by an infected mosquito and who did not develop the disease in the usual incubation period, was injected shortly later with filtered blood of another volunteer, himself infected by filtered blood, and this time he did develop yellow fever: W. Reed and J. Carroll, 'The etiology of yellow fever—a supplementary note', op. cit., note 21 above). Nuno de Andrade did not discuss, however, this precise case. His criticism of the "mosquito hypothesis" was not based on an analysis of the validity of specific knowledge claims but on a global rejection of the new standards of scientific proof.

[49] Andrade, op. cit., note 46 above, pp. 17–20, 52–3.

[50] Letters of Drs L. P. Bareto, A. G. da Silva Rodriguez and A. de Barros (from the São Paulo Yellow Fever Commission) to Dr E. Ribas, 15 January 1903, reproduced in *Le moustique*, op. cit., note 30 above, p. 56.

[51] Ibid., pp. 34–5.

who warmly thanked them for their help. In their reply, the members of the Pasteur Mission explained that the eradication of mosquitoes was the only efficient way to fight yellow fever. They strongly supported the sanitary measures undertaken by Oswaldo Cruz, and predicted that in two or three years these measures would certainly free Rio de Janeiro from this disease.[52] Their intervention was criticized by several Rio de Janeiro newspapers, indignant at this support for "the dictatorship of the new administration", and the "violent introduction of new sanitary measures".[53] They warned that there was no particular reason to subscribe immediately to the ideas of foreigners, the more so if those ideas were contested by several well-known Brazilian scientists.[54] Nuno de Andrade, the latter's main spokesman, claimed that the French government did not adopt the sanitary measures proposed by the Pasteur Mission. He warned against an uncritical acceptance of new doctrines, which were anyway often short-lived, and suggested that more attention and respect be paid to the century-long tradition of epidemiological studies of yellow fever in Brazil.[55] Some newspapers which supported Andrade's views affirmed that Cruz's first statistics indicated that the new sanitary measures in fact increased the number of yellow fever cases in the city.[56] In addition, members of the Pasteur Mission declared in a long interview for the *Jornal de Commercio* that the problem of yellow fever was not yet solved, explaining to a rather bewildered journalist that, as a rule, scientific problems are never definitely closed.[57] But this attempt at elucidating the nature of scientific investigation to the Brazilian public was not very successful. It handed fresh ammunition to the opponents of government policy, who stated that if the problem of yellow fever was not definitely solved, there was no justification whatsoever for Cruz's compulsory sanitary measures.[58]

Three years later, the dramatic decrease in the number of cases of yellow fever in Rio de Janeiro completely modified public opinion in the city. Before the sanitary campaign, there were in Rio de Janeiro several hundred yellow fever cases per year, and several thousand per year during epidemics. There were 984 yellow fever cases in 1902, and 584 in 1903, the year the sanitary campaign began. This number was reduced of 42 cases in 1906, 39 in 1907, 4 in 1908 and none in 1909.[59] The victory over yellow fever became the

[52] 'A cidade', *A Noticias*, 9 July 1903. This and the articles cited below are collected in a press file on Cruz's sanitary campaign in the archives of Casa de Oswaldo Cruz, Manguinhos, Rio de Janeiro. I am indebted to the director of Casa de Oswaldo Cruz, Dr Paulo Gadelha, for making this material available to me.

[53] 'Kaleidoscopio', *A Tribuna*, 9 July 1903.

[54] *A Pais*, 11 July 1903; *A Noticias*, 13 July 1903.

[55] *A Noticias*, 11 July 1903. Nuno de Andrade's claims were not entirely false: the French indeed did not hasten to introduce the measures recommended by the Reed Mission. Although the success of the anti-mosquito measures in Cuba was very favourably commented upon in the French medical press in 1901, a year later, during an outbreak of yellow fever in the French penal colony in Guyana, the only anti-yellow fever measures proposed by the colonial administration were the distribution of "tonics", i.e., wine and coffee, to the prisoners. M. A. Garnier, *La Fièvre jaune en Guyane avant 1902 et l'épidémie de 1902*, Paris, Doin, 1903.

[56] *A Tribuna*, 14 July 1903; 'Dia a Dia', *Jornal do Commercio*, 22 July 1903. In contrast, a journalist of another Rio daily, *Coreiro da Manha*, ridiculed nationalism and chauvinism in science, and proposed to send Nuno de Andrade to the Antiquities Department of the National Museum. Ivo do Val, 'Por ahi a fora', *Coreiro da Manha*, 13 July 1903. This was, however, a minority opinion.

[57] 'A Missão Pasteur', *Jornal do Commercio*, 11 July 1903.

[58] *A Noticias*, 13 July 1903; *A Pais*, 12 July 1903, *A Tribuna*, 14 July 1903.

[59] O. G. Cruz, 'The sanitation of Rio', *The Times*, 28 December 1909, reproduced in Cruz, op. cit., note 41 above, pp. 556–62.

most visible sign of the success of the sanitary campaign, and its director was hailed as a national hero. Cruz was able to use his newly-acquired popularity to obtain in 1907 important government funds to transform the logistic and scientific base of his sanitary campaign, the Instituto Sôrothérapico de Manguinhos, into an autonomous research institute in tropical medicine.[60] The new institute combined high-level bacteriological and parasitological research with detailed epidemiological investigations. The scientists in the new institute were all Brazilians. Some, like Cruz and Lutz, had trained in Europe, while others were trained at the Institute. The institute maintained close links with European science through the prolonged visits of scientists, mostly German; through the frequent trips Brazilian investigators made to Europe in order to participate in international congresses and to visit laboratories of bacteriology, parasitology, and tropical medicine; and through the latest scientific literature, to be found in the institute's library. The scientific success of the new institute was symbolized by the award to the Institute of the Gold Medal of Hygiene during the Fourteenth International Congress of Hygiene and Demography (Berlin, 1907), and by the discovery of a new tropical disease induced by a trypanosoma—Chagas's disease—by Cruz's student Carlos Chagas, in 1909.[61]

The transformation of the Instituto Sôrothérapico de Manguinhos into an internationally recognized research institute in tropical medicine was but one sign of the victory of the ideas propagated by Cruz and his followers. After the triumph of the sanitary campaign no one seriously questioned the importance of new ideas corresponding to the latest state of knowledge in science, or the legitimacy of the judgement of the international scientific community as expressed at international congresses. In discussing the possible role of the Pasteur Mission in the acceptance of international standards of scientific investigation in Brazil, its host in Rio de Janeiro, the Director of the São Sebastião Hospital, Carlos Seidl, declared that at first some Brazilian bacteriologists "who used to conclude on the basis of *a priori* conclusions, insufficiently supported by the experiments", were amazed at how slowly the French scientists constructed their experimental systems, how carefully they repeated their experiments, and how patiently they performed all the necessary controls before publishing their conclusions. The members of the Pasteur Mission showed the bacteriologists in Rio de Janeiro "the futility of premature deductions, which lacked experimental basis".[62] Their studies demonstrated how professional research in tropical medicine should be done. This practical lesson had, in all probability, been well received by the investigators who worked in the Manguinhos Institute.

CONCLUSIONS

In the 1880s and 90s several bacteriologists working in Rio de Janeiro "discovered" the "yellow fever germ". Their studies were rejected by the international scientific

[60] *Idem*, 'Profilaxia de febre amarela: memoria paresentada au 4° Congresso Medico Latino Americano', in ibid., pp. 541–55; *idem*, 'The sanitation of Rio', ibid., pp. 556–62; Oliveira, op. cit., note 42 above, pp. 26–30.

[61] E. Caetano Diaz, *O Instituto Oswaldo Cruz: resumo histórico 1899–1918*. Rio de Janeiro, Manguinhas, 1918; Jaime Larry Benchimor (research coordinator), *Relatorio de pesquisa: Manguinhos: um retrato de corpo inteiro*, Rio de Janeiro, Fundacão Oswaldo Cruz (mimeographed) vol. II, pp. 90–205.

[62] Seidl, op. cit., note 36 above.

community because they did not conform to the new professional standards of bacteriological studies. After 1908, the Instituto Sôrothérapico de Manguinhos was recognized as an important research centre in tropical medicine. In the meantime in the years 1901–5, the Pasteur Institute scientists transferred a model research laboratory to Rio de Janeiro. What was the impact of the Pasteur Mission on the later development of tropical medicine in Brazil?

The birth of the Oswaldo Cruz Institute and the development of Brazilian tropical medicine were closely connected with the specific political, social, and cultural conditions in Brazil at the beginning of the twentieth century.[63] It was also related to the personality of Oswaldo Cruz, an unusually gifted administrator and scientific entrepreneur.[64] A favourable political climate, sufficient funding, and good administration were, however, necessary but not sufficient conditions for the development of an important research centre in Rio de Janeiro. There was, in addition, a need for a cognitive evolution that would allow the development of a scientific community able to sustain internationally recognized research in tropical medicine. The prolonged stay of French investigators in Rio, and the transfer of a modern European laboratory to a peripheral country, contributed to the qualitative transformation of Brazilian bacteriology. More specifically, this transfer enhanced the ability of local scientists to deal with the conceptual modifications in tropical medicine that took place between 1880 and 1900.

In 1880, the tendency to reduce bacteriological studies to attempts at isolating the microbe favoured laboratory studies, and, in the domain of public health, reductionist, individual-centred approaches. The discovery of the complexity of the life cycles of many of the aetiological agents of tropical diseases, and of the importance of insect vectors, was the basis for an important conceptual and practical transformation in tropical medicine.[65] After 1900 work in this discipline included, besides laboratory research, studies in epidemiology, ecology, and hygiene. This does not mean, however, that the laboratory lost its importance, quite the reverse. It remained the obligatory site for the confirmation of field work and of epidemiological findings. If, for practical reasons, the slogan "isolate the microbe" was often replaced by "eradicate the vector", laboratory investigation of both the aetiological agents and their vectors remained central to the investigations in tropical medicine. The new tropical medicine was based on this new alliance between field-work and laboratory.

One should be careful not to confuse the renewed interest in epidemiological observations and in ecological studies around 1900 with the older style of epidemiological observations, inherited from early nineteenth-century medicine and observable in the works of such self-taught Latin American bacteriologists as Lacerda or Nuno de Andrade. These physicians superimposed the new bacteriological

[63] Stepan, op. cit., note 41 above. Stepan's interesting and well documented book studies, however, solely the development of scientific institutions, and does not deal with cognitive aspects of the development of Brazilian medical science.

[64] J. Ben David, 'The implantation of scientific tradition in developing countries', *Minerva*, 1977, **15**: 303–5.

[65] F. Delaporte, 'La fièvre jaune, 1880–1900', paper given at the Colloqium on the History of the Pasteur Institute, Paris, 6–11 June 1988.

knowledge on their traditional vision of infectious diseases. They continued to view these diseases as unique events which depended on so many variables that, in fine, they could be fought only by general and unspecific means. In contrast, the new generation of investigators in tropical medicine, which, in Nuno de Andrade's words, followed only the ideas which were in congruence with the present state of science and which had rejected the century-long experience of investigations in epidemiology, aimed at understanding the general rules governing the complex host(s)/parasite relationships in every given disease. The essential endeavour of scientists in tropical medicine was, exactly as in "classical" bacteriology, the search for specific causes of every particular disease, and for specific ways to fight it. The fumigations, the quarantines, and the burning of suspected clothing proposed by Nuno de Andrade were as different from the specific measures designed to destroy the *Stegomyia* mosquito introduced by Cruz, as the application of the anti-diphtheria serum was from the non-specific treatments for "angina" cases in the early nineteenth century.[66]

The French scientists who came to Rio de Janeiro were leading spokesmen for the new tropical medicine. They combined knowledge of the latest laboratory techniques with the experience of field work. They virtually transported a fully-equipped European laboratory to a peripheral country, and demonstrated how it should be used. They conducted epidemiological investigations, and showed how these investigations should be completed by laboratory studies. They showed what the internationally accepted standards of research in tropical medicine were. They were in Brazil long enough to allow a prolonged demonstration of their methods of work, but not long enough to take the place of Brazilian scientists. Finally, the members of the Pasteur Institute Mission had close relationships with the man who originated modern medical research in Brazil—Oswaldo Cruz—and they supported Cruz in a crucial moment of his political struggle: the first stages of his sanitary campaign. All these elements may have been combined in just the right mixture to allow maximal impact of the Pasteur Mission on Brazilian medical science. Other factors helped later to secure the position of the Manguinhos Institute as a leading research institution in tropical medicine: the maintenance of close contacts between Brazilian investigators and European laboratories, the prolonged visits by German scientists to Rio de Janeiro, the impact of the world-wide response to Chagas's discovery, and above all the efficient organization of bacteriology and parasitology teaching which allowed a smooth transmission of knowledge to a new generation of Brazilian scientists. But, at an earlier stage, the transfer of a small island of the "science of the metropolis" to Rio de Janeiro may have played a significant role in initiating the process of professionalization and institutionalization of Brazilian medical science.

[66] See, e.g., C. E. Rosenberg, 'Medical text and social context: explaining William Buchan's "Domestic Medicine",' *Bull. Hist. Med.*, 1983, **57**: 22–42; J. H. Warner, *The therapeutic perspective: medical practice, knowledge and identity in America, 1820–1885*, Cambridge, Mass., Harvard University Press, 1986.