Metchnikoff and Syphilis Research during a Decade of Discovery, 1900–1910*

Development of an animal model and a preventive treatment set the stage for progress

RICHARD M. KRAUSE

Syphilis research during the first decade of this century in many ways parallels the first decade of research during the AIDS epidemic. Despite 30 years of research following the discovery of microbes as the cause of several other diseases, by the dawn of the 20th century the best and the brightest had failed to make headway on the bacteriology of syphilis. No implicated microbe had been discovered. No diagnostic test had been developed, and there was no animal model. Indeed, for several decades it was believed that syphilis was only a disease of humans. Ignorance on these matters is just where we were at the beginning of the AIDS epidemic: no infectious agent, no diagnostic test, no animal model, and certainly no treatment.

There is a major difference, of course, between the history of syphilis then and the history of AIDS now. Syphilis had been raging for four centuries. While AIDS likely slumbered in rural Africa for many years, only in the 1980s did it spread rapidly into the large cities of Africa, and then elsewhere, as a consequence of population migration, urbanization, and the deterioration of social, community, and medical services.

Initially AIDS in the United States was primarily a sexually transmitted disease among homosexual men. However, I predicted as early as 1982 that it would become a heterosexual epidemic because population groups with different sexual orientations mix at their margins. Not all gays are only gay; not all straights are only straight. Hence, a disease that had become an epidemic among homosexuals was bound to spread into the general population—at least the segment that takes risks with sexual behavior. In this past decade we have seen a pandemic of AIDS emerge like wildfire, east and west, north and south. For most of the world, this is a heterosexual disease. We can now better appreciate the desperation of Europeans first confronting the explosive epidemic of syphilis 400 years ago.

A Decade of Discovery in Syphilis Research

Cautious optimism at the dawn of this century held that the new sciences of bacteriology and immunology would bring syphilis under control. In large measure, these hopes were answered, and the Russian bacteriologist Elie Metchnikoff played an important role in this happy conclusion.

Several important discoveries proved key in the fight against syphilis during the first decade of this century. For instance, in 1903, Metchnikoff and Pierre Roux transmitted the "virus" responsible for causing syphilis to chimpanzees. A little later, two Italians succeeded in producing syphilitic lesions on the testicles and scrota of rabbits, and about this same time lesions were produced in the cornea. Soon thereafter, in 1905, Fritz Schaudinn and Erich Hoffman identified the culprit spirochete in infectious material from a human chancre. They used a staining technique that had been employed for malaria.

Also in that decade, August von Wassermann began research on a diagnostic test for syphilis based on the use of serum from infected patients. He had been working on a serologic test for tuberculosis, but he was

Richard M. Krause is senior scientific advisor at the Fogarty International Center, National Institutes of Health, Bethesda, Md.

*This article is based on Richard Krause's lecture at the 1995 ASM General Meeting in Washington, D.C.

urged to take on the more pressing task of developing a test for syphilis. The tubercle bacillus had been discovered, and the tuberculin test was already available. While this procedure was far from ideal, Wassermann nevertheless shifted his attentions to syphilis. He developed the complement fixation test, and thereafter, a legion of serologists modified it. Indeed, by 1930 there were 10,000 papers in the literature on the Wassermann test. Perhaps no other test has so exasperated laboratory workers, unless it is the Kjeldahl.

Later, during that first decade, Paul Ehrlich began an intensive search for a treatment for syphilis. He had become disenchanted with vaccines for bacterial infections other than those for toxins such as diphtheria. Recall that the efforts to produce typhoid, meningococcal, and pneumococcal vaccines had been unsuccessful. So Ehrlich began a search for antimicrobial chemical compounds, and this effort led after many trials to 606, or salvarsan, for the treatment of syphilis. For all of these reasons the first decade of this century can truly be called a decade of discovery for syphilis research.

In 1900, 16% of the Paris population was infected with syphilis.

Early Research in the Face of a Serious Epidemic

How serious was the syphilis epidemic in 1900? In Paris, 16% of the population was infected. The British Medical Association noted that between 1880 and 1887 the number of men incapacitated with syphilis tripled. Mortality statistics collected by the insurance companies revealed that 11% of deaths were due to syphilis.

Metchnikoff in his 1906 London lectures on *The New Hygiene,* summarized his work on syphilis, including transmission of the disease with human-infected material to the chimpanzee and prevention of the disease after inoculating a man on the penis with infectious material collected from a human chancre. Applying calomel to the inoculation site was preventive. For centuries there had been hundreds of attempts to prevent syphilis after exposure, including cauterizing chancres after they developed. But this procedure did not prevent subsequent development of secondary and tertiary lues, the late complications of the infection including paresis and heart disease.

With no animal model to study the disease, Metchnikoff and Roux reinvestigated this problem. Despite many earlier attempts to inoculate various classes of vertebrates with infectious material from patients with syphilis, results had been negative. From time to time, however, a few experimental animals developed something that resembled syphilitic lesions. For instance, Auzias-Turenne in 1866 reported syphilitic papules and mucus patches in a cat. Later reports described positive lesions in guinea pigs. But because of these variable and unsatisfactory results, some investigators resorted to using primates. One early report in 1882 from Martineau claimed positive results, but this work was not followed up. There are also many negative reports in the literature from this period.

Because of variable results with monkeys, in 1903 Metchnikoff and Roux began testing chimpanzees and soon demonstrated their susceptibility to syphilis. Furthermore, they demonstrated that syphilis can be transmitted from one chimpanzee to another. The "virus" was inoculated either onto the eyebrows or on the genital organs of the animals. The next step was to determine if calomel or other treatments could prevent the development of syphilis lesions. According to the literature, calomel was a potentially useful treatment for syphilis, but results were not conclusive. They massaged an ointment of calomel and lanolin for 5 min on the inoculation site anywhere from 1 to 24 h after the inoculation. Following such treatments, infections were aborted and no syphilitic lesions appeared during subsequent observations, Roux and Metchnikoff reported.

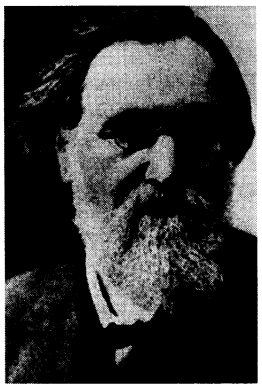
Studies Move from Chimpanzees to Humans

The first experiment to prevent the development of syphilis in a man after inoculation of infectious material soon followed. Paul Maisonneuve, a young medical student in Paris, read about Roux and Metchnikoff's procedure for preventing syphilis in chimpanzees. Late in 1905, he asked Metchnikoff and Roux to test the procedure on him.

They hesitated but then agreed, and on 23 January 1906, a physician examined the student before the experimental inoculation. All was normal except for vesicles of herpes on the mucosal surface of the foreskin, an indication that he was sexually active. On 1 February, he was inoculated with infectious material. To determine whether the material was indeed infectious, a macaque monkey was inoculated on the left eyebrow. One hour after infectious material from a chancre had been inoculated onto the student's penis, the site was rubbed for 5 min with calomel ointment (10 g of,calomel, 30 g of lanolin; full-strength calomel was known to be irritating). A physician examined the student periodically for the next several months. No local lesions were noted except an exacerbation of the prior herpes. The last complete physical examination on 8 May revealed no evidence of syphilis. Meanwhile, the inoculated macaque monkey developed luetic lesions indicating that the inoculum was infectious. A full account of these experiments along with a review of the literature became Maisonneuve's doctoral thesis.

There was a good deal of medical controversy following reports of this result. Max Neisser attempted to repeat it, but was unsuccessful. However, he also could not produce syphilis in monkeys, perhaps indicating his inoculation material was not viable. Some critics noted the data were limited to a single case report, hardly sufficient to justify the use of calomel for routine treatment following sexual intercourse or accidental

exposure to syphilitic material in laboratories, autopsy rooms and clinics.



Metchnikoff

Metchnikoff, himself not a physician, understandably was not inclined to experiment further on humans. He had "proof of principle" to his satisfaction with the prevention studies in chimps. Probably the "green-light pro-stations," which all World War II soldiers were urged to visit for treatment after sojourns to red-light districts, and the widespread use of prophylactic kits, had their historical origins in these early experiments of Metchnikoff and Roux.

This, then, was the beginning of chemotherapy for syphilis, but it was soon overshadowed by the research of Paul Ehrlich on the success of salvarsan and the treatment of syphilis. But then, of course, such measures were soon overshadowed by "Queen Penicillin" as it was called by World War II GIs after it was introduced in *1945.*

Immune therapy for treatment and prevention of infectious diseases was coming into vogue in that early decade, and Metchnikoff also tried his hand at these matters. He attempted to use passive immune therapy to prevent syphilis in chimpanzees by treating them with antiserum prepared in monkeys and goats. When this effort was unsuccessful, he speculated that the antiserum was too weak to provide protection. He was successful in neutralizing the infected material if it was mixed with antiserum prior to challenge.

In Vienna during the first decade of this century, Karl Landsteiner and E. Finger attempted unsuccessfully to treat a patient with syphilis with convalescent-phase serum. In retrospect, this failure is not surprising. They had no idea about the spirochete burden (antigenic load) in the patient or the potency of the antiserum. Landsteiner, after migrating to the United States from Vienna, became one of the towering giants at the Rockefeller Institute for Medical Research, later receiving the Nobel Prize as one of the founders of modern immunochemistry.

What about active immunization with an attenuated strain of the "virus," misnamed because the spirochete had not yet been identified? Metchnikoff had attempted to do so by passage of the "virus" in rhesus monkeys. He believed that attenuation occurred after several passages. If an attenuated syphilis vaccine were developed, to whom should it first be given? Metchnikoff answered his own question: "sexual beginners and prostitutes."

On the matter of sexual education for the young, Metchnikoff was outspoken. For example, during *The New Hygiene* lectures, he declared: "It has been said that syphilis spreads because the young folk are ignorant of the great danger they are running into," and therefore they should be taught what we would call safe sex. "Young boys and girls should be given some information about venereal diseases. More detailed information on the question might be given in higher grade schools. But these suggestions have been ignored. Providing information about the risk of unsafe sex will be difficult. We all know that in spite of having been adequately warned, young doctors and students of medicine furnish a large portion of victims of syphilis. Ignorance is therefore not the only cause."

Metchnikoff also grappled with all-too-familiar issues of morality:

> Many people believe that the measures that limit the spread of syphilis will in fact increase promiscuity and encourage vice. They say it would be better to let the disease spread freely. I am not about to discuss the morality of those who acquire this evil by sexual intercourse. But are not many victims absolutely innocent, and have the right to be protected? Persons who look upon prophylaxis of syphilis as immoral should apply the same reasoning to the use of antiseptics in midwifery, because it facilitates criminal abortion. If this paradox were carried through to the bitter end, one might have opposed not only the prophylaxis, but also any treatment of syphilis. Many geniuses infected with syphilis have produced remarkable works of the creation in which this terrible excitement caused by the disease has undoubtedly played an important part. It is easy to recognize in Schumann, Nietzche, and others, the morbid influence of their general paresis.

Metchnikoff pointed out that despite knowledge, "young doctors and students of medicine furnish a large portion of victims of syphilis."

How all of this rings true even today in the age of AIDS. All of these issues of sexuality, hygiene, morality, and prejudice are as bitterly debated now as they were about syphilis during the decade of discovery, 1900 to 1910.

In truth, it should be said that Metchnikoff's excursion into the problem of syphilis was in many ways a diversion, a useful and pragmatic one to be sure, but a diversion nonetheless. His work on the chimpanzee model for syphilis and the calomel treatment can in no way be compared to his monumental research on developmental biology and the role of leukocytes in the phagocytosis of microbes. This observation laid the foundation for cellular immunology.

Indeed, this work began a bitter controversy between the antibody enthusiasts, Ehrlich, Robert Koch, Emil von Behring, and others, and the cellularists led by Metchnikoff. The controversy between humoral and cellular immunologists simmered for decades even after Almroth Wright and Stewart Douglas in 1906 staked out "common ground" for both contenders with the discovery of opsonins that "buttered up the bacte-

ria"-to use Shaw's phrase in *The Doctor's Dilemma*—so that they were more readily phagocytized. In 1906, the Nobel Committee put the matter in perspective by awarding the Nobel Prize to both Ehrlich and Metchnikoff.

And yet the research of Metchnikoff on syphilis stands as a brilliant beacon in the decade of discovery. Subsequent progress in syphilis research was dependent upon the experimental model for syphilis in chimpanzees, which gave consistent and predictable results. Paul Ehrlich himself recognized this contribution. In the foreword to *The Experimental Chemotherapy of Spirilloses*, published jointly with Sahachiro Hata in 1910, Ehrlich recalled the many colleagues and assistants, both outside and inside his institute, who had helped to further the cause of chemotherapy. They wrote as follows: "We are indebted to Schaudinn, Roux, Metchnikoff and Wassermann for the fact that success has been attained in the particular field of syphilis. Experimental chemotherapeutic research only became possible with the identification of the causative agent of the disease and with the development of a method for its transmission to animals." cl

Suggested Reading

Baumer, E. 1984. Paul Ehrlich, scientist for life. Holmes and Meier Inc., New York.

Bibel, D. J. 1989. Santayana's warning unheeded: the parallels of syphilis and acquired immune deficiency syndrome (AIDS). Sex. Transm. Dis. 16:202.

Fleck, L. 1979. Genesis and development of a scientific fact. T. T. Trenn and R. K. Merton (ed.). University of Chicago Press, Chicago.

Krause, R. M. 1991. Syphilis during 1900-1910; similarity to present day AIDS. Allergy Proc. 12:2, 127.

Maisonneuve, P. 1908. The experimental prophylaxis of syphilis. F. De Verteuil (ed.). William Wood & Co., New York.

Metchnikoff, E. 1906. The new hygiene; three lectures on the prevention of infectious diseases. William Heinemann, London.