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HISTORY A woodcut from the late 1490s, left, depicts a man infected with syphilis, and an engraving from 1689 shows people being treated for the disease.

Sheila Terry/Photo Researchers (left); National Library of Medicine/Photo Researchers

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Genetic Study Bolsters Columbus Link to Syphilis

By John Noble Wilford

Columbus, it seems, made another discovery of something that he was not looking for.

In a comprehensive genetic study, scientists have found what they say is the strongest evidence yet linking the first European explorers of the New World to the origin of sexually transmitted syphilis.

The research, they say, supports the hypothesis that returning explorers introduced organisms leading, in probably modified forms, to the first recorded syphilis epidemic, beginning in Europe in 1493.

The so-called Columbus hypothesis had previously rested on circumstantial evidence, mainly the timing of the epidemic. It was further noted that earlier traces of syphilis or related diseases had been few and inconclusive in Europe. Yet nonvenereal forms of the diseases were widespread in the American tropics.

Leaders of the new study said the most telling results were that the bacterium causing sexually transmitted syphilis arose relatively recently in humans and was closely related to a strain responsible for the nonvenereal infection known as yaws. The similarity was especially evident, the researchers said, in a variation of the yaws pathogen isolated recently among afflicted children in a remote region of Guyana in South America.

Researchers who conducted the study and others familiar with it said the findings suggested Columbus and his men could have carried the nonvenereal tropical bacteria home, where the organisms may have mutated into a more deadly form in the different conditions of Europe.

In the New World, the infecting organisms for nonvenereal syphilis, known as bejel, and yaws were transmitted by skin-to-skin and oral contact, more often in children. The symptoms are lesions primarily on the legs, not on or near the genitals.

Kristin N. Harper, a researcher in molecular genetics at Emory University who was the principal investigator in the study, said the findings supported "the hypothesis that syphilis, or some progenitor, came from the New World."

The examination of the evolutionary relatedness of organisms associated with syphilis was reported on Monday in the online journal Public Library of Science/Neglected Tropical Diseases.

Ms. Harper, a doctoral student in the Emory department of population biology, ecology and evolution, was the lead author. Her co-authors included George J. Armelagos, an Emory anthropologist who has studied the origins of syphilis for more than 30 years, and Dr. Michael S. Silverman, a Canadian infectious diseases physician who collected and tested specimens from yaws lesions in Guyana, the only known site today of yaws infections in the Western Hemisphere.

The researchers said their study "represents the first attempt to address the problem of the origin of syphilis using molecular genetics, as well as the first source of information regarding the genetic makeup of nonvenereal strains from the Western Hemisphere."

They applied phylogenetics, the study of evolutionary relationships between organisms, in examining 26 geographically disparate strains in the family of *Treponema* bacteria. *Treponema pallidum* subspecies *pallidum* is the agent for the scourge

of venereal syphilis. The subspecies *endemicum* causes bejel, usually in hot, arid climates, and *pertenue* spreads yaws in hot, humid places.

Della Collins Cook, a paleopathologist at Indiana University who did not participate in the study but specializes in treponemal diseases, praised the research as a “very, very interesting step” advancing understanding of syphilis. “They have looked at a wider range of the genome” of these bacteria, Dr. Cook said, “and have scared up some new samples from parts of the world and the group of related diseases that hadn’t been available to researchers before.”

But she recommended an even broader investigation of the natural history of these diseases, making an effort to find more people with active treponemal cases where they probably still exist in parts of South America. Cases of yaws in Africa and Asia are periodically reported.

John W. Verano, an anthropologist at Tulane, said the findings would “probably not settle the debate” over the origins of venereal syphilis, though most scientists had become convinced that the disease was not transmitted sexually before Europeans made contact with the New World.

Donald J. Ortner, an anthropologist at the Smithsonian Institution, questioned whether the organisms causing the first European epidemic were actually distinct from others in the treponemal family. “What we are seeing is an organism with a long history, and it is very adaptable to different modes of transmission that produce different manifestations,” Dr. Ortner said.

Three medical scientists, responding to the new study, pointed out what they considered shortcomings in its methods and interpretations.

In a critique also published by the online journal, Connie J. Mulligan of the University of Florida, Steven J. Norris of the University of Texas at Houston and Sheila A. Lukehart of the University of Washington wrote that caution “must be used in drawing conclusions about the evolution of ‘subspecies’ that may represent a biological continuum, rather than discrete agents.”

“Firm conclusions should not be based,” for example, on the two samples from one location in Guyana, they added.

But scientists generally agreed that the molecular approach would overcome some limitations of other investigations.

Paleopathologists like Dr. Cook have for years analyzed skeletons for the bone scars from lesions produced by treponemal diseases, except for the mild form called pinta. In this way, they traced the existence of these infections in the New World back at least 7,000 years. But it has often been difficult to determine the age of the bones and distinguish the different diseases that share symptoms but have different modes of transmission.

Dr. Cook said the skeletal evidence for treponemal disease in pre-Columbian Europe and Africa was sketchy and even more ambiguous than in the New World. In the 1990s, scientists reported finding bones in Italy and England, from before Columbus’s return, that bore lesion scars that they said appeared to have been caused by venereal syphilis.

Scientists remain skeptical of this interpretation. If highly contagious venereal syphilis had existed in Europe in antiquity, said Dr. Armelagos, the Emory anthropologist, there should be more supporting epidemiological evidence than two or three skeletons bearing suggestive scars.

In her investigation, Ms. Harper studied 22 human *Treponemal pallidum* strains. The DNA in their genes was sequenced in nearly all cases, examined for changes and eventually used in constructing phylogenetic trees incorporating all variations in the strains.

An Old World yaws subspecies was found to occupy the base of the tree, indicating its ancestral position in the treponemal family, she said. The terminal position of the venereal syphilis subspecies on the tree showed it had diverged most recently from the rest of the bacterial family.

Specimens from two Guyana yaws cases were included in the study, after they were collected and processed by Dr. Silverman. Genetic analysis showed that this yaws strain was the closest known relative to venereal syphilis.

Ms. Harper’s team concluded that New World yaws belonged to a group distinct from Old World strains, thus occupying the place on the tree more likely to be intermediate between the nonvenereal strains previously existing in Europe and the one for modern syphilis.

If this seemed to solidify the Columbus hypothesis, the researchers cautioned that a “transfer agent between humans and nonhuman primates cannot be ruled out using the available genetic data.”

Dr. Armelagos said research into the origins of syphilis would continue, because “understanding its evolution is important not just for biology, but for understanding social and political history.”

Noting that the disease was a major killer in Renaissance Europe, he said, “It could be argued that syphilis is one of the important early examples of globalization and disease, and globalization remains an important factor in emerging diseases.”