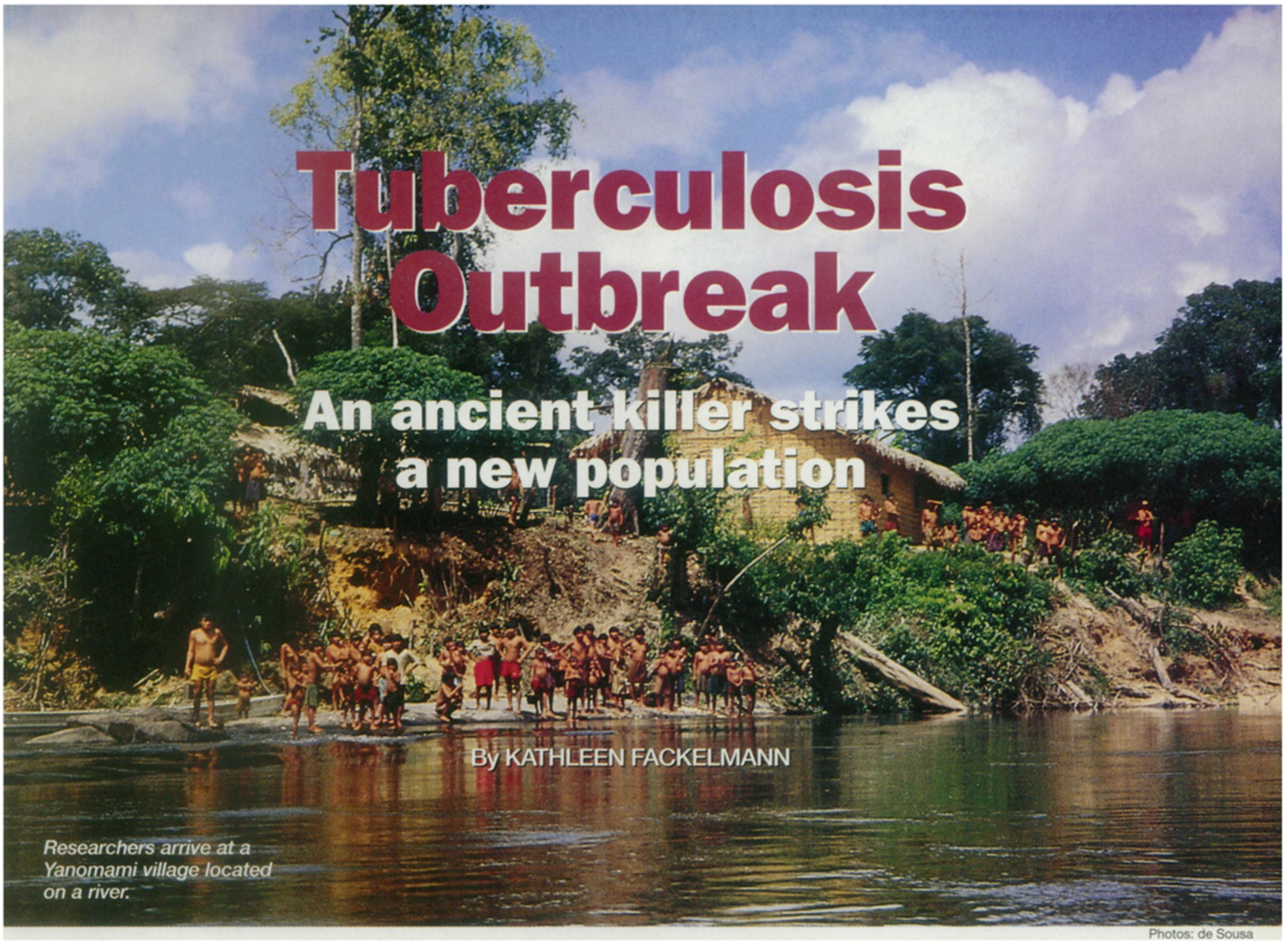


Tuberculosis Outbreak

An ancient killer strikes a new population

By KATHLEEN FACKELMANN

Researchers arrive at a Yanomami village located on a river.

Photos: de Sousa

The discovery of gold in Brazil in the 1980s sent an estimated 40,000 miners rushing into the heart of the Amazon rain forest. There, they encountered the Yanomami Indians, an indigenous population that had very rarely encountered outsiders.

The miners brought with them such 20th-century accoutrements as guns and plastic. They also brought an age-old plague—tuberculosis. *Mycobacterium tuberculosis*, the organism that causes tuberculosis, swept through the Yanomami like wildfire.

Epidemics are not unusual when indigenous populations first encounter Europeans. This time, however, there was a new twist.

The tuberculosis produced such atypical symptoms that doctors initially had no idea what was killing the Yanomami. They thought a lethal pneumonia might be responsible.

Now, researchers have documented for the first time the toll tuberculosis is taking on these people. The report is also one of the few to describe an initial outbreak in a population.

The findings suggest that an unusual immune reaction to *M. tuberculosis* increased the Indians' vulnerability. In fact, the researchers say, the Yanomami demonstrate how the human immune system first responded to *M. tuberculosis* eons ago.

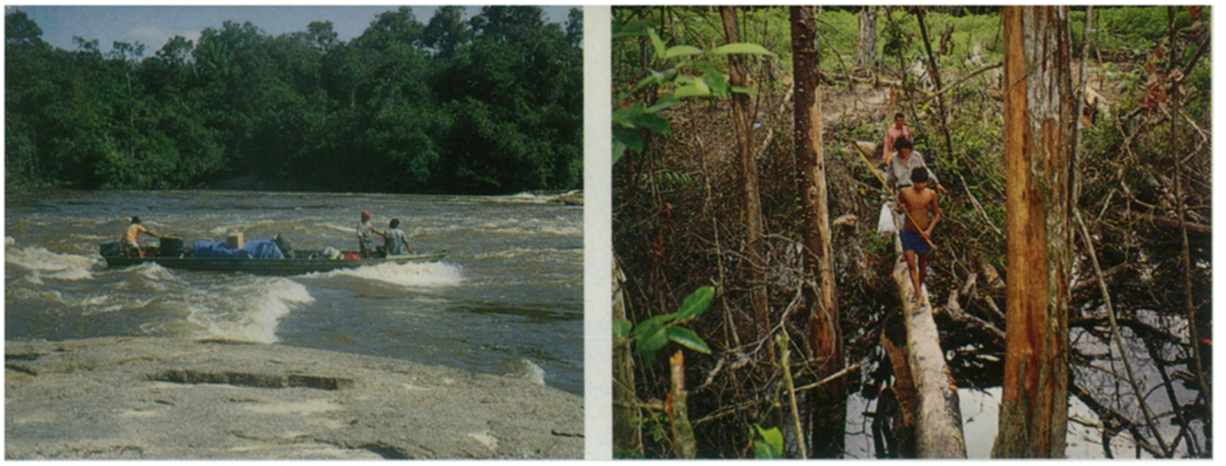
Yanomami teenagers use decorative body paint and feathers to attract members of the opposite sex.

"This is probably the last time we will see a worldwide disease like tuberculosis arriving for the first time," says Alexandra O. de Sousa of the Howard Hughes Medical Institute (HHMI) at Albert Einstein College of Medicine in New York. She and her colleagues report their findings in the Nov. 25, 1997 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

"This is the first really good study of the situation," comments James V. Neel, a geneticist at the University of Michigan Medical School in Ann Arbor who has studied the Yanomami population.

In 1992, de Sousa and her colleagues began their arduous journey into the rain forest. They boarded a boat in Manaus for a 5-day trip up the Black River. From there, they embarked on a 2-day canoe trek to the remote region where the Yanomami have lived for centuries.

The goal of their research project, funded in part by the



Alexandra O. de Sousa's team traveled for about a week on remote rivers in the Amazon to reach the territory of the Yanomami Indians. To get to some inland villages, the researchers had to hike through the dense rain forest or even travel by helicopter.

Brazilian Health Department, was to determine the extent of the tuberculosis outbreak among the Yanomami. During the 3-month study, de Sousa and her colleagues examined 625 Yanomami in five villages scattered throughout some 900 acres of forest. They did skin and blood tests, a physical exam, and checked sputum for *M. tuberculosis*.

Forty of the Indians had active tuberculosis, a prevalence of 6.4 percent, which is "astronomically high," says coauthor Barry R. Bloom, also of HHMI at Albert Einstein. "That rate is as high as any epidemic of tuberculosis that I know about," he adds.

The researchers knew that the first recorded case of tuberculosis in the Yanomami occurred in 1965 and was probably contracted from a researcher or one of the few other outsiders who reached the remote territory. But it wasn't until the 1980s gold rush that the illness really caught hold, creating an epidemic.

Tuberculosis in the Yanomami seems to run an unusual course, de Sousa says. The Indians quickly develop high fevers and become very ill, in contrast to North American or European patients, who usually suffer a low-grade fever, weight loss, and a cough—symptoms that can persist for years.

The Yanomami Indians live in crowded huts. One infected person comes in close contact with many others, thus facilitating the spread of tuberculosis.

The researchers note that the Yanomami suffer from a form of tuberculosis that was common in medieval Europe but is rare in the United States and Europe today. The condition is called scrofula, an infection of the lymph nodes in the neck, which produces sores on the neck and face. Shakespeare mentions this unsightly condition in *Macbeth,* de Sousa says.

What could explain the way the Yanomami respond to *M. tuberculosis*? De Sousa, an immunologist by trade, decided to look more closely at the immune system of the Yanomami. Her team had performed tuberculin skin tests on 556 Yanomami. A positive skin test indicates that an individual has been exposed to *M. tuberculosis*.

The test also measures the response of T lymphocytes, a type of white cell, to *M. tuberculosis*. A successful attack on *M. tuberculosis* requires the mobilization of T cells and the cytokines they manufacture. This mobilization is called cell-mediated immunity.

People with an active cell-mediated response to *M. tuberculosis* develop a characteristic welt when given the tuberculin skin test. Surprisingly, only 50 percent of the Yanomami actively infected with *M. tuberculosis* had a positive skin test. If a similar test were performed on North Americans or Europeans, about 90 percent of those actively infected would test positive, Bloom says.

These findings suggest that in many cases, the Indians' T cells don't effectively rout *M. tuberculosis*, which multiplies in immune cells called macrophages. The T cells seem to react sluggishly or not at all to this microbial threat.

Even more curious, when de Sousa and her colleagues drew blood, they found that compared to Brazilians of European ancestry, the Yanomami have higher concentrations of antibodies, immune proteins directed against *M. tuberculosis*.

White cells called B lymphocytes help produce antibodies as part of the body's

Egyptian Mummy Reveals Tuberculosis

Tuberculosis is a disease with a very long history, one that has been difficult to piece together with the standard tools of the pathologist.

In 1994, Arthur C. Aufderheide and his colleagues at the University of Minnesota in Duluth used a new molecular technique to identify traces of *Mycobacterium tuberculosis* DNA in a 1,000-year-old Peruvian mummy (SN: 8/30/97, p. 136).

Now, a German team has found molecular evidence of this microbe in a 3,000-year-old Egyptian mummy—the oldest such evidence of tuberculosis in any population, says Andreas G. Nerlich of Ludwig Maximilians University in Munich. He and his colleagues describe the finding in the Nov. 8, 1997 LANCET.

The researchers discovered the linen-wrapped body in a tomb at Thebes-West, an ancient city on the Nile River. A pathological examination showed evidence of tuberculosis infection in the right lung, Nerlich says.

To confirm the diagnosis, the researchers removed samples of tissue from the lungs and extracted DNA from them. They searched for a particular stretch of DNA that is common to several microorganisms, including *M. tuberculosis*. Nerlich and his colleagues found the target DNA in tissue from the mummy's right lung. They then matched that stretch of DNA to one in *M. tuberculosis*.

To make sure the samples had not been contaminated with *M. tuberculosis*, the researchers also tested tissue from the mummy's unaffected left lung and lung tissue taken from modern people without the disease. They found no evidence of *M. tuberculosis* in those controls.

Nerlich and his colleagues plan to determine how widespread tuberculosis was in ancient Egypt. Their research already suggests that *M. tuberculosis* might have affected more Egyptians than previously believed—they have unpublished molecular evidence of *M. tuberculosis* in five additional mummies at the same burial site. —*K.F.*

humoral immunity. Antibodies neutralize microbes and toxins circulating in the bloodstream. They are helpless when faced with a bacterium like *M. tuberculosis*, which is sequestered in the body's cells, de Sousa points out.

The Yanomami's reliance on antibodies probably represents an ancient method of fighting off microorganisms.

"If our speculation is right, this would be how naive man would respond to a bug that is global now," Bloom says.

A Yanomami elder entreats his ancestors to save the village from tuberculosis.

Tuberculosis is an age-old killer (see sidebar). Early in human history, tuberculosis was only a sporadic problem. For much of that time, people lived in small, isolated groups. Tuberculosis needs a large base of people crowded together in order to spread efficiently.

During the Industrial Revolution, however, tuberculosis exploded into a full-fledged epidemic in Europe, says William W. Stead of the Arkansas Department of Health in Little Rock. At that time, workers crowded into filthy, makeshift cities, where *M. tuberculosis* and other nasty microbes quickly made their way from person to person.

Infected people spread *M. tuberculosis* by coughing or sneezing. Microscopic droplets may contain the organism, which, if inhaled, can cause the disease in another person.

Tuberculosis ripped through the population, killing one-third of those infected, usually at a young age. Immunologists believe that people who survived the plague must have had a vigorous, cell-mediated immune response.

Over generations, people of European descent became relatively resistant to *M. tuberculosis*. Those who survived may have passed down a gene or genes that promote a vigorous T cell defense against the bacterium, Stead says. Today, such people fight off the bug and don't develop the disease.

"[Tuberculosis] has been a major factor in shaping the evolution of the human genome," Bloom suggests.

Consider, then, the plight of the Yanomami. *M. tuberculosis* has, in epidemiological terms, just arrived. Moreover, the Indians have an immune system ill-equipped to handle the bug, says Stead, author of a study on the origin and global spread of tuberculosis that appeared in the March 1997 CLINICS IN CHEST MEDICINE.

The Yanomami have no way to change their genome. They can, however, take advantage of medicine's progress against tuberculosis.

The Brazilian government and other groups are treating the Yanomami with standard drugs against *M. tuberculosis*. There is nothing different about the bacterium itself, so an aggressive drug campaign should help stem the tide of tuberculosis deaths in the Yanomami, de Sousa says.

Still, successful treatment might be difficult for the Yanomami, who move frequently in search of food. Drugs to combat tuberculosis must be taken for 6 months, de Sousa notes.

Even if tuberculosis is contained, the Yanomami face other dangers to their health. The miners also brought malaria to the rain forest, says Jose Roberto Borges of the Rainforest Action Network, an environmental and human rights group based in San Francisco. What's more, the Yanomami must contend with mercury poisoning of their water supply, he adds. "All of that poses a very serious threat to their survival."

M. tuberculosis continues to wage war, not just against the Yanomami, but against all peoples, notes biologist Christopher Wills of the University of California, San Diego. The recent emergence of drug-resistant strains of *M. tuberculosis* means that people who get the illness in the future may be harder to treat. Furthermore, as people continue to crowd into cities, *M. tuberculosis* may once again come to the fore.

Wills elaborated on the increasingly precarious relationship between *M. tuberculosis* and people in *Yellow Fever, Black Goddess: The Coevolution of People and Plagues* (1996, Reading, Mass.:Addison-Wesley).

"A lot of diseases that really do depend on people's proximity to one another might be in for quite a resurgence," says Wills. □