Iowa City. The authors, who used magnetic resonance imaging (MRI) to compare the brains of living apes and humans, also suggest that the size of the frontal lobe relative to that of the overall brain has not changed significantly during human evolution, contrary to popular evolutionary models. "The myth has been that we have these big, big frontal lobes," says anthropologist Ralph Holloway of Columbia University in New York City, who predicted in 1964 that the human frontal lobe was not enlarged. "Now, we'll have to look at something else" to explain what is special about the human brain.

Semendeferi began her study as a graduate student a decade ago, when she was surprised to find that only a few isolated studies supported the notion that the frontal cortex was enlarged in humans. "There were almost no comparative data on the great apes," she recalls. So she and Damasio, her postdoctoral mentor, scanned the brains of a few living humans and dead zoo apes with MRI. When they found that the human frontal lobe was not enlarged, they met with so much skepticism, including criticism about comparing living and dead tissue, that they expanded their study. They scanned 10 living humans and enlisted the help of Tom Insel at Yerkes Regional Primate Research Center in Atlanta to scan 19 living apes—chimpanzees, bonobos, gorillas, orangutans, and gibbons.

They compared the size and volume of the overall brain as well as both hemispheres (halves of the forebrain), frontal lobes, temporal lobes, cerebellums, and other regions. The result: The frontal lobes make up 36.8% of the hemispheres in humans, compared with 34.9% in bonobos, 34.8% in chimpanzees, 35.1% in gorillas, and 36.3% in the orangutan. The gibbon was the only standout—its frontal lobes account for only 28.4% of its hemispheres. And the cerebellum is smallest in humans—only 11.2% of the brain—and largest in the gorilla—16.1% of the brain. That was surprising, too, because arboreal species like orangutans were expected to have the largest cerebellum, a structure involved in balance. The findings imply that our ape ancestors devoted the same proportion of their brains as we do to the frontal lobe, notes Semendeferi.

The results also dovetail with studies suggesting that other brain structures, such as the neocortex, scale up as expected in large-brained animals such as apes, dolphins, and elephants. "The bottom line is that humans' brains are perfectly predictable," says Barbara Finlay, a developmental neuroscientist at Cornell University in Ithaca, New York. "They're large, but they scale up like they are supposed to for their body size." **–ANN GIBBONS**

MEETING GENOMES 2000

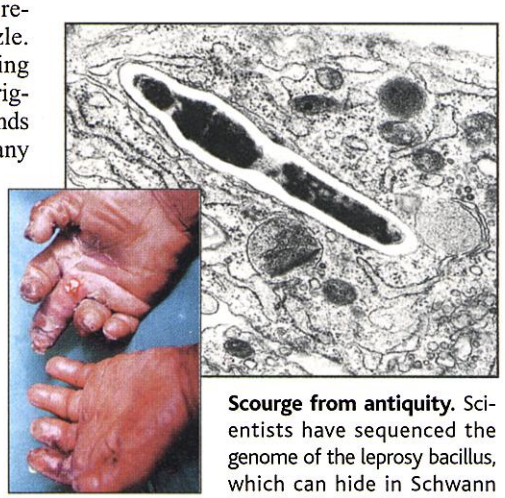
# Intimate Portraits of Bacterial Nemeses

**PARIS—Attendance was limited to 600, but that didn't stop geneticists who gathered here 11 to 15 April from creating a big buzz over a dozen bacterial genomes unveiled at a meeting sponsored by the Institut Pasteur and the American Society for Microbiology. Among the highlights were a peek at leprosy's blighted genome and a heartening tale behind the sequencing of a nasty plant pathogen.**

## Leprosy's Dying Genome

Even though it has been disfiguring and stigmatizing people since the dawn of civilization, leprosy remains a scientific puzzle. Nobody is sure how the slowest growing bacterial pathogen spreads, or how it triggers the gruesome degeneration of the hands and feet that for centuries doomed many victims to leper colonies. And although *Mycobacterium leprae* was the first bacterium linked to a human disease, more than a century later it's still impossible to grow in the test tube. Now, this mysterious microbe's genetic code has been laid bare to reveal yet another conundrum: The bacterium has one of the most blighted genomes ever seen, with vast stretches of "junk" DNA and hundreds of genes that no longer function. Scientists are hoping that this genetic wasteland will provide some new leads on how to combat leprosy. "We've waited for this for a long time," says microbiologist Anura Rambukkana of The Rockefeller University in New York City.

A chronic infectious disease that affects the peripheral nerves, the skin, and the upper respiratory tract, leprosy, also called Hansen's disease, still flourishes in developing countries such as India, Brazil, Indonesia, and Myanmar, where more than 750,000 people contract the disease each year. Scientists think the rod-shaped bacterium spreads through the air or through direct contact, entering the body via the mucosal linings of the nose or through open wounds. From there it somehow infiltrates Schwann cells, which insulate nerves. The bacterium can hide there for years without causing symptoms. Eventually, the body's immune system attacks the infected Schwann cells, destroying the nerves in the process. Accompanying the telltale sensory loss are secondary infections that whip the immune system into a frenzy. Under siege, soft tissues and even bones become degraded, particularly in the limbs and digits.



**Scourge from antiquity.** Scientists have sequenced the genome of the leprosy bacillus, which can hide in Schwann cells *(above)* for years before causing crippling disfigurement.

CREDITS: ANURA RAMBUKKANA

Like other leprosy researchers, a team at the Institut Pasteur in Paris, in collaboration with the Sanger Centre in Cambridge, U.K., resorted to growing *M. leprae* in a rather unusual "test tube": the nine-banded armadillo, a critter whose cool body temperature appears ideal for the bacterium. (*M. leprae* can also be grown poorly in the footpads of mice.) This provided the raw material for a 5-year sequencing effort.

The researchers found a depauperate genome, half of which appears devoid of genes, says Institut Pasteur's Stewart Cole. On closer inspection, he and his colleagues found that most of the so-called junk DNA consists of more than 1000 degraded genes whose functions were lost in the course of evolution. Although noncoding DNA makes up less than 15% of the genomes of most bacteria studied so far, it accounts for half of *M. leprae*'s genome. Compared to the closely related *M. tuberculosis*, with which it shares a common ancestor, *M. leprae* appears to have lost more than its degraded genes. The genome of *M. tuberculosis* is a third bigger than that of *M. leprae*, suggesting to researchers that the leprosy bug has lost an additional 1000 genes, including ones coding for enzymes used in energy production and for DNA replication. Cole thinks this massive gene loss has crippled

the leprosy bacillus, which would explain its slow growth rate—its population doubles in mice only every 2 weeks, compared to hours for most other bugs. *M. leprae*, it would seem, has few working genes to spare. "I think it is on its way out," says Cole.

What genes are left, however, may lead to new tools for fighting the bug. Cole's group has spotted some 100 genes that have no counterpart in *M. tuberculosis*. If any code for a unique protein on *M. leprae*'s surface, identifying that protein could enable researchers to develop a simple skin-prick test for detecting an infection early. Being able to treat patients with a course of three drugs before symptoms begin, says Cole, "may prevent nerve damage, which would make leprosy a rather harmless skin disease, something like acne." And learning how leprosy triggers nerve loss may offer clues to multiple sclerosis and other common neurodegenerative diseases. "My guess is that the initial events are very similar," says Rambukkana.

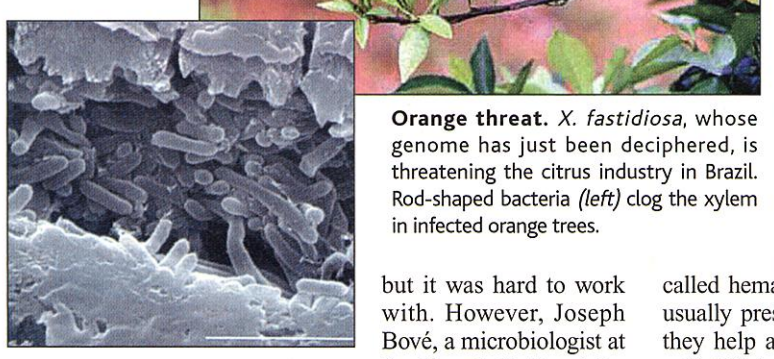
## A Genome Cinderella Story

In 1987 orange growers in the Brazilian state of São Paulo first noticed the telltale signs of a new disease: conspicuous yellow patches on individual leaves. The fruits on these spotted trees turned out to be small, hard, and gave little juice, rendering them commercially useless. Today, citrus variegated chlorosis (CVC)—as the disease is known—threatens the entire citrus industry in São Paulo state, the world's largest exporter of concentrated orange juice. The disease affects more than 30% of all trees and causes losses estimated at $100 million each year.

Now scientists have a new tool to attack this devastating microbe. On 12 April a team reported at the meeting that they had deciphered the 2.7-million-base-pair genome of *Xylella fastidiosa*, the causative agent. *X. fastidiosa* is the first bacterial plant pathogen ever to be fully sequenced. What's more, the feat was pulled off not by one of the sequencing superstars in the United States or Europe but by a consortium of some 30 labs in São Paulo state—groups with little or no previous genomic expertise.

This coup earned the Brazilian scientists ample praise from their international peers. Raves biochemist André Goffeau of the École Normale Superieure in Paris: "The quality [of the sequence] is superb. It's incredible how fast they've done it, given that 2 years ago they didn't even have the [sequencing] machines." The *X. fastidiosa* genome "is quite a big deal," says Edwin Civerolo, a plant pathologist with the U.S. Department of Agriculture (USDA) who works at the University of California, Davis. Indeed, the work is so impressive that the USDA and the state of California have just enlisted—to the tune of $250,000—the Brazilian team to sequence a related strain of *X. fastidiosa* that causes Pierce's disease and is threatening vineyards across California.

The *X. fastidiosa* genome project was conceived in 1997 when Fernando Perez, scientific director of the State of São Paulo Research Foundation (FAPESP), a state-run public funding agency, became concerned about the lack of genomics research in Brazil. After consulting some of Brazil's top life scientists, Perez and his scientific advisers decided that Brazil should embark on its own genome project. But what to sequence? Given its economic impact, *X. fastidiosa* was a logical choice, but it was hard to work with. However, Joseph Bové, a microbiologist at the French National Institute for Agricultural Research in Bordeaux, whose team was among the first to identify the CVC pathogen in plant material from Brazil, convinced them to try.



**Orange threat.** *X. fastidiosa*, whose genome has just been deciphered, is threatening the citrus industry in Brazil. Rod-shaped bacteria *(left)* clog the xylem in infected orange trees.

Rather than follow the U.S. model and set up a few supercenters for sequencing, Perez suggested a diffuse approach: a "virtual genome center" of more than 30 labs. He admits that this may not have been the most cost-effective approach—the project cost more than $13 million—"but it wasn't designed to be cheap or quick. The main goal was to create a broad competence in the field of molecular genetics in Brazil," says Perez, and the foundation apparently achieved it. More than 30 sequencing machines were up and running by May 1998, and by January 2000 the job was done; the work has now been submitted for publication.

At the meeting, geneticist Andrew Simpson of the Ludwig Institute of Cancer Research in São Paulo and one of the coordinators of the project provided a first peek into the inner workings of this agricultural pest. On its single circular chromosome, *X. fastidiosa* harbors some 2800 potential genes, half of which have been assigned a putative function. From these and others yet to be identified, the scientists hope to discover how *X. fastidiosa* wreaks its havoc.

A common theory is that the microbe clogs up the xylem tubes in orange trees and thus starves the affected branches and leaves of water and other nutrients. Some of the new evidence seems to support that view. Explains Simpson: "The biosynthetic machinery [for producing essential cell components] is fairly complete, and there are a lot of nutrient-sequestering and energy-providing genes. That's what you'd expect for a bacterium that lives in the rather nutrient-poor xylem." The team has also found genes that produce an extracellular "gum" that may help stick the bacteria together and, eventually, clog the xylem tubes or help attach the bacteria to the foregut of sharpshooter leafhoppers that transmit the bacterium by feeding on xylem sap. These, speculates Goffeau, "may be promising targets for new antimicrobials."

An unexpected find were genes for surface molecules called hemagglutinins and adhesins that are usually present in animal pathogens, where they help anchor the microbe to the target cell. "This suggests that this hardware is very well conserved within pathogens across a broad host range, and that only the software, or the details, change," says Simpson.

Buoyed by this success, FAPESP is expanding its genome efforts beyond *X. fastidiosa* and the collaboration with USDA. The agency is now supporting efforts to sequence snippets of genes that are active in various human cancers, as well as the genomes of sugarcane and several other plant pathogens. Says Simpson, "Agricultural genomics is crucial for an agricultural country like Brazil—and it's a research area where almost by omission we are now world leaders."

–MICHAEL HAGMANN

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