eign companies and organizations with sufficient sequencing power, Chinese authorities want to extend existing rules on foreign access to the country's human genetic materials to cover all organisms. Xu Xinlai, head of the MOST bioengineering center, which supervises the ministry's high-tech enterprises and drafts related regulations, says the new rules will uphold the idea that "resources have monetary values" and that China is entitled to its fair share. Under the draft, which has not been made public, Xu says that "if a foreign commercial company wants to make use of China's genetic resources, it has to do it through collaboration with a Chinese partner. The resources to be used should be considered as a kind of investment."

MOST began drafting the new regulations earlier this year in response to concerns raised by Chinese scientists when GeneCore was acquired by PE Corp., Celera's parent company. Yang says Chinese scientists were "alarmed" when Celera's president, J. Craig Venter, announced in January that the deal will "provide access to" many new sources of genetic information. "The intention expressed in Celera's wording is very obvious—to monopolize our country's genetic resources," says Yang. "We need foreign collaborations and even fair competition. But such collaboration and competition should abide by Chinese law."

Celera spokesperson Paul Gilman says Celera has no intention of monopolizing resources: "The only thing that we would negotiate is something that is satisfactory to all parties."

In addition to the effort to sequence part of the human genome and the planned project to sequence China's key organisms, China has already begun deciphering the genome of its staple crop, rice. While an international consortium is working on the Japonica variety (*Science*, 1 October 1999, p. 24), China has pursued a different strain, Indica, grown throughout China and in most of the rest of rice-eating Asia. CAS's Hong says that parallel sequencing of the two rice varieties "provides a unique way to understand their functions." The decision to work on Indica was made early in 1992 at the beginning of the rice genome project. Since then the mapping and sequencing have been sticking with this strain.

With the government committed to raising its investment in genomics, the debate over how to distribute limited funds is likely to remain fierce. But China's research community appears increasingly confident that it will be able to keep up with the rest of the world. "Some scientists see Celera as a hungry wolf," says Chen. "But China is not as weak as it was 5 years ago. We should have confidence in our current capacity." **–LI HUI**

Li Hui writes for *China Features*. Additional reporting by Elizabeth Pennisi.

MEETING AMERICAN ASSOCIATION OF PHYSICAL ANTHROPOLOGISTS

# From Field to Lab, New Insights on Being Human

**SAN ANTONIO—More than 1100 researchers gathered for the 69th Annual Meeting of the American Association of Physical Anthropologists here, presenting a record 665 papers. Analyses ranged from field reports to lab experiments, including a genetic study of the evolution of a deadly gene, a description of a rare hominid fossil, and brain scans comparing humans and other apes.**

## Tracing the Genealogy of a Deadly Gene

If there were a Most Wanted list of common deadly genes, the apolipoprotein E (*APOE*) gene surely would be near the top. In its most dangerous form, this gene increases the risk of cardiovascular disease and Alzheimer's disease. Ever since geneticists discovered that there are three types of *APOE* proteins—the worst is known as *E4*—scientists have wondered where and when the killer variant arose. Now a powerful piece of evolutionary sleuthing presented at the meeting reveals the ancestry of the gene's three forms. An international team found that the dangerous *E4* type was inherited from our apelike ancestors and has given rise in the past 300,000 years to the two less harmful forms of the gene, *E3* and *E2*. *E3* is now moving through the world's populations and replacing the deadlier form. "We've actually caught a gene in the process of being changed to a favorable type," says S. Malia Fullerton, a population geneticist at Pennsylvania State University, University Park, and a member of the team headed by genetic epidemiologist Charles Sing at the University of Michigan Medical School in Ann Arbor.

The group also found that each of the three types of *APOE* has many variations, which may help explain why people who have inherited the *E4* type have different degrees of risk for developing heart disease or Alzheimer's. "This shows that it's important when we do these assessments of risk that we do not just use these simplistic three types," says pathologist George Martin of the University of Washington (UW), Seattle, who hopes that better diagnostic tests can now be developed.

The gene has been a target since 1985, when researchers found that people with the APOE4 protein have a higher risk of heart disease than those who inherit the other two types. In 1993, researchers linked *E4* to Alzheimer's (*Science*, 13 August 1993, p. 921), and soon after found that chimps only have *E4*. That sparked much debate about which type of *APOE* was ancestral, because *APOE3* is most common today.

To answer that question, the team sampled 96 people from four populations and began massive sequencing, done by UW geneticist Debbie Nickerson, of a 5491–base pair region of the gene on chromosome 19. When the team organized the sequences into a tree where the most similar sequences clustered together, they found 31 distinct subtypes of DNA that sorted into the three major types of *APOE*. Each of the variants within the three types preserves the genetic code necessary to produce one of the three *APOE* proteins, but the sequence varies in other regions. Those changes may subtly affect the way the *APOE* proteins are regulated and expressed, and may help explain why in some populations, such as African Americans, those with *E4* get Alzheimer's less than expected.

"It's ground-breaking that they did large-scale sequencing of a long stretch of DNA on so many people," says human population geneticist Jeffrey Long of the National Institutes of Health. Although geneticist Allen Roses's group at Glaxo Wellcome in Research Triangle Park, North Carolina, also has found variation at the DNA level within the three seemingly simple *APOE* types (*Science*, 15 May 1998, p. 1001), this new report also traces, step by step, the DNA changes that led from *E4* in the chimpanzee to *E3* and *E2*, and proves that *E4* was the ancestral form of the gene.

The limited variation within the *E3* and *E2* haplotypes shows that they emerged fairly recently, sometime in the past 300,000 years, according to a molecular clock based on the apparent rate of divergence between human and chimp. The good news, says Fullerton, is that the new and less dangerous *E3* type seems to be under selection pressure, as it is spreading most rapidly. Martin speculates that *E4* may have persisted for millions of years in human ancestors, offering some advantage, perhaps

against parasites.

One intriguing idea is that *E4* slows the rate at which lipids such as cholesterol are delivered to pathogens. That could have been an advantage against trypanosomes that cause African sleeping sickness, as the parasite must suck up cholesterol in a few hours to survive. Now that the gene's evolutionary history is revealed, Martin and colleagues plan to test such ideas, using mice bred to express the different types of *APOE*.

## "Little Foot" Hominid Gets a Hand

In December 1998, researchers announced a spectacular discovery: the nearly complete skeleton of a 3.3-million-year-old australopithecine from a South African cave (*Science*, 1 January 1999, p. 9). The skeleton was known as Little Foot because its foot was found first—in a box in a storeroom—but it is now the most complete ancient hominid known, even more complete than its Ethiopian contemporary, the famed Lucy fossil. Anthropologists have been eagerly awaiting news of the rest of its anatomy, and to their delight ex-

**Handyman.** "Little Foot's" hand and arm suggest that it had more manual dexterity than apes and didn't knuckle walk.

cavator Ron Clarke of J. W. Goethe University in Frankfurt, Germany, showed his hand, so to speak, in San Antonio.

Clarke presented slides of what is the only complete hand and arm of an early hominid—still partly encased in rock—and noted that its short palm and fingers look quite modern. Although his analysis is preliminary, Clarke concludes that Little Foot did not knuckle walk like living apes, but walked upright while also spending some time feeding and sleeping in the trees. "The old concept of having us come out of a knuckle walker is not borne out by this skeleton," Clarke told the audience.

But not all of his listeners were convinced, because even if Little Foot didn't knuckle walk, its ancestors—not to mention human ancestors—might have (*Science*, 24 March 2000, p. 2131). "It's not a knuckle walker, but I don't see how you can tell what kind of creature it evolved from," says paleoanthropologist David Begun of the University of Toronto in Canada.

Little Foot entered the modern world foot first, as Clarke discovered its left foot and ankle in 1994 while picking through a box of animal bones from the Sterkfontein grotto in a University of the Witwatersrand storeroom in Johannesburg, where he was then director of field operations. Chimplike characters, such as a slightly divergent big toe, imply that this hominid spent some time in the trees as well as on the ground, according to Clarke and Phillip Tobias of the University of the Witwatersrand (*Science*, 28 July 1995, p. 521). Two years later Clarke found more bones of the skeleton in another box, including a partial shinbone. Incredibly, 2 days later his team returned to the dark cave with the shinbone and found a lower leg and foot that fit perfectly; soon after they found a skull and almost all the skeleton. The team is now chipping away the breccia that encases the skeleton, which has been dated to 3.3 million years ago using reversals in the Earth's magnetic field and associated animal fossils.

Last July, Clarke partially prepared the hand and arm. Although he could not measure the fossils still in rock, he says that all five metacarpals and some of the phalanges of the hand are short, like those of humans, and don't resemble the elongated finger and palm bones other apes use to move through trees or stabilize themselves while knuckle walking. The ancient hominid's long, powerful thumb also looks modern and may suggest more manual dexterity. The forearm also appears shorter than the long arms needed in knuckle walking.

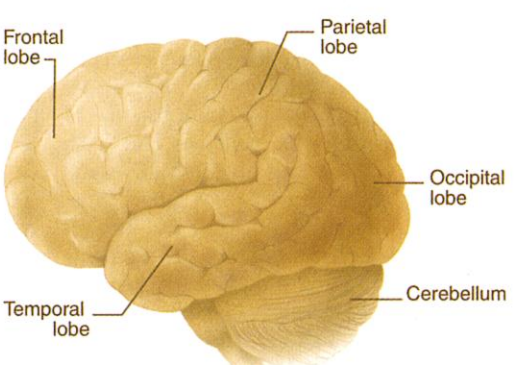
But evidence that Little Foot also spent some time in the trees comes from its grasping, primitive foot, and from the phalanges in the hand, which are curved in a way that differs from humans and resembles the hand bones attributed to Lucy's species, *Australopithecus afarensis*. Clarke suggests that both hominids gripped tree branches. He argues that this shortened hand is a primitive trait in australopithecines (and was therefore present in human ancestors), and that other apes' long hands are specialized for knuckle walking.

Those who saw Clarke's presentation say the skeleton, which may be a new species, is an interesting mix of modern and primitive traits—although there is debate about how primitive the foot is. "Both the hand and foot show intermediacy between an arboreal ape and bipedal hominid," says Elwyn Simons of Duke University. "It is evidence of how we moved from one stage to another."

## Human Frontal Lobes Sized Right

Ever since the Greeks portrayed gods, artists, and poets with large foreheads to signify intelligence, the frontal lobe—the portion of the brain situated just behind the forehead—has been seen as the mark of a highly evolved person. Indeed, brain-mapping studies have shown that it is the seat of creativity, decision-making, working memory, and planning—in short, of the characters that make us human. So it was no surprise when anatomists studied human and chimp brains early this century and concluded that the human's frontal lobe occupied a larger percentage of its brain than did the chimp's. "It has almost been received wisdom that the frontal lobe is enlarged in humans," says paleoanthropologist Dean Falk of the University at Albany in New York.

Now, however, a new comparative study finds nothing disproportionate about the frontal lobe in humans. Although humans do have larger brains for their bodies than other primates, no particular section of the brain is swollen. Rather, all large parts of the brain scale up proportionately—except for the cerebellum, which is actually smaller than expected, according to a presentation by anthropologist Katerina Semendeferi of the University of California, San Diego, and neuroscientist Hanna Damasio of the University of Iowa in




**Sizing up.** Most parts of the human brain, including the frontal lobe, scale up as expected when compared to the brains of other apes.

CREDITS: R. CLARKE

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

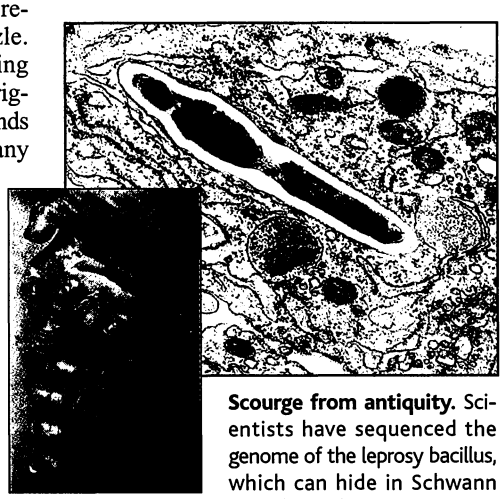
# Intimate Portraits of Bacterial Nemeses

**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