DNA SEQUENCING

Genome of TB Culprit Deciphered

CAMBRIDGE, UNITED KINGDOM—A collaboration of European laboratories has unraveled the complete sequence of the organism responsible for one of the world's biggest scourges, tuberculosis. The sequence, announced last month, was unusually hard to decipher because of peculiarities in the TB genome. It should open new approaches to fighting the disease, which is estimated to kill 3 million people annually. "We have been waiting for a long time for a major advance in tackling this disease," says epidemiologist Paul Fine of the London School of Hygiene and Tropical Medicine.

The organism that causes the disease, *Mycobacterium tuberculosis*, presents a challenge because it is difficult to grow in the lab. "That has led to mycobacterial research lagging behind other fields," says immunologist Gilla Kaplan of Rockefeller University in New York City. "Completion of the sequence pushes *Mycobacterium* research into the mainstream," she says.

Britain's Wellcome Trust, which helped support a successful effort by some of the same researchers to sequence the genome of brewer's yeast (*Science*, 26 April 1996, p. 481), announced backing for projects to sequence *M. tuberculosis* along with the malaria parasite in April last year. Although the *M. tuberculosis* genome is not large, at 4.41 million base pairs, it has some troublesome peculiarities. The organism's gene sequence includes many regions rich in just two bases—guanine and cytosine—out of the four that encode gene sequences in DNA. "Overall, the genome is 65% GC-rich regions, but some parts are as high as 80% to 85% GC-rich," says Julian Parkhill, a sequence analyst at Wellcome's Sanger Centre near Cambridge. This imbalance causes the DNA strand to curl into complex and tortuous secondary structures, which hamper the normal cloning technology used in sequencing.

As a result, the project, headed by Bart Barrell of the Sanger Centre in collaboration with a group led by Stewart Cole at the Pasteur Institute in Paris, initially started as a pilot to determine if such regions could be sequenced reliably. "We were pushed to the limits of current technology," says Parkhill. But the team found that the difficult regions could be sequenced using shorter fragments with considerable effort, so the pilot project became a full-scale sequencing project.

The approach could aid efforts to sequence other genomes. For instance, says Parkhill, "we can also use the lessons learned to help with the human genome, which has specific GC-rich sequences." TB researchers, for their part, are excited at the new prospects opened up by the genome sequence. "Research on the bacterium will now become much more interesting and imaginative," says Kaplan.

Some researchers foresee near-term payoffs in medicine—for example, ways to distinguish the TB organism from the many closely related but innocuous species of *Mycobacterium* that can cross-react with TB tests. "I hope one of the earliest outcomes of the genome project will be the development of more sensitive diagnostic tools which can distinguish between *M. tuberculosis* antigens and those of its relatives," says Fine. Ken Duncan, manager of Action TB at the British pharmaceutical company Glaxo Wellcome in Stevenage, also sees the potential for new therapies. "We now know the sequence of every potential drug target and antigen. It's an enormous boost," he says.

–Nigel Williams

ARCHAEOLOGY

Kennewick Man: More Bones to Pick

Last week, scientists added another bit of bone to the skeleton of Kennewick Man, the oldest, most complete—and most disputed—ancient human from the Pacific Northwest. A partial rib of the 9300-year-old skeleton was found when independent scientists, Native Americans, and the Army Corps of Engineers cooperated in a limited study of the Columbia River beach where the other remains were recovered. But the chip of rib, like everything else connected to this ancient American, is a bone of contention. With the rest of his skeleton, it has been locked away in a vault, pending the outcome of a suit filed by a group of scientists against the corps for the right to study the remains (*Science*, 11 July 1997, p. 173).

Kennewick Man's new bone is the latest twist in a strange saga that occasionally verges on farce, as various groups vie for access to his bones and history. Since the skeleton's discovery about a year and a half ago on corps land leased to the city of Kennewick, archaeologists have longed to study the skeleton, which reputedly has "Caucasoid" rather than modern Native American traits. Native American groups, however, regard the skeleton as the remains of an ancestor, and they want it given to them for burial under the 1990 Native American Graves Protection and Repatriation Act (NAGPRA). Citing NAGPRA, the corps has limited scientists' access to the skeleton, forcing them to subsist on rumors about its significance and even its authenticity—while both Indians and latter-day Norse pagans have visited it.

J. CHATTERS

Disputed territory. Scientists were allowed only limited work along the beach where Kennewick Man was found.

The newest addition to the skeleton, a 2-centimeter-square piece of rib, was found along the reservoir's beach by James Chatters, an independent archaeologist who led the original recovery of Kennewick Man in July 1996. Chatters was part of the weeklong, three-team effort coordinated by the corps to study the site's geology and archaeology.

The rib joins three other bones that have been added to the skeleton since its discovery—and at least one does not belong to Kennewick Man. According to corps spokesperson Nola Conway, the other bones turned up during two corps surveys of the site this past year, done with members of the Umatilla Tribe. A metatarsal, cervical vertebra, and pubis bone were found and put in the vault, says Conway. The Native Americans, in keeping with their beliefs, also put incense cedar boughs in the box with the bones.

All this came to the attention of scientists last fall via newspaper accounts, after members of the Asatru, a group of Norse pagans who claim Kennewick Man was a descendant of early Norse in North America, were allowed to visit their putative ancestor. The scientists criticized the corps for possibly harming the skeleton, saying that moisture from the cedar boughs might

damage the bones.

The corps then called in two scientific curators—Michael Trimble, the corps' chief of curation, and Madeleine Fang of the Hearst Museum of Anthropology at the University of California, Berkeley—to inventory and repackage the bones. They found that Kennewick Man now has three pubis bones, says Conway—which means that one doesn't belong to the original skeleton.

Newspaper accounts—a key source of information about Kennewick Man these days—cited corps sources as saying that the extra bone was among the original material handed over by Chatters. That prompted rumors of sloppy research and even suspicions that the original skeleton collected by Chatters was a hoax, concocted from various remains, several archaeologists told *Science*. Asked for clarification, Conway told *Science* "this [pubis] bone was not part of the original material collected by Chatters and turned over to the corps." Rather, the extra bone was gathered during the later surveys.

The latest round of research began when Gary Huckleberry, a geoarchaeologist at Washington State University in Pullman, and a team of independent scientists including Chatters asked to study the sedimentary environment of the site. Huckleberry wanted to dig a trench, 1.5 meters deep and 15 to 30 meters long, to understand the skeleton's geologic context. The Umatilla Tribe opposed the digging, saying that the site is a cemetery and is culturally sensitive. The tribe then filed its own research plan to search for artifacts by screening sediments. And the corps decided to investigate the age of the sediments, says Lillian Wakeley, a corps geologist from the Waterways Experiment Station in Vicksburg, Mississippi, who oversaw last week's project.

Wakeley described the group effort as "one big hug," but Huckleberry's crew says their research was limited and that they were not allowed to dig a trench. "Hug, schmug," says Chatters. The corps geologists did confirm that the age of the sediments supports the radiocarbon date for the skeleton, but the Native Americans failed to uncover any relevant artifacts.

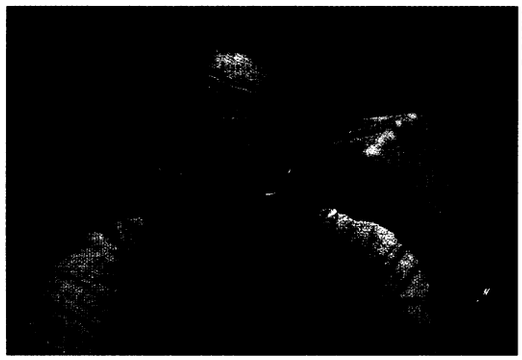
Chatters estimates that the skeleton is now 90% to 95% complete. Any chance of recovering the few remaining pieces are slim, however. Corps spokesperson Dutch Meier says that sometime in early January, the corps will cover the beach with an undisclosed quantity of rock to protect it from further erosion. The site is "not getting the kind of rigorous study" it deserves, laments Robson Bonnichsen, director of the Center for Study of the First Americans at Oregon State University in Corvallis. "And now they're going to bury it."

–Virginia Morell

AGRICULTURAL RESEARCH

Midlife Crisis Threatens Center for Semiarid Crops

PATANCHERU, INDIA—Twenty-five years ago, the industrialized world launched an effort to improve prospects for the 850 million people living under harsh conditions in the semiarid tropics in Africa and Asia. Their goal in establishing the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) here was to transform production of the region's chief subsistence crops—sorghum, pearl millet, chickpea, pigeon pea, and groundnut—in the same way the Green Revolution had transformed the cultivation of wheat and rice. But few of ICRISAT's scientists are in a mood to celebrate the institution's silver jubilee, which was marked last month. Indeed, this fall an external review noted somberly that "senior staff are hesitant in recommending ICRISAT as a place to work."



P. BAGLA

At the helm. Barghouti likens ICRISAT to "a ship with a broken engine being steered in muddy waters."

It's not hard to see why. A severe budget shortfall (see graph) has triggered massive staff cuts and raised concern about organizational deficiencies. Those problems, in turn, led to a thorough house cleaning of senior management this summer. The turmoil comes on top of persistent criticism that the institute has had too little impact on the practices of local farmers, despite a gene bank of 110,000 plant varieties and its success in developing a fast-growing, high-yield hybrid of pigeon pea. Ironically, the crisis comes amid forecasts that the arid regions are spreading and that climate variability poses an increasing threat to productivity.

The crisis is real, admits Director-General Shawki M. Barghouti, a Jordanian agronomist who took the helm on 1 September. "ICRISAT today is akin to a ship with a broken engine being steered in muddy waters where the going is certainly not easy," says Barghouti, who succeeded James Ryan, an Australian agricultural economist who left in July after a 6-year tenure.

ICRISAT's scientists admit that the turmoil is making it harder to stay on task. "Protecting their positions takes up most of their effort. As a consequence, they have little time to do innovative research," says Yeshwant Nene, a plant pathologist and senior ICRISAT official who retired last year. Surinder Mohan Virmani, an agro-climatologist who survived the layoffs, estimates that a 50% cut in his research budget has set him back a year. If the situation does not improve soon, he says, "long-term research could suffer drastically."

Some of the problems facing ICRISAT are familiar to other members of the Washington, D.C.–based network known as the Consultative Group on International Agricultural Research (CGIAR), which includes ICRISAT. For example, the International Rice Research Institute in Los Baños, the Philippines, laid off 576 workers this year, most of them administrative staff, after it lost about a quarter of its $30 million budget. The center in Mexico City that pioneered the development of high-yielding varieties of wheat and maize (CIMMYT) also imposed large layoffs this year after budget cuts. "These older institutions of the CGIAR system were doing traditional research and had collected a lot of flab over the years. Some downsizing was essential to make them lean and efficient," says Virender Lal Chopra, a plant geneticist at the Indian Agricultural Research Institute (IARI) in New Delhi and vice chair of CIMMYT's board of trustees.

But ICRISAT's woes go beyond the need to streamline its operations and are not amenable to quick fixes, say those who have reviewed its activities. Its challenge is in some ways greater than that of the centers that nurtured the original Green Revolution, because it deals with a broader range of crops—called "orphan crops" because they are mainly grown by subsistence farmers and have little commercial value—and serves a diverse eco-region. (Besides its Indian headquarters, ICRISAT operates half a dozen research stations in central Africa and small programs in Latin America and Australia.)

Experts say a sharper focus over the years on fewer varieties more applicable to local conditions would have helped. "ICRISAT