clues, they say. The sequence, posted online by the Michael Smith Genome Sciences Centre in Vancouver, Canada, on 12 April and 2 days later by CDC, confirmed what researchers had gleaned from a few small snippets of the genome a week earlier: The new coronavirus does not fit into any of the clusters but is in a new one by itself.

That leaves wide open the question of where the virus came from. Experiments in animals co-infected with two coronaviruses have shown that as many as 50% of newly formed virus particles are the result of a recombination, and some researchers have suggested that the new virus, too, is a hybrid. But if that's true, neither of the two progenitor viruses is known, Enjuanes says—nor is it clear how such a recombined virus would end up in humans if neither of the parent viruses infects people.

Another possibility is that the virus has been infecting one animal species for a long time—perhaps without causing noticeable disease—and accidentally jumped to humans, where it found a favorable environment. If so, the animal host may be difficult to find, says Snijder. Researchers know only about a dozen coronaviruses because they haven't looked much beyond domestic animals and humans. "We may well find a coronavirus in every mammalian or avian species we look at," says Snijder.

The heavy economic toll that animal coronaviruses have inflicted on agriculture has led to vaccines for several types, some of them based on killed vaccine, others on weakened, live viruses. That's "encouraging," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, because it suggests that SARS, too, might be contained by a vaccine. But there are pitfalls as well, Rottier says. A live vaccine to prevent feline infectious peritonitis is controversial, he notes: Many researchers think it predisposes cats to more serious disease.

Developing a vaccine may become crucial because it seems increasingly unlikely that the disease can be stamped out by rigorous isolation of patients. As *Science* went to press, Hong Kong was reporting ever-growing numbers of patients, along with the rest of China. Nor is there any sign that SARS is becoming less virulent as it spreads from one human to another, a phenomenon that is believed to have prevented uncontrolled spread of other zoonotic diseases. But how serious the pandemic could become is anyone's guess.

Coronavirologists, who have sometimes found it hard to get funding, say they regret the human toll but welcome the attention for their field. And there's another bright side, says Rottier: When he tells people he's working on coronaviruses, he doesn't get that blank stare anymore. **–MARTIN ENSERINK**

With reporting by Gretchen Vogel in Berlin.

Anthrax

From Bioweapons Backwater to Main Attraction

Anthrax researchers, like experts on coronaviruses (see above story), find themselves thrust into a new environment

NICE, FRANCE—As they strolled in from the mellow French Riviera sun to the conference desk at the chic Boscolo Plaza Hotel to collect registration packs and satchels—compliments of IGEN International Inc.—one thing was clear to the attendees of the 5th International Conference on Anthrax, which began here late last month: Anthrax research ain't what it used to be. The last time they all got together was in June 2001 at a small liberal arts college in Annapolis, Maryland, where they shared a picnic on the lawn and slept in dormitory rooms for $20 a night. This time around, everyone has enjoyed sumptuous three-course lunches and a banquet—compliments of BioPort Corp. in Lansing, Michigan—and many have stayed at the Boscolo for $167 a night.

Fewer than 4 months after that 2001 meeting, the United States became the victim of the first intentional use of anthrax as a bioweapon since World War I. As a result, an enormous amount of attention and money has been focused on the causative agent, the bacterium *Bacillus anthracis*. "It's a completely different field now," says Stephen Leppla, a molecular biologist who leads an anthrax research group at the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland. NIAID's budget for anthrax research has ballooned from $3.2 million in 2001 to around $75 million this year.

Patient assassin. Anthrax can lie in wait in the soil for decades until inhaled or eaten by cattle.

CREDIT: KATIE BLUNK/APHIS/USDA

The first fruits of increased funding were on display in Nice, with new progress on vaccines and therapies as well as the basic biology of the anthrax bacterium. In August 2001, says Paul Keim, a veteran anthrax researcher at Northern Arizona University in Flagstaff, "I was being told to prepare for a 20% budget cut." Now he's more concerned about how to deploy the windfall of anthrax funding most efficiently.

Sorting out the basics

Opening the conference's first session, Tim Read of The Institute for Genomic Research (TIGR) in Rockville, Maryland, gave a sneak preview of a tool that many in his audience have eagerly awaited. TIGR finished sequencing the 5.23 million base pairs of DNA that make up the single circular chromosome of *B. anthracis* months ago and has made it available in a fragmented form online. Read provided an overview of the now fully assembled genome, which TIGR says will be published "soon."

With the genetic blueprint of *B. anthracis* known, many newcomers to this fast-growing field assume "that much of the basic work is complete," says microbiologist Paul Jackson of Los Alamos National Laboratory in New Mexico, but "that is just not true." What is known is that *B. anthracis* is a naturally occurring pathogen, mainly of herbivores such as cattle and sheep. It appears to spend its life as a tiny, robust spore waiting in the soil for

years—even decades—before being ingested or inhaled or entering a mammal's body through a wound. Researchers also know that the basic weapons in the anthrax armory—the toxic secreted proteins and the protein capsule that helps the bacterium evade the immune system—are encoded on two plasmids, small loops of DNA separate from the chromosome.

But there are still big gaps to be filled in the bug's molecular biology, says Theresa Koehler, a microbial geneticist at the University of Texas Medical School in Houston. Koehler presented work, done with Agathe Bourgogne in her lab using a DNA microarray developed by Scott Peterson of TIGR, revealing that the way genes regulate anthrax's attack on the body is far more complex than has been assumed. Each of the plasmids toted by *B. anthracis* carries regulatory genes that orchestrate the synthesis of the toxin and capsule proteins. But Koehler has demonstrated that one of these plasmid-based regulators, called *atxA*, controls an unexpectedly broad array of other genes on both plasmids and the chromosome.

Aside from identifying several new genes potentially important in the progress of the disease—and thus drug development—the work may call for a reassessment of both accepted data and standard lab practices. Many researchers, who are unable to meet the strict safety guidelines set for strains containing both plasmids, use a strain containing only the plasmid with *atxA* and the toxin genes on it. This then exempts them from the toughest safety regulations. Such strains are used with the assumption that they are just like the double-plasmid strain but without the capsule. However, Koehler's results reveal this to be too simple, and "for certain investigations employing strains with only one of the two plasmids," she says, "the physiological significance of the results could be questionable."

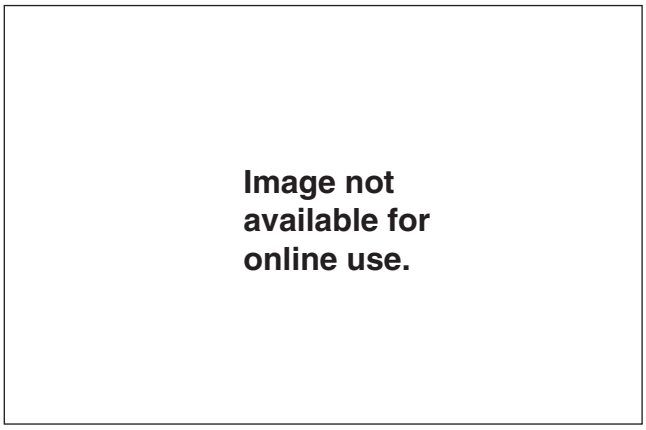
Another strategy for finding new genes important for pathogenesis is to identify those that differ between *B. anthracis* and its already sequenced relatives, the opportunistic pathogen *B. cereus* and *B. thuringiensis*, a harmless bacterium whose insect-killing Bt toxin has been engineered into many crop plants. This analysis is under way at TIGR, and Read reports that their genomes are remarkably similar, but *B. anthracis* appears to have 150 genes that the other two species lack. Drug researchers, intent on finding weaknesses to exploit, are now looking very closely at these genes.

A new urgency

In principle, anthrax infections are easy to treat because the bacteria can be wiped out with antibiotics—as long as they are not resistant. But if too many of the bacterial spores have germinated within the body, it is often too late: They have already begun releasing the toxic proteins that do most of the damage.

One way to save someone with an anthrax infection would be to neutralize these toxin proteins. Rather than synthesize a chemical to do the job, several groups are mass-producing human antibodies that can bind to the toxin and prevent it from making mischief.

Herman Groen, a cell biologist at IQ Therapeutics in Groningen, the Netherlands, has been working on this idea for several years. Human antibodies against anthrax are hard to come by, so Groen tacked up a sign at the 2001 anthrax meeting, promising a "free trip to Holland" for any anthrax researcher who had been vaccinated. Several took him up on the offer, and IQ harvested some of their antibody-producing cells and fused them with cancer cells. The resulting hybrids are living factories, pumping out antibodies that neutralize the toxic proteins. Groen and his colleagues have found that these antibodies protect mice against injected anthrax, and they are now testing their protection of rabbits from inhalational anthrax.



Headline news. The 2001 anthrax attacks put bioterrorism on the public agenda; above, a Greek biohazard team in training.

IQ isn't the only company on this track. Conspicuously absent from the conference was Human Genome Sciences (HGS), another Rockville biotech company. HGS announced on 18 March that it has not only produced human antibodies to neutralize anthrax toxin—a treatment they have named ABthrax—but has already proven their effectiveness in trials with rabbits and monkeys and plans to move soon to human trials to test for any side effects. "They seem to be ahead of everyone at the moment," admits Groen, "but it's not a zero-sum game. Having multiple antianthrax drugs on the market will reduce the chances of people getting killed by the disease, which is always a good thing."

The need for new drugs would be less urgent if everyone could simply be vaccinated to prevent infection, but *B. anthracis* has proved a difficult bug to immunize against. BioPort produces the only licensed anthrax vaccine, called BioThrax, a mixture of harmless proteins from the anthrax bacterium. But it must be taken several weeks before exposure and requires multiple injections over an 18-month period and annual boosters. It is also unknown whether the vaccine can protect against inhalational anthrax, the route of infection that most worries bioweapons experts.

The U.S. National Institutes of Health is funding tests of a new vaccine based on a single protein called protective antigen that is likely to be added to the nation's emergency stockpile (*Science*, 26 April 2002, p. 639). But some groups are pursuing more novel approaches. Darrell Galloway of the Naval Medical Research Center in Silver Spring, Maryland, told the meeting that rabbits can be immunized against inhalational anthrax with a so-called DNA vaccine, although such vaccines have had limited success in the past. Galloway made plasmids carrying DNA encoding two anthrax proteins, including a truncated form of the toxin. When this was injected into rabbits, says Galloway, their own cells took up the DNA, expressed the anthrax proteins, and presented them to the immune system. The method could prove far cheaper and more effective than the traditional method of injecting the proteins themselves.

The flip side of trying to find ways to fight the disease is the danger of doing the opposite. During the last session of the conference, Lance Price, now a microbiologist at Johns Hopkins University in Baltimore, described his work in Keim's lab cultivating anthrax resistant to ciprofloxacin, the antibiotic that is a first line of defense against infection. His conclusion: "It was pretty easy, unfortunately."

The purpose of the work is to develop quick molecular tests for resistance in anthrax, says Jackson of Los Alamos. But it was still controversial to make it public at the time. Such work could, in principle, encourage terrorists to develop nastier strains of anthrax. There's no easy answer for how best to strike the balance between keeping anthrax research open (and useful to scientists) versus closed (and safe from terrorists), but "it is crucial to err on the side of an open research environment," says Keim. "You can view this as a race between us and the terrorist in which you never win, you can just stay ahead."

–JOHN BOHANNON

John Bohannon is a former *Science* intern now based in Lyon, France.

CREDIT: AFP/CORBIS