

# Calling All Coronavirologists

The ongoing epidemic of acute respiratory disease is shining an intense spotlight on one of virology's backwaters

In December, Kathryn Holmes gave a talk at a meeting on respiratory viruses titled "Coronaviruses: How Important?" Although the audience listened politely, Holmes recalls, most would probably have answered the question with "not very." After all, coronaviruses caused serious disease in farm animals and pets but nothing more than the common cold in humans. "It wasn't really on their radar screen," Holmes says.

It is now.

Three weeks ago, studies fingered an unknown new member of the coronavirus genus as the most likely culprit behind SARS, or severe acute respiratory syndrome. Shortly after, the U.S. Centers for Disease Control and Prevention (CDC) flew Holmes, a researcher at the University of Colorado Health Sciences Center in Denver, to Atlanta to give public health experts and scientists a crash course on her field. Like most of the 12 labs that teamed up to identify the cause of SARS, CDC didn't have much experience with coronaviruses, but "they're very quick studies," Holmes assures.

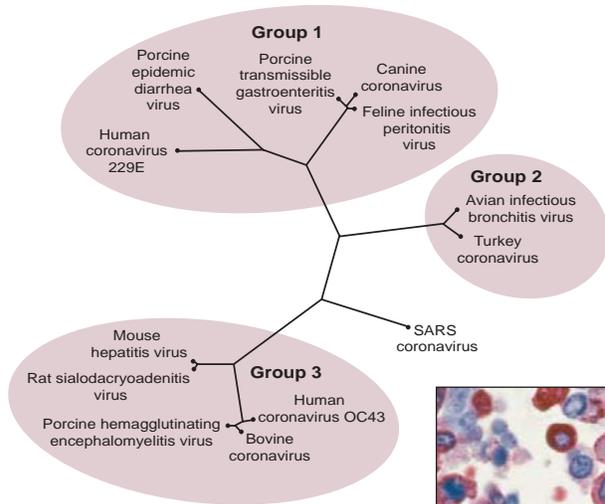
So are others. Hordes of government, academic, and corporate scientists have rushed in to characterize the virus further and test possible drugs and vaccines. Last weekend, a group of Canadian researchers was the first to announce that it had deciphered the new virus's entire genome. All of a sudden, coronavirologists (and their research community) find themselves in the thick of a fast-moving global drama.

It's little less than a culture shock. Accustomed to publishing in specialized virology journals, these virologists are watching *The New England Journal of Medicine* and *The Lancet* rush one paper after another about the epidemic onto their Web sites. The program for a conference about coronaviruses and the related arteriviruses, scheduled for next month in a small seaside town in the Netherlands,\* has been hastily revised, say

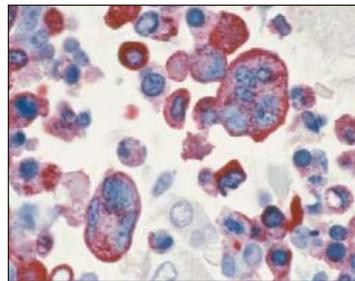
\* www.nido2003.nl

organizers Eric Snijder and Willy Spaan of Leiden University Medical Center. So many new faces are expected beyond the 120 or so regulars at the triannual meeting that hotel rooms are running out.

Many coronavirologists have, like Holmes, helped researchers investigating the outbreak with advice and reagents. Now that the pathogen is coming into view, many want a



**New bug on the block.** Based on the genome sequence, it appears that the new virus associated with SARS (*inset*) is not closely related to any known coronavirus; it has been placed in a new, fourth cluster.



piece of the action and have started to grow and study the virus themselves. Decades of dogged labor and thousands of scientific papers may now pay off when it comes to fighting the outbreak, Holmes says. At Utrecht University in the Netherlands, for instance, Peter Rottier's group has developed several candidate cat coronavirus vaccines; the researchers have also found peptides that block the entry into cat and mouse cells of the feline and murine coronaviruses, respectively. Some of that work may be applicable to the SARS virus, Rottier says.

### Unknown origins

For the moment, researchers are still trying to prove that the new coronavirus really is the cause of the outbreak. The final piece of evidence could come from ongoing experiments at U.S. and Dutch labs, in which monkeys are infected with the virus to see if they develop

SARS-like symptoms. Meanwhile, several of the 12 labs participating in the World Health Organization network (*Science*, 11 April, p. 224) are also trying to determine whether the virus has an accomplice, such as the human metapneumovirus that Canadian researchers first discovered in SARS patients.

But already, the indictment of a coronavirus is a surprising twist in the field's 60-year history. The first coronavirus isolated, in 1937, was the avian infectious bronchitis virus, which can cause devastating disease in chicken flocks. Since then researchers have found its cousins to infect cattle, pigs, horses, turkeys, cats, dogs, rats, and mice. The first human family member was cultivated from nasal cavities in the 1960s, after researchers realized that another group, the rhinoviruses, were responsible for only about half of all common cold infections. Today, the two known human coronaviruses, OC43 and 229E, are thought to cause about 30% of cases, depending on the year.

The viruses themselves are something of an oddity. With a genome of more than 30,000 nucleotides, coronaviruses are relative giants, and they have a complex two-step replication mechanism. Many RNA virus genomes contain a single, large gene that is translated by the host's cellular machinery to produce all viral proteins. Coronaviruses, instead, can have up to 10 separate genes.

Most ribosomes translate the biggest one of these, called replicase, which by itself is twice the size of many other RNA viral genomes. The replicase gene produces a series of enzymes that use the rest of the genome as a template to produce a set of smaller, overlapping messenger

RNA molecules, which are then translated into the so-called structural proteins—the building blocks of new viral particles.

Most coronaviruses cause either a respiratory or an enteric disease, and some do both. But the differences among these types can be small. In 1999, for instance, a team led by Luis Enjuanes of the Autonomous University of Madrid, Spain, showed that just two point mutations can change a mostly enteric virus that can kill piglets into a nondeadly one that excels at the respiratory route but replicates poorly in the gut.

Researchers have grouped coronaviruses into three categories based on cross-reactivity of antibodies backed up by genetic data (see figure); the two previously known human viruses fall into different groups. Investigators had hoped that the genome sequence of the new virus would help pinpoint its origins. But a first glance at the data has yielded few

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



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

(NIAID) in Bethesda, Maryland. NIAID's budget for anthrax research has ballooned from \$3.2 million in 2001 to around \$75 million this year.

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

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