AP/EUGENE HOSHIKO

OPEN SEASON

SARS caught China unawares. But the ensuing struggle to characterize and contain the virus has put the country's work on infectious diseases back on target. **Apoorva Mandavilli** reports.

Like anyone who was in Beijing in the spring of 2003, Hongkui Deng remembers it vividly. The Chinese government could no longer deny that the country was in the grip of a new and potentially fatal disease: severe acute respiratory syndrome (SARS). By July, the epidemic would have spread, affecting more than 8,000 people worldwide and claiming 813 lives; but in April, the panic was already palpable.

Normally bustling, the streets of Beijing were virtually deserted. The few people who ventured out wore masks and gloves, and avoided even eye contact with others. Cinemas, schools and shops were closed. It was, as many describe it, frightening and eerie — even apocalyptic. "Everyone was scared," Deng recalls.

Deng, a cell biologist, had returned home in 2001 after more than a decade in the United States. Now based at Peking University, he was pursuing his research on embryonic stem cells. Returning from a conference in April 2003, he learnt that the mother of one of his students had SARS. Once officials had sprayed the lab, Deng's students began asking if they could work on the disease that was paralysing the nation. "Everybody wanted to do something," he says.

Deng had limited experience in virology, apart from a short stint working on HIV, and his students had even less. But like many other scientists in China, the team saw research on SARS as both an opportunity and a duty, and set about mastering the basics — fast.

Feverish activity

For at least six months, Deng's lab stopped working on stem cells and focused entirely on SARS. It wasn't alone. Across the country, scientists trained in protein science, anatomy, immunology and biochemistry — almost anybody who could contribute in any way — were shelving their normal projects. "Everyone was working on SARS," says Deng. "You just had to."

That commitment has paid off. Although China still faces a great many hurdles, its government and scientific community are becoming better prepared to combat epidemics, say some US scientists. Long after global interest in SARS has waned, Chinese scientists are still publishing important work on the disease. In September 2005, for instance, one team identified bats as a natural reservoir of the SARS virus[1]. And in October, another group reported a molecule that can inhibit the replication of a wide range of SARS-like viruses[2].

In part, the boom in China's infectious-disease research reflects the country's growing activity in science. Government spending on the sector in 2004 was up 16% on the previous year, outpacing the country's economic growth of about 10% per year. Since the late 1990s, the number of Chinese papers published in international journals has risen dramatically[3] and the number of domestic patent applications has also gone up. But SARS was in many ways a wake-up call. It served as a grim preview of the disaster — and public humiliation — that awaited China if it did not take infectious diseases seriously[4].

Since 2003, two new infectious-disease institutes — one set up by the Chinese Academy of Sciences, the other a joint effort with the Pasteur Institute in Paris — have been set up in China. Plans for another, a collaboration with Columbia University in New York, are expected to be announced next month. Chinese scientists say that an increasing number of students are choosing to work in infectious disease, and many scientific collaborations born during the SARS epidemic are still thriving. "Before SARS, scientists routinely didn't work together," says Deng. "China is doing much better now."

China is a hotbed of infectious diseases: according to agencies such as the World Health Organization (WHO), hepatitis, tuberculosis, diarrhoea, encephalitis and HIV are all prevalent at epidemic rates. And with people,

poultry and animals of all kinds living in close quarters, there are plenty of opportunities for pathogens to jump between species.

SARS was an unknown entity when it struck, and was probably spread to people by infected palm civets in China's wild-animal markets. In 2005, the country also saw an unusual cluster of infections from the pig bacterium *Streptococcus suis*, which jumped from swine to infect more than 200 people. These days, all eyes are on avian influenza, and the government has already banned poultry from markets and culled millions of birds in an attempt to prevent the virus from jumping to humans.

Slow start

Given such dangers, infectious-disease experts are delighted at the changes in China. "I think SARS prepared the ground for being willing to work with emerging infectious diseases," says Robert Webster, a leading flu expert at St Jude Children's Research Hospital in Memphis, Tennessee. Looking at the way China has handled outbreaks of bird flu, Webster says, the government seems to be much more transparent and willing to share information than it was during the SARS crisis, when it denied the existence of the disease for several months. "There are still problems out there but the situation is much improved," he says.

During the initial months of the SARS epidemic, scientists on China's mainland contributed little to the understanding of the disease. Even in May 2003, weeks after virologist Albert Osterhaus of Erasmus University in Rotterdam, the Netherlands, and his colleagues had identified a novel form of coronavirus as the cause of SARS[5], some senior Chinese scientists still refused to acknowledge that it was the culprit, backing *Chlamydia* bacteria instead. In fact, researchers at a Chinese military institute in Beijing had come to a conclusion similar to that of Osterhaus as early as March, but internal politics reportedly stifled their finding.

At a May meeting in Beijing organized by the Chinese Academy of Sciences, Ian Lipkin witnessed the disagreements firsthand. "Even at this point, there was this argument back and forth about who was right and who was wrong," recalls Lipkin, director of Columbia University's Jerome L. and Dawn Greene Infectious Disease Laboratory. Ultimately, several government officials were sacked over the handling of the crisis.

But after its initial failures — for which China was openly chastised by the international community — things changed dramatically. Lipkin says that an enormous medical facility, intended to quarantine and treat those infected, was built about 50 kilometres outside Shanghai in just a few months.

At the May meeting, Lipkin had presented a roadmap for the government to help it combat SARS, covering drugs, vaccines and research on the basic biology of the virus. By the time he returned to China in July, "they had virtually finished everything there was on this roadmap", he says. "I can't tell you how impressed I was. It was extraordinary."

"These are emerging and re-emerging diseases. This is research that will be very useful."
— Zihe Rao

The government also realized the need for cooperating both with the international health agencies and with its own scientists. The ministries made special concessions. They created funding pools, extended grants that were about to expire and forgave deadlines so that researchers could focus on SARS.

The incentives worked, drawing some of China's most successful scientists to the field. Among them was Zihe Rao, a structural biologist who heads the Institute of Biophysics in Beijing. By October 2003, Rao's team had published the structure of a SARS protein[6] and has since designed a molecule that inhibits the replication of SARS and several related coronaviruses[2]. These days, more than half of Rao's lab still works on infectious diseases. "These are emerging and re-emerging diseases. This is research that will be very useful," says Rao.

Learning curve

Will SARS come back? Quite possibly. Zhihong Hu, director of the Wuhan Institute of Virology, is tracking the SARS coronavirus in palm civets, looking in particular for a strain with the two mutations required for the virus to jump to humans[7]. She says there is some evidence that the strain is already circulating in farm civets, but is waiting for confirmation before publishing her findings.

Hu says her work is progressing slowly, in part because research on SARS now faces more obstacles than it did initially, which to some degree results from a shift in government attitudes. At the height of the epidemic, the government had few restrictions on who could work with the coronavirus. But that stopped abruptly in April 2004, after it was discovered that the virus had escaped the previous month from the Chinese National Institute of Virology in Beijing. Although the lab was among the few in China equipped to work with dangerous pathogens, the incident prompted the government to introduce strict regulations.

During the SARS epidemic, the Chinese Center for Disease Control and Prevention (CDC) freely shared samples of the SARS virus with various scientists, including Guo-Ping Zhao, executive director of the Chinese National Human Genome Center in Shanghai. Zhao had never worked with viruses before but he and his team quickly learned enough to track the evolution of the virus through sequence analysis. In just four months, they had completed their analysis and soon after, published a paper showing the molecular evolution of the virus during the epidemic[8]. Apart from a crash course in epidemiology, Zhao says the group learned to sequence viruses from tissue samples. This expertise, he adds, could prove useful with bird flu.

But that is if China can straighten out the remaining kinks in its research structure. Not surprisingly, the Chinese CDC and the Ministry of Agriculture keep a tight rein on SARS and avian flu viruses and allow only the few labs that have biosafety level 3 facilities to work with them. But tissue samples, such those used by Zhao, are similarly controlled.

"I think the key issue in China now is all the government agencies," says Zhao. The government may have learned to share more openly with the WHO and with international experts, but it is not open enough with Chinese scientists, he says. "The government agencies should learn how to work together with research institutes," he says. "I think Dr Webster in the United States knows much more information than I do." That may be so, but the international lines of communication are not trouble-free: the WHO, for example, has complained on several occasions that it has yet to be granted access to virus samples from last year's outbreak of bird flu.

Still, Zhao and others say that they are optimistic about China's growing expertise in infectious diseases. "I think we are learning, but it's not so easy to change in one night," Zhao says. "Things have improved a lot; I hope they improve more." ■

Researchers including Ian Lipkin (far right) discuss the 2003 SARS outbreak.

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