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SARS In China: Tracking The Origin of the Outbreak

Where did SARS come from? The question is crucial for understanding whether the disease will reemerge, but so far, there's lots of dissent with no solid answers.

At Dongmen market, almost everything that's vaguely edible is for sale. The cavernous 2-story concrete building in Shenzhen, close to the Hong Kong border, houses hundreds of vendors selling live animals and seafood. Geese, ducks, chickens, pigeons, doves, and wild birds are packed wing to wing in metal cages stacked 2 and 3 high, their minders napping on top as they wait for the next shopper. Nearby, rabbits are squashed in cages, and turtles and crabs in huge metal tubs scramble over each other.

But the market has lost some of its legendary variety. Masked palm civets, for one, are missing. Before the SARS virus erupted out of nowhere in Guangdong last fall, eventually sweeping through Hong Kong, Beijing, Taiwan, and Toronto and killing more than 800 people, these distinctive catlike creatures were readily available at Dongmen and similar markets across the province. Restaurateurs bought them for meat, said to be tasty and fabled to strengthen the body against winter chills. Now, however, the civets, raccoon dogs, and many of the other exotic species that are staples of Guangdong's eclectic cuisine are gone. Asking about civets brings either an amused chuckle or, occasionally, a glare and a dismissive wave of the hand.

Here at Dongmen, a research team from the University of Hong Kong (HKU) and the Shenzhen Center for Disease Control and Prevention (CDC) has found the most intriguing leads yet about the possible origins of SARS. 2 different animal species on sale here were found to harbor the virus: civets and raccoon dogs. Antibodies to the virus were detected in a Chinese ferret badger. The government intervened, and since then, Shenzhen shopping has not been the same.

If the virus does not have a reservoir or permanent hideout in animals, the world can breathe a little more easily. But virologists suspect there is an animal reservoir, an ecological niche in which the virus evolved and

continues to thrive. "Until we know what that source is and until steps have been taken to neutralize the source, then clearly the potential [for the virus to re-emerge] exists," says Meirion Evans, an epidemiologist at the Communicable Disease Surveillance Center in Cardiff, U.K., who has been working with the World Health Organization (WHO) to understand the SARS outbreak. Despite the heightened awareness of the disease, "the experience of SARS is that it doesn't take very long to break out of a local area and go cross-border, if not global," Evans adds.

So far, however, the hunt for the reservoir is yielding more confusion than clarity. Unlike the HKU-Shenzhen CDC investigators, a research team at the China Agriculture University (CAU) in Beijing has been unable to find any trace of the SARS virus in civets or dozens of other species it has sampled. The Beijing scientists have questioned the earlier work and criticized the group for not sharing its data; the Hong Kong group has responded in kind. But emerging-disease experts say that both groups could be right, and the apparent discrepancy shows just how tricky the hunt for the reservoir will be.

A large, well-coordinated effort by multiple teams is needed to sort out these questions and identify the reservoir, assert WHO officials, who last week won permission from Chinese authorities to send in 4 teams of experienced animal-virus hunters from the Netherlands, Australia, the United States, and Japan. member states, says Henk Bekedam, who leads WHO's Beijing office. The foreign teams are expected to be on the ground in 1 to 2 weeks and work together with their Chinese colleagues, to cover many more markets and test hundreds of species, both domestic and wild. Also planned are extensive lab experiments to check different species' susceptibility to the SARS virus. But tracing the route of infection back to the animal reservoir "could take years," says Hume Field, a veterinary epidemiologist who has already served on WHO SARS missions.

A WHO fact-finding mission in April 2003 picked up the first clues about the origins of SARS. When the researchers were reviewing data on the earliest cases of an unusual form of pneumonia that had appeared in Guangdong between November 2002 and February of 2003, team member Evans was struck by the fact that "a fairly high proportion" of early SARS patients were classified as "food handlers," a category that includes everyone from animal wholesalers through the supply chain to cooks. In May, Evans led a second delegation that reviewed the data with Chinese epidemiologists and found that 9 of 23 early patients worked in the food industry. People living in the vicinity of markets were overrepresented as well. Evans also learned that many restaurants in the province keep live animals on the premises and slaughter them as needed, a practice that could expose restaurant workers to virus-laden blood and excrement. Yet, there was no evidence that the disease was spread by eating infected animals. Speculation soon centered on Guangdong's palate for exotic fare.

By that time, several teams had fingered a previously unknown coronavirus as the cause of SARS. Its novel RNA sequence suggested that, unlike coronaviruses normally found in pigs, cattle, chickens, or humans, this virus had probably evolved in isolation for a long time before making the leap to humans. Realizing that the live animal markets provided fertile grounds for animals and humans to swap infectious agents, Yi Guan, a virologist and member of the HKU team that was among the first to identify the virus, decided to investigate. With colleagues at the Shenzhen CDC, he drove to the Dongmen market, just 15 minutes from the Hong Kong border. The team sampled 25 animals, representing 8 exotic species.

Analyzing the samples back at their labs in Hong Kong, the researchers isolated a coronavirus almost identical to the human SARS virus from all 6 masked palm civets and from a single raccoon dog. They also detected antibodies to the virus, indicating prior exposure, in a Chinese ferret badger. The 5 other species sampled, also tested by polymerase chain reaction (PCR), proved negative. Underscoring the disease link, the

researchers found evidence of antibodies to the SARS virus in a number of animal market workers, whereas previous studies had shown that antibodies were not present in the wider population. Only one difference appeared in the viral RNA isolated from the market animals: It was 29 nucleotides longer than RNA isolated from humans. This has fueled speculation that the virus may have become more adept at propagating in humans after losing a piece of its genome. But the picture is complicated by the fact that researchers at the Beijing Genomics Institute say they have found at least 2 humans who were infected with the longer variety. Researchers hope further studies of each strain's characteristics -- including animal experiments -- may clarify whether the minuscule difference really is important.

As had become the norm among researchers working on the SARS frontline, the HKU team on 23 May 2003 announced its findings at a press conference before submitting the results for scientific review. Although the team emphasized that the study simply indicated a link between the virus and the exotic animal trade, press reports implied that civets were spreading the disease, if not functioning as the hotly sought reservoir. Chinese authorities immediately, although temporarily, banned hunting, selling, transporting, and exporting all wild animals. They also quarantined all farm-raised civets in Guangdong.

Then on 19 Jun 2003, a competing group at CAU held its own press conference to announce results from its exhaustive search for the reservoir. The researchers, led by the university's vice president, agronomist Sun Qixin, had cast a wide net, sampling 54 wild and 11 domestic animal species from 6 provinces and Beijing. Using the PCR technique, they found not a trace of the SARS virus -- an apparent contradiction to the findings of the HKU-Shenzhen CDC team. Intrigued by Guan's report on infected animals, the Beijing team had paid extra attention to the masked palm civet, buying 3 of them in Guangdong and another 73 wild and farmed animals elsewhere. All samples were negative. (The researchers claim that they isolated a different coronavirus from the civets, but its sequence is only 77 percent similar to that of the SARS virus.) Although the CAU researchers stop short of saying Guan's findings are wrong, they sharply criticize his team members for refusing to release additional details that might allow others to verify their claims.

Guan says he will open access to the sequence data once his team's paper, which he says is now under review at [the journal] Science, is accepted. But the difficulty lies in interpreting those results. Guan declines to discuss the details until the paper is published. But he emphasizes, "We never claimed that civets were the animal reservoir, nor even that civets were the source of the human infection." Guan says his findings simply "open the door for further investigations" to trace the chain of transmission back to the source.

Guan, Field, and Chen all agree that it's unlikely that civets are a crucial part of the natural life cycle of the SARS virus. A more probable scenario, they say, is that the civets picked up the virus from another more exotic animal, perhaps in the markets or holding facilities, where many different species are confined in close quarters. Or these particular civets could have been infected in the wild before being brought to market. Field notes that the Nipah virus, which killed more than 100 in an outbreak in Malaysia in 1998 and 1999, was ultimately found to have traveled from its reservoir, fruit bats, through pigs to humans. A similarly circuitous transmission route is likely for the SARS virus.

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[see also:
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