The SARS Scare

// A cautionary tale of emerging disease caught in the act

by Jonathan Shaw

In a matter of months in early 2003, severe acute respiratory syndrome spread to 29 countries, killing nearly 10 percent of the people it infected. No drug could stop SARS, and the disease propagated wildly through the ranks of healthcare workers. One patient, a "super-spreader," infected 143 people, including every one of the 50 doctors and nurses who treated him. Eerie scenes of Chinese cities being disinfected by spray trucks and Canadian doctors in full biological containment gear flashed on television screens around the world. At the height of the epidemic, one Canadian infectious-disease expert who had come down with SARS herself predicted that the virus would spread around the globe: "If we don't have a vaccine—yes, we are all going to get it," she told Canadian television. Her opinion was shared by many that spring. With symptoms resembling those of a common cold or garden-variety flu, SARS frequently escaped diagnosis, aiding its spread. And once the symptoms did become known to the public, every cough in a subway or a plane was suspect. Then SARS became a super-spreader of another sort, a scourge of national economies: it became a carrier of fear itself, with costs measured in billions of dollars.

Ironically, in this age of high-tech medicine, the virus was eventually brought under control by public-health measures typically associated with the nineteenth century—isolation of SARS patients themselves and quarantine of all their known and suspected contacts—rather than a vaccine. But it was tools of the modern era, including high-speed communications and sophisticated computer modeling, that allowed epidemiologists at Harvard and in the United Kingdom to initially determine that such an approach could work at all. The relatively slow spread of the SARS virus as compared to flu made it more a warning to humanity than the full-fledged pandemic that was feared: had SARS been more infectious or incubated more rapidly, such old-fashioned containment methods would have failed.

The threat, of course, is that our luck might not hold next time. That makes it vital to learn from the scientific, public-health, and political responses to what did happen. SARS is the story of a global network of medical workers, epidemiologists, virologists, and other scientists who responded to a sudden threat with record speed, aided by new technologies that allowed them to identify the virus, decipher its genetic code, and publish it on the Internet. Harvard microbiologists and molecular geneticists then played a central role, using the published genome to build the virus's entry mechanism, a spike-like protein, from scratch, and used that, in turn, to identify the receptor the virus uses to penetrate human cells. This breakthrough laid the groundwork for short-term therapeutic interventions and targeted vaccine development.

After a second, small outbreak in 2004, scientists were able to pinpoint the genetic change in the viral genome that had allowed SARS to infect humans, and to validate initial suspicions about what animal had last incubated the disease before it jumped to humans. Harvard School of Public Health (HSPH) professionals briefed domestic political leaders during the initial outbreak, and China, criticized at first for being slow to respond, invited HSPH dean Barry Bloom to meet the minister of health to consider how the school "might help them improve their response to emerging public-health challenges." (In August 2006, the first group of rising mid-level officials in China's central and provincial ministries of health completed a three-week training program at the school, led by Yuanli Liu, an assistant professor of international health.)

SARS was declared eradicated by the World Health Organization (WHO) in 2005. Whether or not it returns to afflict humans, the disease has taught us much about our lack of readiness for the next emergent infection; raised many questions about the conditions that lead to surprisingly frequent outbreaks such as SARS, Ebola, bird flu, and Nipah virus; and suggested how public-health and molecular medicine best work together in the prevention and control of new diseases.

// The Healthcare Workers' Disease

Allan Detsky, M.D. '78, chief of medicine at Mount Sinai Hospital in Toronto, worked at the epicenter of the outbreak in North America. "I was in Vancouver attending my niece's bat mitzvah," he recalls, "and there was a story on the news about a

GOH CHAI HIN/AFP/GETTY IMAGES

case of this weird disease in Toronto. This was around March 15, 2003." Detsky had read reports of a new pneumonia-like illness that was spreading rapidly in Hong Kong. Now it appeared it might have reached Canada. "Then they showed a picture of my hospital," he says, and he cursed.

"As it turned out, the SARS case was not in my hospital after all," Detsky continues. Two of his infection-control specialists were consulting to Scarborough Grace Hospital, about 10 miles away, where the patient was being treated. But Detsky was right to be worried. SARS—a zoonosis, or disease that spreads through animals—had first infected a man in Guangdong Province, in China, the previous November. A second, epidemiologically unrelated case cropped up there in mid December. By the end of January, numerous instances of the disease had been reported, with a cluster among people who worked in the flourishing live-animal markets of the area, which provide exotic meats for a growing middle-class clientele. Then, on January 30, the first known super-spreading event took place, when a 44-year-old seafood seller hospitalized in Guangzhou passed the virus to 19 relatives and 50 or more hospital staff members. Three weeks later, a doctor from that hospital—he had been suffering flu-like symptoms for a

CHINA PHOTOS/REUTERS/CORBIS

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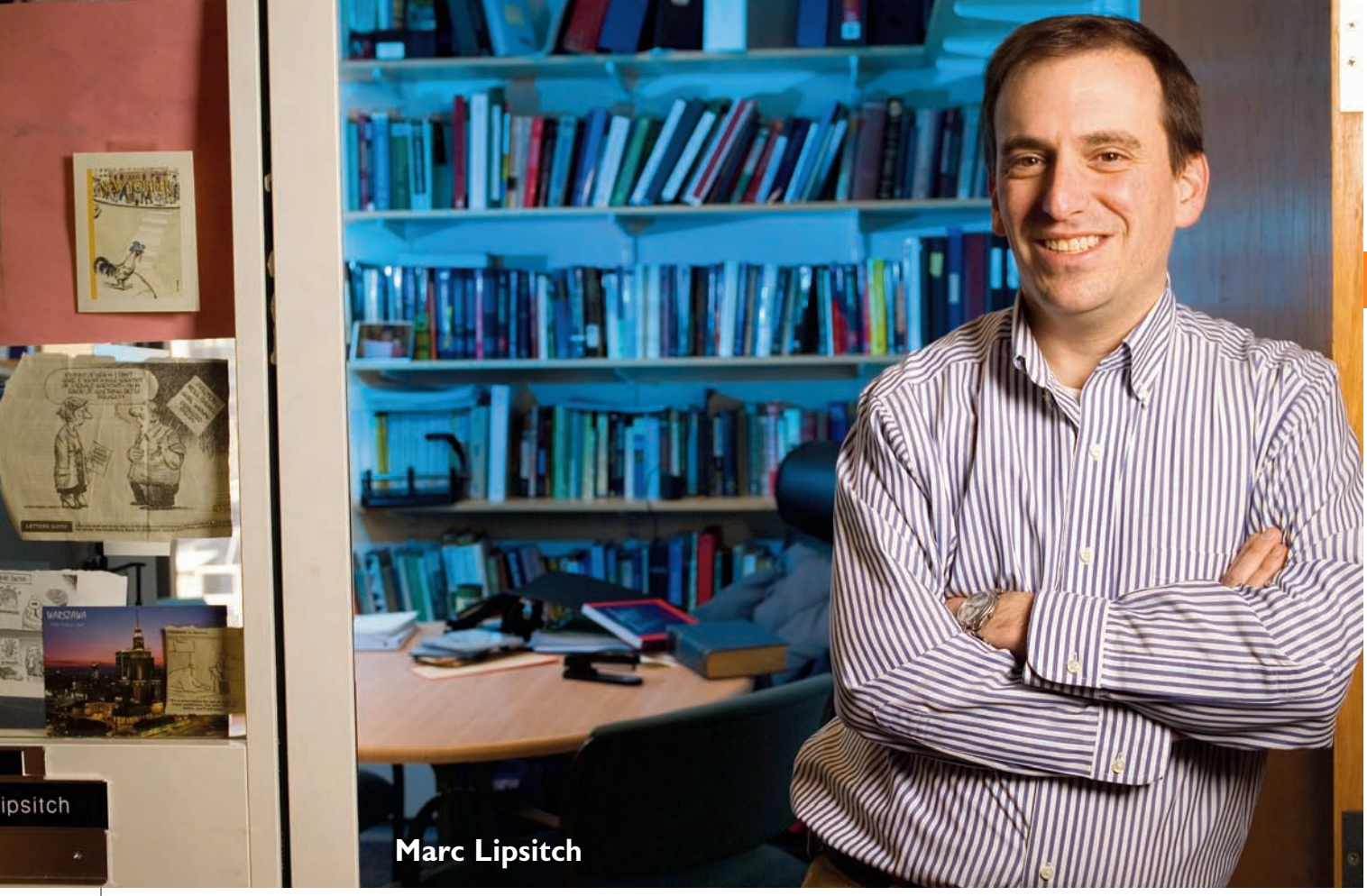
Clockwise from above: Thermal scanners at a railroad station in Beijing check passengers for fever; workers disinfect a Beijing street as part of the government's effort to eradicate SARS; primary-school children in Hong Kong wear masks to school on May 12, 2003, the first day of classes after a six-week suspension due to SARS.



Marc Lipsitch

week—traveled to Hong Kong to attend a wedding. During a one-night stay on the ninth floor of the Metropole Hotel, he infected 17 people. None of the other Metropole cases had had any known contact with him, suggesting that the live virus had become airborne. From the cosmopolitan nexus of the hotel, SARS began to spread internationally to Singapore, Vietnam, the Philippines, Australia, and Canada.

The first Canadian case went undetected: a 78-year-old woman who had stayed in the Metropole on February 21, nearly two weeks before, died at her home back in Canada. The official cause of death was a heart attack. But that proved to be a complication of SARS, which she had unwittingly passed on to four family members. Two days later, on March 7, the woman's son appeared in the emergency room of a hospital in Scarborough with a cough, fever, and difficulty breathing. Though quickly isolated when a doctor suspected tuberculosis, the man had already passed the virus to three other people while waiting 18 to 20 hours to be seen. A week later, one of them returned to the hospital after suffering a heart attack. Although that victim's contact with the woman's son (who died the very same day) was already known, the patient's symptoms were not thought to be pneumonia-like, and he was transferred to another hospital. There he infected more than 50 people.

"SARS has about a 10-day incubation," says Detsky, "so for the first 10 days we lowered our guard and thought maybe this was overblown, maybe the problem was that in Hong Kong they don't really know how to do respiratory care. Of course, that is bullshit. They are as advanced in Hong Kong as they are anywhere."

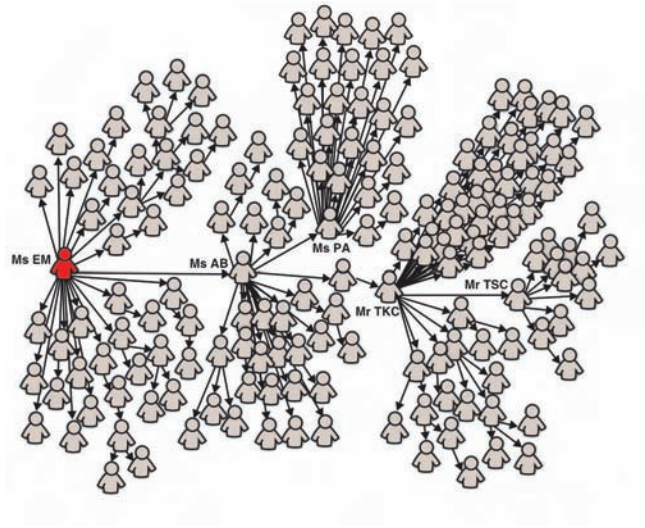
Overconfidence in the efficacy of Western medicine may have contributed to what happened next: Detsky's infection-control officer decided to transfer SARS patients from other hospitals to Mount Sinai, an internationally renowned teaching hospital and health-sciences research center affiliated with the University of Toronto. She also transferred patients not thought to have SARS, in order to remove them from facilities stressed by the disease. "But they did [have it], of course," adds Detsky, "and then that infected people in our ICU, and the whole thing went wild from there."

SARS was difficult to diagnose and easy to spread. Some patients had no symptoms, or only mild flu-like indications. Others had severe, pneumonia-like lung infections that led to respiratory failure and death. From initial symptoms that last about a week and include fever, chills, muscle pain, headache, dizziness, dry cough, and sometimes diarrhea, the disease progresses to a second phase in which a massive immune-system response begins to damage lung tissue. Eventually the pulmonary destruction leads to low oxygen saturation in the blood. Nearly a quarter of SARS patients developed respiratory failure and required intensive care and even mechanical ventilation, which dispersed infectious particles widely. In Canada, where most transmission took place in hospitals among patients with pre-existing conditions, the disease was fatal in one-sixth of the cases.

When the infection-control officer came down with SARS herself, "That was a huge psychological blow, as well as [raising] a whole set of other issues," Detsky remembers. "Because she sat on the provincial steering committee with all the other experts and leaders in the province, they *all* had to be quarantined. As soon as that happened, we realized that leadership could not meet with each other." (In fact, all hospital employees were told to avoid each other except at work.) Detsky isolated himself in

Photograph by Jim Harrison

"The reason why scientists in this country can respond to the disease of the moment is because they spend a lot of time on diseases that are not 'of the moment.'" —Marc Lipsitch



WORLD HEALTH ORGANIZATION REGIONAL OFFICE FOR THE WESTERN PACIFIC 2005

This diagram detailing SARS transmission in Singapore shows the important role of "super-spreaders" in transmitting the disease. Five people caused more than half of the 205 cases there.

his office for four weeks, communicating by phone and e-mail, hoping that no more of his staff would fall ill.

During that time, as chair of a daily conference call among officials organizing the provincial response, Detsky was well-situated to observe the epidemic unfold. He arranged for 11 hospitals to share and swiftly publish their data on SARS. The most telling conclusion of the study (which was rushed to publication in the *Journal of the American Medical Association*) was the one Detsky also shared with his Harvard Medical School (HMS) classmates at a twenty-fifth-reunion symposium that June. "SARS," he told them, "is a disease of healthcare workers": 77 percent of the 144 patients followed had been exposed to SARS in a hospital setting. The outbreak at that point seemed to be winding down, even in Canada. Detsky looked forward to gathering informally with classmates that evening. But he never made it.

// A Community Threat

Back at his hotel, Detsky got a phone call from Toronto. A few days earlier, he had ridden a hospital elevator with a third-year medical student who, he learned, had come down with SARS. Detsky did not have to be quarantined because SARS is thought to be communicable only when a patient displays symptoms, and the contact had come more than 24 hours before the student became ill. "But I had to go home."

He returned to Toronto, where, "on the street, you'd never have known anything was wrong." At hospitals, however, the scene remained Orwellian. Entrances were locked or monitored. Everyone's temperature had to be taken. Doctors wore gloves, goggles, gowns, and masks every time they saw a patient.

SARS probably would have been eradicated in Canada well before the beginning of June, when Detsky was exposed, if economics and politics had not been allowed to trump public health. "As far as I know, Toronto is the only place that had a full-blown, bi-modal SARS outbreak, with two big peaks," says David Fisman, M.D., M.P.H. '00, the medical epidemiologist for the Ontario public-health laboratory. On April 23, as the initial outbreak was winding down, WHO issued a travel advisory for Toronto urging postponement of "all but essential travel." Conferences and conventions were canceled, and tourists changed their plans. Many Canadians were outraged, and the government protested, "There is no evidence of any casual transmission of SARS in Toronto."

But even as SARS cases were dropping in hospitals, where the outbreak was concentrated, community transmission continued: people with no known SARS contacts were still getting SARS.

That's when an "egregious thing" happened, says Fisman, who is also an infectious-disease researcher at the Hospital for Sick Children in Toronto. "Because of the economic damage [expected to ensue from the travel advisory], the political forces—the former government here and their former chief medical officer—decided they needed to change the situation in a way that would not result in any further travel advisories," he says. The officials changed case definitions so that counts would go down. "In order to be a SARS case, they said, you had to have had contact with a SARS case, and because WHO was on the lookout for *de novo* SARS cases popping up *without* known links to prior SARS cases—this was their working definition of community transmission—that effectively made it impossible for community transmission of SARS to happen in Toronto."

Once this Catch-22 was in place, "in the short term it had exactly the desired effect," Fisman says. "The numbers went down and down and down. In the multi-week term, as you'd expect, if you sweep a number of hand grenades under your rug...it is not good for your health. And what happened was that they had SARS 2." Just 10 days after WHO declared Toronto free of recent local transmission, clusters of SARS cases were reported in four Toronto hospitals. The anger over economic damage that had been directed at WHO dissolved into dismay about decisions made by public-health officials and politicians locally.

// Modeling the Menace

At the time, Fisman worked in the department of public health in Hamilton, Ontario, 50 miles away. Asked to help his overwhelmed counterparts in Toronto, he also volunteered to serve on the SARS Science Committee, and like Detsky, was exposed to the disease by an infected colleague at a meeting.

A recent graduate of HSPH, he was also in touch with two faculty members there: professor of epidemiology Marc Lipsitch, a mathematical biologist, and associate professor of epidemiology and HMS assistant professor Megan Murray, M.D. '90, M.P.H. '96, S.D. '01, an expert on tuberculosis who teaches infectious-

disease dynamics. Fisman's descriptions of the spread of SARS in Scarborough Grace Hospital got the professors' attention, because they suggested that the R_0, or average reproductive number of the SARS virus—a measure of its infectiousness in an unexposed population in the absence of interventions—was high enough to drive a frightening, exponential spread of the disease. The R_0 tells how many people an individual with the illness is likely to infect. "The critical step in controlling an epidemic is to stop transmission," writes HSPH dean Bloom in the *Harvard Public Health Review.* R_0 "not only tells epidemiologists the potential of the outbreak to spread in the absence of interventions but also allows them to predict the ability of control measures to reduce transmission. If R_0 is greater than 1, each patient will on average infect more than one individual, and thus an epidemic will be propagated. If interventions can reduce the reproductive number to less than 1, the epidemic will be reduced and hopefully dissipate." In Scarborough Grace Hospital, each primary case was leading to as many as six secondary cases, suggesting that SARS might be as dangerous as smallpox.

Murray recalls how, as the disease spread, scientists around the world began searching for a model of SARS transmission. Finally she and Lipsitch decided, "Let's do it ourselves.'"

In order to understand just how dangerous SARS was, the epidemiologists had to know more than just the average reproductive number. They had to be able to calculate the "serial interval," or how long it takes one infected person at a particular stage of the disease to infect another person who then reaches the same stage of the disease. The 1918 "Spanish flu," which killed 20 million to 40 million people, had a serial interval of only four or five days, so it spread quickly, yet it killed just 1 to 2 percent of the people it infected. SARS, with a much higher case-fatality rate, had the potential to be devastating.

Murray and Lipsitch needed better data than they could get from the small sample in Scarborough Grace Hospital. They found it in Singapore, where researchers at the ministry of public health had carefully recorded contacts, dates of exposure and onset of symptoms, as well as death dates from that small country's brush with the novel disease. The groups agreed to collaborate. Racing to get a result, they came up with the key numbers within a month: the virus had an R_0 of 3. This told them that although SARS was not as infectious as smallpox (with an R_0 of 5 to 6), it nevertheless had the potential to infect millions within six months.

Equally important, the two researchers estimated the serial interval at eight to 10 days, more than double that of flu. This meant that public-health officials had time to track down and quarantine the contacts of SARS patients before they in turn started shedding virus. "With a flu, when the serial interval is three or four days, that is much harder," Lipsitch says. After three weeks of working almost without sleep, Murray and Lipsitch's paper, "Transmission Dynamics and Control of Severe Acute Repiratory Syndrome," was published in *Science* on line on May 23, along with an article by the pioneering English epidemiologist Roy Anderson, whose group reached similar conclusions using data from Hong Kong.

Complicating Murray and Lipsitch's efforts to build a transmission model for SARS, however, had been the fact that just five super-spreaders had caused more than half of the 205 cases in the Singapore outbreak. Most infected individuals had not transmitted their illness to *anyone.* This pattern of transmission is a peculiarity of SARS, but not uniquely so: super-spreaders also play an important role in transmitting tuberculosis and other diseases. Why this is so is not well understood. Theories have ranged from the virulence of a particular strain of a disease to behavioral or anatomical differences among patients.

"We don't know the answer for any disease," says Lipsitch, "except for sexually transmitted diseases where there is a clear behavioral component. We do know that in tuberculosis, if you are infected in the larynx, you aerosolize more bacteria than if you are infected only in the lungs.

"But the super-spreaders who have been identified in SARS were not people who had huge numbers of contacts," he continues. "They were not people who had some obvious behavioral reason." And the fact that "lots of super-spreading events infected people who then were not themselves super-spreaders" argues against a strong viral component. "There is something different about super-spreaders," says Lipsitch, "but whether it is inherent or just some chance event, we don't know."

REUTERS/CORBIS

The mode of transmission for the super-spreading event that occurred at the Metropole Hotel has never been established with certainty. The doctor infected only fellow guests and a visitor to the ninth floor. Rooms were pressurized, so aerosolized virus could not have entered through cracks under bedroom doors while people slept. None of the hotel staff became ill. But WHO investigators found "genetic traces" of the virus in a recirculating fan inlet above the elevator doors on the ninth floor and in samples they collected from the hallway near the entrance to the man's room. They speculate that he may have vomited there, and because staff had no recollection of such an event, his wife may have cleaned up any traces of it. Both she and her husband died of SARS, so we will never know what happened, but clearly, the live virus somehow became aerosolized in the common areas of the ninth floor.

Even more perplexing was a super-spreading event that occurred at the Amoy Gardens apartment complex in Hong Kong, where 329 residents became infected with SARS. Michael Farzan '82, G '92, Ph.D. '97, an HMS assistant professor of microbiology and molecular genetics who studies the mechanism that viruses use to enter cells, remembers vividly a graphic of one of the buildings that was published at the time: "The infection was spreading vertically in the building between apartments that were stacked on top of one of another in a column." This was very strange, he says: if the virus was being transmitted by a respiratory route, "the expected pattern of infection should have been by floor," horizontally.

The outbreak was traced to one man who had been undergoing kidney dialysis at a local hospital and was staying at his

brother's apartment. The patient's symptoms included fever and diarrhea. Investigators found that plumbing in the building was likely to blame for the virus's unusual transmission pattern: drain traps in the shower floors were either dry, faulty, or missing. When residents turned on bathroom fans, this sucked air from the common waste drainpipe into their living space. Virus in droplets or aerosol from the victim's stool entered other apartments with these ambient air currents. This demonstrated that the virus could infect people via the fecal-oral route as well as the respiratory route, and became the working hypothesis for most of the transmission that occurred in the building, Block E, where the man stayed. But that explained only part of this unusual super-spreading event: residents of apartment buildings downwind of the building where the man stayed also became ill. That suggested that the virus might have been carried some distance by prevailing winds on the night the man visited his brother—a frightening prospect indeed. A better understanding of what made this indi-

PETER PARKS/AFP/GETTY IMAGES

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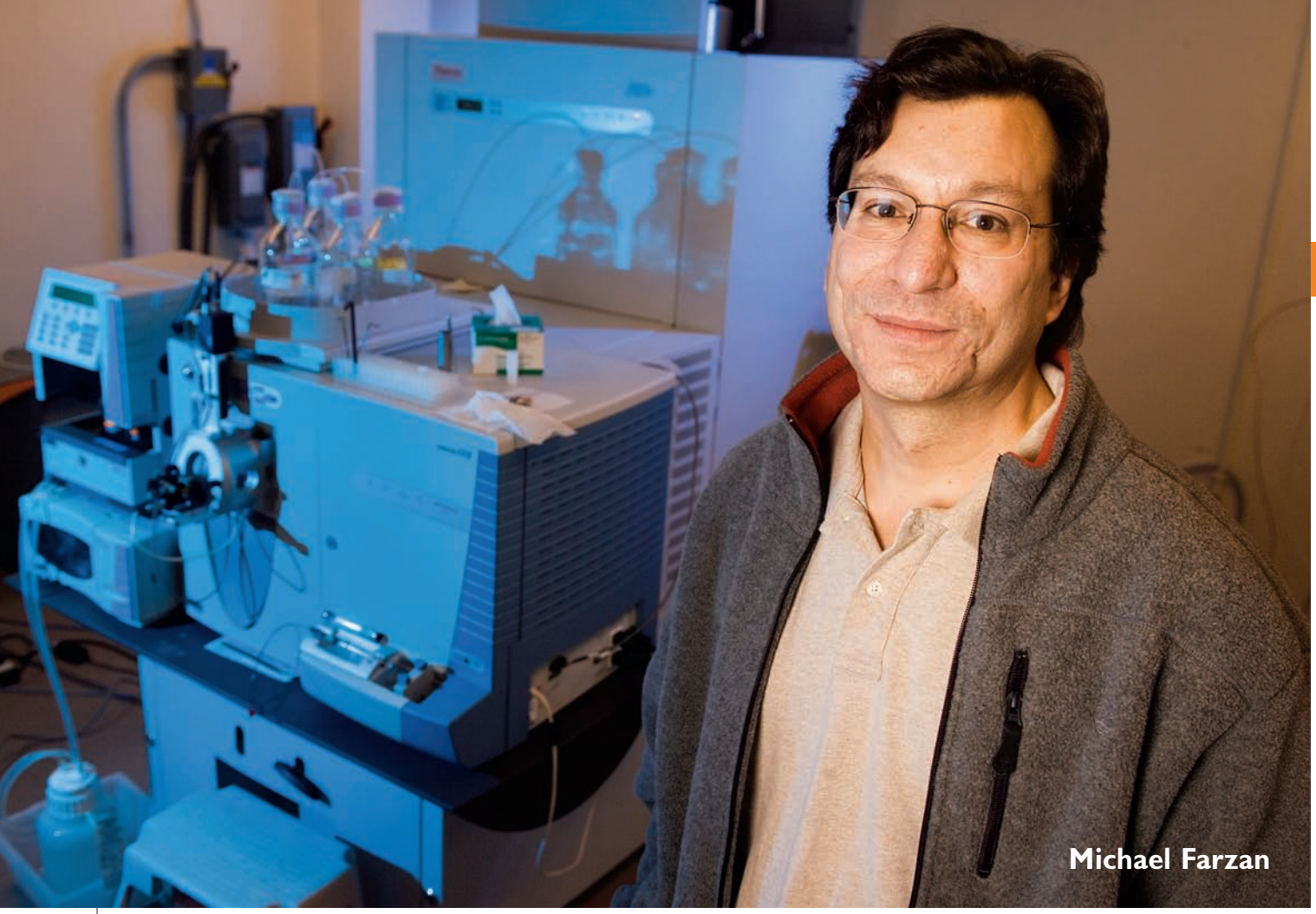
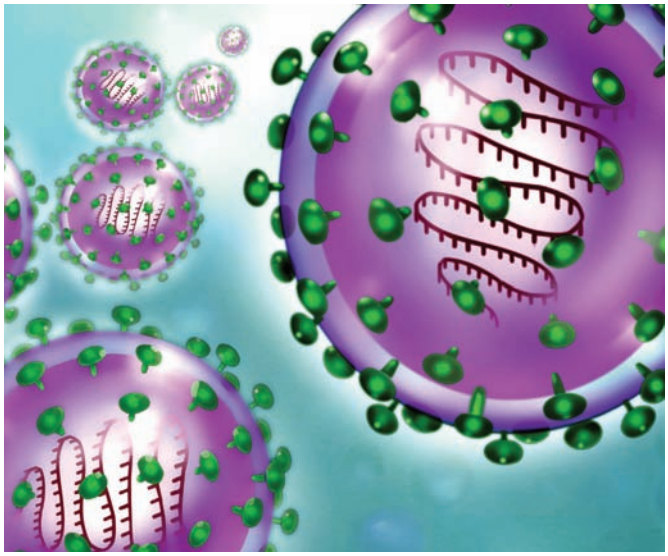
Clockwise from top: Chinese doctors and nurses wear protective suits as they tend to a SARS patient in a Beijing hospital; a masked resident of the Amoy Gardens apartment complex; a disinfection team enters Block E, ground-zero for the super-spreading event at Amoy Gardens.



Michael Farzan



MEDISCAN/CORBIS

"Spike proteins" on the surface of the SARS virus clamp onto human cells, facilitating entry of the viral RNA within.

vidual hypercontagious would have to wait for identification of SARS's causative agent.

// Characterizing a Novel Coronavirus

The research response to SARS was rapid, says Farzan, whose lab identified the virus's human receptor. Less than a month after WHO's first global health alert in March 2003, scientists pinpointed the probable cause of the disease: a novel coronavirus. Coronaviruses had been known to cause mild colds in healthy individuals and pneumonia in infants, but none had ever been implicated as a cause of death in healthy adults. By April, two groups had independently sequenced the entire viral genome. With unprecedented swiftness, researchers worldwide now had the tools to figure out where the virus came from and how it had gained the ability to unlock human cells with decimating results.

Farzan runs a lab focused on HIV, perhaps the most famous zoonosis of all. His research is vertically integrated on the study of HIV in particular—he studies the entire viral life cycle in a facility at the New England Primate Research Center—but horizontally integrated on processes of viral entry into cells. "When SARS hit, Wenhui Li, a postdoc in the lab from China, was very interested in it. Then the genome was published and we looked at it and said, 'God, we *understand* this!' It was just like, in a sense, falling off a log. It was a system we understood, we could translate all the HIV work immediately to the SARS entry process, and so it was easy for us to set up the systems and study it quickly."

Viruses are incapable of reproducing on their own. At their core, they are a set of instructions, encoded in RNA, that instruct the machinery of a cell to make more virus. Some, like polio, are "naked viruses," little more than the RNA itself. But most of the medically important viruses are encapsulated, says Farzan, meaning they are surrounded by a fatty lipid membrane. These "enveloped viruses" use a standard mechanism for gaining entry into cells that was worked out during the 1980s and 1990s by Har-

Photograph by Jim Harrison

"If you put the human receptor into a mouse, the mouse gets SARS. Making the interaction efficient is enough to cause the disease."
—Michael Farzan

vard's late Loeb professor of biochemistry and biophysics Don C. Wiley in the course of creating a model for understanding flu. "The level of work he did on this was worth the Nobel Prize," says Farzan, who considers himself fortunate to have taken classes with Wiley. "He established a model for this very broad class of proteins that mediate the fusion of the cell membrane and the viral membrane," Farzan says. "These are negatively charged repulsive membranes, so they don't want to get together." To overcome this repulsion, proteins reaching out from the virus interact with proteins on the cell surface, and together they undergo a change that forms a clamp, forcing the virus and cell together. What happens next "is a little bit magic," says Farzan: the lipid membranes mix and an aqueous pore forms between the two. This becomes a neck that tends to expand. Once the neck is large enough, the viral capsid enters the cell, bringing with it the biogenetic material that initiates the process of replication.

The importance of Wiley's model (developed with many other significant contributors) is that it applies to the majority of enveloped viruses, including HIV, flu, Ebola, arenaviruses, and SARS: all use essentially the same mechanism for entering cells. A couple of years ago, professor of biological chemistry and molecular pharmacology Stephen C. Harrison, a close collaborator of Wiley's, showed that another class of fusion molecules used by viruses that include yellow fever, dengue, and West Nile, also employ very similar mechanisms. "That was a breakthrough," Farzan says, "because when you look at [these other viruses] initially, they look very different. But after they go through some conformational changes," they start looking very much like a classic fusion molecule. "Harvard can be very proud of these guys."

"These guys" were the two who got Farzan interested in viral entry in the first place. He was, by any measure, a latecomer to biology: at 30, he didn't know what a protein was. As an undergraduate, he'd concentrated in government before switching to computer science. But after a career in computer graphics, he began to feel that his work was not significant enough. "Harvard is great," he says, "a world of second chances." He took classes as a special student, giving himself an undergraduate science education minus the Core, then entered the Ph.D. program at HMS, from which he graduated four years later. While studying HIV in the lab of his mentor, professor of pathology Joseph Sodroski, Farzan met his wife and close collaborator, Hyeryun Choe, now an assistant professor of pediatrics based at Children's Hospital.

In the spring of 2003, Farzan's group, in collaboration with Choe's team ("They did half the work on SARS," he notes), decided to try to identify the human receptor that SARS uses to break into human cells. Receptor identification is not a requirement for creating a vaccine (which teaches the immune system how to recognize and neutralize a viral invader) or for creating a protein therapeutic (insulin is among the first and certainly the most famous of this class of medication), but it is a key piece of scientific information about a virus. Viruses create a lot of decoys for the immune system, trying to prevent antibodies from binding with and neutralizing the one viral protein that initiates entry into cells. "With respect to vaccines, knowing the receptor is knowing where to focus the immune system," says Farzan, who teaches virology to graduate students. In the development of protein therapeutics, knowing the receptor allows drug designers to find or create a protein that binds the same receptor as the virus. This weakens the virus's attack and can work as a stopgap therapy against the disease.

"Where I think we got lucky [with SARS] is that we had all these technologies available that weren't available even when I graduated in 1997, particularly the human genome and new techniques in mass spectrometry," Farzan says. Though unconventional at the time, the shortest path to identifying the receptor would involve using those techniques. "We knew that we had to do it that way because it was going to be a highly competitive field," he explains. Many labs worldwide were racing toward the same goal.

Farzan's team used the viral genome that had been published on the Internet to build a synthetic SARS entry protein, often depicted as a spike-like structure with a ball on the end. Coronaviruses are covered with these spike proteins. In fact, they give the virus a crown (corona)-like appearance when viewed through an electron microscope—hence the name. Farzan's group took this spike-like protein structure (with no SARS virus inside it) and allowed it to attach to human cells. Then they pulled the spike protein out to see what human receptor it had grabbed. Because the receptor is too tiny to identify visually, they ran the protein and receptor complex through a mass spectrometer, got a distinctive pattern, and then compared that to the database of human proteins that had been catalogued as part of the human genome project. (Before that project was officially completed in April 2003, this critical technique would not have been possible.)

The team's method, pioneering at the time, is extremely fast and is now widely used for receptor identification. "It is trivially simple," says Farzan. Although the work wasn't published until November 2003, Farzan's team knew the name of the human receptor—ACE2—by late July. Because they knew SARS spread via both respiratory and fecal-oral routes, they were happy to see the tissue distribution of the receptor: "All over the lungs and gastrointestinal tract, and almost exclusively in those two locations, with the exception of the kidneys." This was just what they would have expected based on the viral life cycle: "This virus wants to transmit efficiently; it doesn't even care about infecting you systemically," Farzan says. "It just wants to go into the lung and come out or go into the GI tract and come out, so it chooses a receptor that is very efficiently expressed on these tissues and is completely indifferent to the fact that it is not in other sites or immune cells or any of the other places that other viruses infect."

(Not to be overlooked here was the contribution of basic research. Farzan notes that "sequencing the coronavirus was stunningly rapid," but the "guys who get short shrift on this are the ones who have been working on this obscure virus for years. They developed a body of knowledge about what coronaviruses are like, and what their conserved sequences are, and then some hotshot with the right machine swoops in and takes his bows. The basic virologists have been doing this work for more than a decade, having trouble getting funded, but they built this body of information and they deserve credit." HSPH's Marc Lipsitch agrees. "The reason why scientists in this country can respond to the disease of the moment," he says, "is because they spend a lot of time on diseases that are not 'of the moment.'" Coronavirus experts, who described their field as a "backwater" prior to SARS, suddenly found themselves "the hottest properties around," Lipsitch continues. "Keeping good science alive, and development of methods alive, is at least as important as jumping on bandwagons." He thinks that looking at basic evolutionary questions about how diseases evolve may prove useful in controlling future epidemics.)

Although there was a typical delay before publication of their findings, "Nobody was going to beat us on this," Farzan recalls. Part of the reason was that other labs were using the fusion protein from the live virus to bind the human receptor. His group had synthesized that protein themselves. When they were deciding how to write the code for a particular amino-acid building block in the SARS spike or entry protein, they chose one that was particularly well-expressed in mammalian cells. This bit of engineering allowed them to circumvent a technical hurdle that confronted researchers working with protein from the live virus, which used a different coding sequence that happened not to work as well in an experimental setting.

// Seeking the Source

While the laboratory work proceeded at high speed, researchers in China had been zeroing in on an environmental source for SARS. Tipped off by the high proportion of individuals working in the exotic-animal food trade among the earliest SARS cases, they began testing animals for sale at markets in southern China for signs of the SARS coronavirus. By late May 2003, they had found genetically similar viruses in two animals, masked palm civets and raccoon dogs. Another species, the Chinese ferret badger, had antibodies to the SARS virus. Separately, researchers in Hong Kong were studying virus collected from human cases to estimate the timing of the last common ancestor of the epidemic strain of SARS that had infected humans. The date they came up with was December 12, 2002. All signs now pointed to an animal origin in Guangdong Province, where the first cases had appeared 90 miles inland from Hong Kong, along the Pearl River, in late 2002. Unlike HIV, which is now thought to have entered the human population on many undocumented occasions since about 1930, SARS had made the jump in the glare of modern medical scrutiny.

In late December 2003 and early January 2004, China reported a new outbreak of SARS. Four mild cases, not linked epidemiologically, appeared in Guangdong Province. These independent, zoonotic transmissions showed clearly that the environmental source of SARS

AFP/GETTY IMAGES

// Bird Flu

Bird flu has captured headlines recently as intermittent, independent zoonotic transmissions from birds to people have resulted in case mortality of about 50 percent. Because the disease is spreading globally through wild and domestic bird populations, the question of what would happen if the virus propagated successfully among humans has been the subject of much speculation.

Scientists know that garden-variety flu has a reproductive number (R_0) of between 1 and 2, meaning that each case can lead to as many as two new cases. In addition, the disease has a relatively short incubation, and people can become infectious up to 24 hours *before* they show symptoms. A disease that communicable cannot be controlled by public-health measures alone.

If human-adapted bird flu became as contagious as seasonal flu, the mathematical models of Marc Lipsitch of the Harvard School of Public Health suggest that a vaccine would be needed, in addition to public-health measures, in order to control it. But it might take as much as a year to develop the vaccine. The interim strategy, at least in the United States, says Lipsitch, is "targeted layered containment. The idea is to use existing antivirals in combination with social-distancing measures such as school closures and relief from work"; planners hope that would lead to reductions in transmission, delaying the spread of the virus. "These aren't long-term protections," Lipsitch says. "They're just delaying tactics to buy time until a vaccine is ready."

But the reliance on antivirals in this scheme concerns him. Although studies in flu indicate that "most strains appear to be fairly compromised by their resistance mutations, in a pandemic we would be using much more drug than was ever used in normal flu. And there would be so many more cases that the opportunity for the virus to find some way to be resistant without being badly compromised is greater," he says. "One strategy that's been proposed, which would make a lot of sense if a virus was susceptible to more than one class of antiviral, would be to treat people with *both* drugs, in the same way we do for TB or HIV. Rather than doing it one at a time, we'd come at them with both, so if there's one mutant in the person, it can't even start the game."

Yet historical evidence from the flu pandemic of 1918 suggests that cities that adopted public-health strategies such as closing schools and theaters early on were more successful at controlling the outbreak than cities that waited. Thus, a successful response to epidemic emergence of bird flu among humans still seems likely to depend as much on political responses—a willingness to bear the costs of oppressive public-health measures—as on the modern tools of genetic sequencing and biomedical science.

Clockwise from top: The masked palm civet *(Paguma larvata),* the "bridge species" that allowed SARS to jump to humans; a health worker in Beijing checks temperatures at a roadblock; Chinese police confiscate civets at an animal market in Guangzhou, the capital of Guangdong Province, in January 2004. The government killed about 10,000 civets, halting new cases of zoonotic transmission.

CHINA PHOTO/REUTERS/CORBIS

STR/AFP/GETTY IMAGES

was still around. This time, genetic testing of the virus from one of the cases revealed that even though it differed from the epidemic SARS strain that had circulated the previous year, it was very similar to the SARS coronavirus variant found in palm civets. The Chinese government ordered that every palm civet in captivity in the province, about 10,000, be killed immediately.

"Now we had an opportunity for a comparison of these viruses," says Farzan. Analysis of the virus circulating in the civets showed that changing *just one* of the 1,255 amino acids making up the civet viral entry protein made it possible for the virus to bind to the human variant of the receptor. This was the single change necessary to allow SARS to infect humans in both outbreaks.

But that was not the whole story. Although the outbreak of 2002-2003 was deadly, the four-case outbreak of 2003-2004 was mild. Farzan wondered if other changes in the viral fusion protein might account for the differences in virulence. After months of analysis, he and his colleagues found just one tiny change: in a small part of the area where the viral fusion protein contacts the human receptor (called the receptor binding domain), the virus of 2003-2004 had used the amino acid serine, but the deadly 2002-2003 strain used a very similar *(please turn to page 93)*

"INSIDER LUCK"

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be set at the *average* price level of the company's shares during the month of the grant (or an even longer period). Similarly, executives should not continue to have broad freedom to unload equity incentives and to time the unloading based on their private information.

Because the design of options can easily be improved, investors should not be tempted to endorse the move by some companies from stock options to bonus compensation. The problem with stock options is not *inherent* to this instrument, but rather lies in how it has been used. To the extent that those designing pay arrangements do not have the right incentives, bonus payments are as susceptible—probably more susceptible—to gaming than stock-option plans. Indeed, bonus payments have historically been only weakly linked to performance. And insiders' ability to game bonus compensation is currently greatly facilitated by companies' common use of constantly shifting short-term performance metrics whose specifics are generally not disclosed to shareholders.

In the end, however, there is a limit to what imperfectly informed outsiders can do, which is why the most fundamental solution lies in improving the incentives and performance of corporate directors. To reduce the influence that executives have on the setting of their own pay arrangements, one possible approach is to require that the compensation of top executives, or at least of the CEO, not only be approved by the compensation committee but also ratified by a super-majority of the independent directors. Such a requirement would ensure that arrangements unable to gain widespread support among the company's independent directors would not be adopted. Furthermore, directors' own recognition that a small number of them *can* make a difference in pay decisions may counteract whatever factors might otherwise induce them to go along with flawed compensation arrangements.

Most important, to improve executive compensation we need to provide directors with stronger incentives to focus on and serve shareholder interests. Legal rules and corporate arrangements have long weakened shareholder rights and insulated the board from shareholder involvement. The rules governing corporate elections should be reformed to provide shareholders with a viable power to replace directors. And barriers to shareholders' ability to place changes in governance arrangements on the ballot and adopt them should be dismantled. Even though significant backdating may belong to the past, its underlying causes are problems with which the corporate governance system must continue to wrestle. Reforms that make directors more accountable and more focused on shareholder interests are long overdue.

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THE SARS SCARE

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but distinct amino acid, threonine. "There is just one methyl group—a carbon and three hydrogens—that makes the difference here," says Farzan. "And that didn't make any sense." The expectation was that multiple changes would be necessary to make a viral zoonosis deadly to humans. "But all the data showed that if you make that change, you get a much more efficient replication on the palm-civet receptor, and a much more efficient replication on the human receptor." This particular change was rare—so rare as to be found in only one of 20 sequences in animals—but it was 100 percent present in all the epidemic SARS viruses that replicated and transmitted in humans in 2002-2003. The 2003-2004 virus contained the preliminary change required for it to jump to humans, but lacked this additional change that made the earlier outbreak so explosive.

Working with Stephen Harrison's lab, Farzan then analyzed the structure of the viral fusion protein and receptor complex. X-ray crystallography immediately revealed that the substitution of threonine for serine—"this little, subtle change"—directly interacted with the most important amino acid on the receptor. "So it was satisfying," he recalls. "There we had this tiny little change, one we couldn't imagine would make a big difference, but it turned out to be the highest-energy binding point on this interaction with the receptor." In fact, the single methyl group of four atoms made a thousand-fold difference in the "binding energy" of virus and target cell. "Not only was there a huge difference in the physical association of these two things," Farzan says, "but also in the efficiency of replication. A whole lot of characterization work came down to two amino acids and their counterparts on the receptor. And this is probably the change that made SARS SARS."

Recent work has proven the importance of the receptor-protein interaction. "If you put the human receptor into a mouse," Farzan says, "the mouse gets SARS. Making the interaction efficient is enough to cause the disease."

// The Evolution of an Epidemic

How an ancestor of the SARS virus, hosted in some animal, acquired this particular, human-adapted change is a more difficult question to answer, demanding knowledge of both viruses and zoonoses. There is a common misconception about how zoonoses infect humans, Farzan says. In our anthropocentric way, we imagine that the process is linear: for example, that a virus jumps from a bird to a pig to a human. But a typical zoonosis is more like an explosion: the virus somehow escapes its reservoir host and infects all kinds of animals, changing rapidly, perhaps multiple times, as it spreads in a network of recombination and cross-transmission through many different hosts.

"It randomly bumps into humans, usually when there has been a change in population or a change in patterns with respect to some animal," he explains. In the animal markets of Guangdong Province, cages of bats, badgers, palm civets, raccoon dogs, and other animals were stacked one on top of the other. The opportunity for fecal-oral viral transmission in this context was tremendous, recalling the vertical human transmission at Amoy

Megan Murray

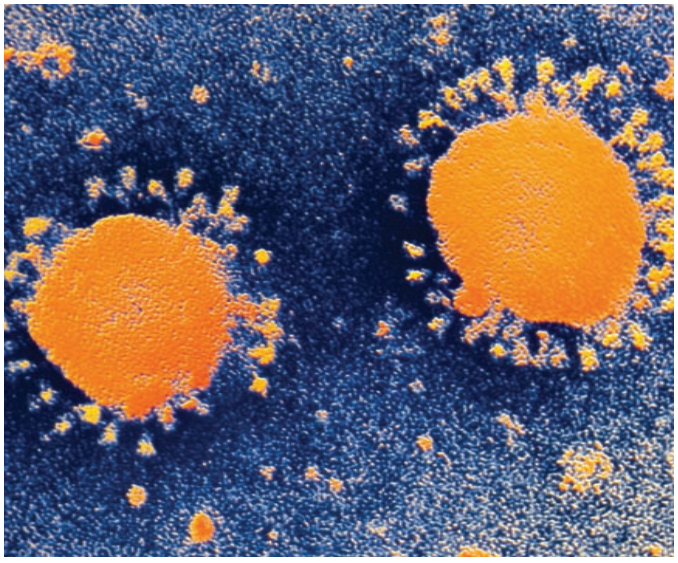

PHOTO RESEARCHERS, INC.

A colored transmission electron micrograph of two human coronaviruses shows the fusion proteins that give this family of viruses its name.

Gardens. We may never know the precise event that allowed SARS to infect humans, but the scale of the Guangdong markets and the proximity of humans and animals there probably contributed to the emergence of SARS.

"There's a saying, 'Quantitative change leads to qualitative change,'" Farzan notes. When there is a lot of virus in a population, that contributes to its genetic diversity, which then raises the probability that a variant will emerge that can efficiently infect humans. Viruses have developed evolutionary strategies to accelerate their diversity above and beyond the normal mutation rate caused by errors in their replication machinery—they have "evolved to evolve." Different viruses have various ways of doing this. SARS uses recombination: two viruses meet, mix together a little, and create a new virus—"kind of like virus sex," Farzan says. Flu is even more sophisticated, he says, because it has eight independent segments that it can reassort to create, theoretically, 256 combinations.

One speculation about the origin of SARS that Farzan's lab has explored involves a little-known human coronavirus discovered within the last two years. Unusually, it uses the ACE2 receptor, like SARS. Other scientists have shown that bats in China host a coronavirus, non-lethal to them, that is 92 percent similar to SARS. "That's a long way to go to get to SARS," Farzan cautions, but if there is an animal variant of this recently discovered coronavirus, as well as another animal that is vulnerable to infection from the bat virus, that would provide a host for a recombination event. Exploring this further, he says, would require fieldwork in China, "so this will not be our work."

// Toward Therapies—and Prevention

The irony of all this, Farzan knows, is that all the research "really didn't help us address the first wave. Had there been a second wave, we would have had vaccines, we would have had therapies, we would have been ready." In fact, the lab of HMS associate professor of medicine Wayne Marasco used Farzan's synthetic SARS protein to identify an antibody therapy that might block the virus's entry apparatus. Eight antibodies from Maras-

Photograph by Jim Harrison

"The places least likely to have surveillance—those with the most social disruption and economic stress—are the places where diseases are most likely to emerge." —Megan Murray

co's 27-billion antibody library, one of the world's largest, recognized and bound to the SARS entry protein. Of the eight, one actually prevented live SARS viruses from entering human cells in testing at the Centers for Disease Control.

Now, four years later, Farzan says the science "has progressed to a point where, for example, if we had an Ebola outbreak, we would be in a position to immediately vaccinate individuals with vaccines we would be pretty sure would work, [based on] animal studies. We would also be able to treat people with stopgap therapies. So we would have a lot of things to hit these viruses with early on. SARS taught us how to [identify viral receptors more quickly,] and it also left people who worked on SARS vaccines in a better position to develop an Ebola vaccine, and so forth.

"I think the lesson from SARS and the lesson from flu as well," he continues, "is that they started us thinking about the mechanisms that viruses use to accelerate their diversity. Focusing on the molecular details by which they do this is not going to give us a quick therapy, but understanding the evolution and diversity of viruses certainly could give us a better handle on what [threats] might emerge out of an animal population." Some of Farzan's current flu work focuses on the basic viral-reassortment process and what things humans do, accidentally or intentionally, to change the efficiency of that reassortment.

Humans, for instance, have created antiviral drugs like Tamiflu. These can be invaluable tools for disrupting a viral attack, but they work by *increasing* the level of reassortment of the virus so much that after replication it can't escape the interior of the cell, or "bud out" of the cell membrane. "[But] if one of the viruses being treated with the drug is resistant, reassorts, *and* buds out, you get the worst of both worlds," Farzan says. With just *one* resistant virus in the population, accelerated diversity results. "These drugs are not an unalloyed good, and may end up [losing their efficacy] like antibiotics in some [future] time frame," he explains. "I wish people wouldn't treat a normal flu with these drugs. For the good of humanity, *save them*!"

SARS has also renewed interest in the cultural circumstances that contribute to novel zoonotic infections. "Too little is known about the social, economic, and historical context in which new diseases emerge," says HSPH's Megan Murray. She notes as one example that the epidemic of pneumonic plague that swept Manchuria from 1910 to 1911, killing 95 percent of the people it infected, took place during "a huge labor migration to the north of China, partly due to famine in the south of China at the time, and partly related to the price of sable in Europe, which had become so expensive that people were now buying tarbagan [a type of marmot] fur. This huge migration of hunters who didn't know how to handle ill animals led to this pneumonic plague epidemic."

Change of another sort led to the emergence of Nipah virus in 1999. "Global climate changes were a factor in massive fires in Indonesia so extreme that cities lost sunshine for several days because of the smoke," Murray continues. The disaster also caused giant fruit-eating bats to leave the rain forest where they were living and begin feeding in mango trees near pig farms in neighboring Malaysia. When bat-saliva-covered fruit fell to the ground, the pigs ate it, ingesting a load of virus as well—and when they were slaughtered, the virus infected butchers, with a case-mortality rate approaching 50 percent.

Knowing this history will not tell us where the next disease will emerge, says Murray. But one of the things SARS has demonstrated is the effectiveness of tactics that help prevent emerging diseases. Farzan says that the culling of palm civets, which were a necessary conduit or "bridge species" for the virus to reach humans, almost certainly prevented the reemergence of the disease after 2003-4. Murray adds, "If you're thinking intelligently about what kinds of infectious-disease surveillance need to be in place, then you know that the places where you're *least* likely to have surveillance—the places where there's the most social disruption and the most economic stress—are the places where diseases are most likely to emerge." That tells us how, globally, we should organize surveillance and exposes "the inadequacy of the [merely] national approach to infectious-disease control."

But even if adequate surveillance is in place, there is the further question of "country-specific practices" of control. In the current, sporadic bird-flu outbreaks, for example, whether or not poultry farmers are paid for culling their birds may influence whether or not they hide their sick poultry. "These are not places like Toronto," says Murray. "These are subsistence farmers whose absolute livelihood depends on their backyard poultry. Is some global group supposed to deal with that? WHO is trying to work with [local governments] on it, but where will the funds come from for that kind of reparation? As these policies are brought to the forefront, it has become increasingly obvious what *should* be done, though effecting intelligent change may be hard."

One of the most lasting impacts of SARS, says Marc Lipsitch, was the way it raised awareness of how much social disruption even a relatively small epidemic could cause. "Fewer than 10,000 cases, and Toronto lost tourism. Hong Kong experienced all sorts of economic losses, as did Asia as a whole. Medical care was disrupted in these places. Travel was disrupted. So SARS certainly increased the talk about the need to transparently report infectious outbreaks."

Yet he worries that the world is inadequately prepared for anything more infectious than SARS. On the one hand, he said at a May 2005 symposium on avian flu, "The control of SARS was a tremendous public-health success." Stopping an outbreak of respiratory disease without any biological interventions such as a vaccine or drugs, he notes, was close to unprecedented. "But overall, the sum total of control for SARS was barely adequate. Flu is a considerably harder problem. The fact that we barely controlled SARS is not at all reassuring."

Jonathan Shaw '89 is managing editor of this magazine.