underwater instruments to continuously track temperature, salinity, and current velocity at various depths across the North Atlantic Ocean for 4 years. The goal of this joint U.S.-European effort, planned to run for 10 years, is to understand how ocean circulation is changing, which in turn will affect how climate change plays out. The instruments take data automatically, but if Straneo doesn't update them, they'll likely stop recording after this summer. "Having a 1-year gap will be a major loss," she says.

This year is also a missed opportunity for one of ecology's biggest data projects, the National Ecological Observatory Network (NEON). Decades in the making, NEON aims to monitor environmental changes in a range of North American ecosystems (*Science*, 25 September 2015, p. 1436), and 2019–20 was to be the first full year when it could gather standardized physical, chemical, environmental, and biological data from all its 81 U.S. sites. Some sites are new, but others have been operational for almost 10 years.

But on 23 March, NEON ceased all inperson and onsite work, such as trapping mammals and insects and sampling soil and water. Automated instruments collect much of NEON's data. But Paula Mabee, NEON's scientific director, says she was surprised by how many automated instruments need human tenders for calibration or to manage hazardous chemicals. Of the 73 data products on autopilot, "we proactively shut down" 24, including measurements of carbon dioxide and rainfall, she says.

The missing data will have short- and long-term implications, says Michael Dietze, an ecologist at Boston University. For example, data on tick and mammal populations are key to his team's annual predictions about when and how many nymphs of the deer tick that transmits Lyme disease will emerge.

One of the biggest blows is the grounding of NEON's airplanes. They are outfitted with cameras and remote sensing equipment to keep tabs on such variables such as the heights of trees and the chlorophyll and nitrogen content of plants, which are important for calculating carbon uptake. Philip Townsend, an ecologist at the University of Wisconsin, Madison, has been working to turn those measurements into easy-to-use maps. He'd planned to groundtruth his efforts by collecting leaves this season. But this spring, there will be both airborne measurements and leaf collection are on hold.

Yet as disappointed as he and others are, delaying or shutting down such operations "is clearly the right decision," Townsend says. "You want people to be safe." ■

With reporting by Ann Gibbons and Paul Voosen.

COVID-19

From mice to monkeys, animals studied for coronavirus answers

Infected lab animals can assess drugs and vaccines

By **Jon Cohen**

Beloved as pets, Syrian hamsters are winning another kind of attention from scientists trying to understand and defeat COVID-19. Fifteen years ago, scientists found the hamsters could readily be infected with the coronavirus that causes severe acute respiratory syndrome (SARS). Their symptoms were subtle, so the animals didn't get much traction as a model for the disease. But with COVID-19, caused by a related virus, SARS-CoV-2, the model's prospects appear brighter.

When physician scientist Jasper Fuk-Woo Chan of the University of Hong Kong (HKU) and co-workers recently infected eight hamsters, the animals lost weight, became lethargic, and developed ruffled fur, a hunched posture, and rapid breathing. High levels of SARS-CoV-2 were found in the hamsters' lungs and intestines, tissues studded with the virus' target, a protein receptor called angiotensin-converting enzyme 2 (ACE2). These findings "closely resemble the manifestations of upper and lower respiratory tract infection in humans," Chan and co-authors wrote in a 26 March paper in *Clinical Infectious Diseases*.

> **"Everybody has been thrown into a rush to get an animal model that's faithful to the human condition and reproducible."**
>
> **Chad Roy**, Tulane National Primate Research Center

That team is but one of dozens of groups racing to develop animal models that can help find effective COVID-19 vaccines and treatments and clarify precisely how SARS-CoV-2 causes disease. The teams are often shorthanded because of the pandemic's shelter-in-place restrictions, but they are collaborating intensively. Each Thursday, the World Health Organization arranges a video conference of nearly 100 scientists, regulators, and funders who are collectively working with a menagerie of lab animals, including mice, ferrets, and several species of monkeys. "A lot of the traditional silos of information are really coming down," says the group's co-chair, William Dowling, who works on vaccine development at the Coalition for Epidemic Preparedness Innovations.

The group swaps the latest data and tips, such as the efficiency of different infection routes and the most likely places to find the pathogen in animals. "Everybody has been thrown into a rush to get an animal model that's faithful to the human condition and reproducible," says Chad Roy of the Tulane National Primate Research Center.

One monkey study has already delivered an encouraging result, suggesting that infection produces at least short-lived immunity. But a wide range of species may be an asset. "You need the right model for the right question," says Vincent Munster of the Rocky Mountain Laboratories branch of the U.S. National Institute of Allergy and Infectious Diseases, whose team focuses on monkeys. He cautions against dismissing an animal model simply because SARS-CoV-2 produces an effect, such as death from a brain infection, that doesn't reflect typical disease in humans. "That's a big misunderstanding," he says, noting that "humans don't have a tail, either."

A top priority is to test experimental vaccines by immunizing animals and then "challenging" them with the virus—experiments that must be done in biosafety level 3 labs. Animal models could also warn of dangers of COVID-19 vaccines and drugs; some experimental vaccines against the related SARS virus, for example, triggered antibodies that enhanced disease severity when test animals were challenged. Furthermore, experiments with animals may explain why children rarely develop symptoms, how readily SARS-CoV-2 transmits through fine aerosolized particles, and whether host genetic factors make some people more susceptible to severe disease.

Mice—easy to handle and breed—have long been the mainstay of biomedicine, and a good mouse model would be a boon for COVID-19 research. But mice shrug off infection with SARS-CoV-2, because the mouse ACE2 has key differences from the human one. "It's funny how the virus can have such devastation in humans, and then you can give a million particles to a mouse and it's inert," says Timothy Sheahan, who is developing mouse

COVID-19 models at the University of North Carolina (UNC), Chapel Hill.

Chan, working with HKU's microbiologist Kwok-Yung Yuen and others, pinpointed the problem by doing a cross-species comparison of the region of ACE2 to which SARS-CoV-2 first attaches. In the mouse, 11 of 29 amino acids of this domain differed from the human version. (Rats had 13 differences, but hamsters only had four.)

One way around the roadblock is to engineer mice that express both the mouse and the human versions of the receptor's gene, *ACE2*. In 2007, Stanley Perlman of the University of Iowa did just that to study SARS. Although the SARS coronavirus can infect mice through their ACE2, they only develop mild symptoms. Equipped with the human ACE2, mice succumb to a lethal brain disease. This model helped evaluate potential SARS vaccines and treatments, and also teased out the impact of different immune responses.

But demand for the modified animals dwindled after the SARS outbreak subsided in 2003, and Perlman gave them to Jackson Laboratory (JAX), the mammoth nonprofit mouse supplier. It froze the animals' sperm, and since SARS-CoV-2 surfaced, has raced to breed the mouse again. "We've had over 1000 requests at this point," says Nadia Rosenthal, JAX's scientific director.

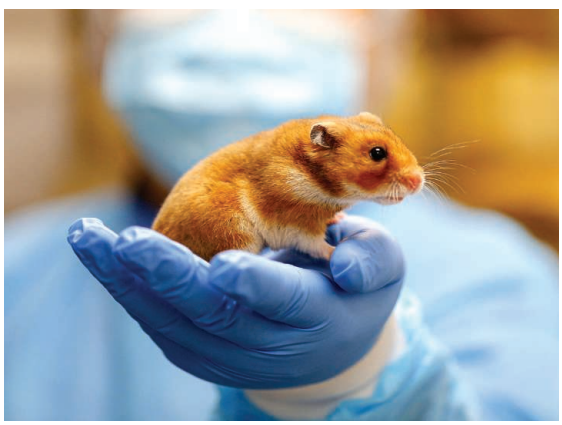
A Chinese team that also engineered mice to express the human ACE2 protein to study SARS kept some of the transgenic animals and has already infected them with SARS-CoV-2. They lost weight and showed signs of pneumonia but little else, Qin Chuan of Peking Medical Union College and colleagues reported in a preprint published on bioRxiv 28 February. "That's really very, very, very mild disease," Perlman says.

Perlman is waiting for JAX to supply the modified mice, but as a stopgap measure he stitched the human gene for ACE2 into an adenovirus, which he used to infect mice so that some of their lung cells made the receptor. When infected with SARS-CoV-2, the mice lost 20% of their weight—more than twice what Qin's team saw—but none died.

To create what Rosenthal calls a more "authentic" mouse model, researchers at JAX are using the genome editor CRISPR to change the sequence of the native mouse ACE2 so that the encoded protein is recognized by the virus. Sheahan, in collaboration with UNC's Ralph Baric, is instead tailoring the virus to the mouse, genetically tweaking its surface protein so that it can infect unaltered mice.

Other SARS-CoV-2 researchers are turning to rats. They are no more susceptible to COVID-19 than mice, but their larger size is an advantage. "You often want to do repetitive bleeding in an experiment, and you can't do that with mice," says Prem Premsrirut of Mirimus, a company that is collaborating with an academic group to engineer a rat model by altering its ACE2 receptor. Vaccine studies, for example, often assess how different doses affect antibody responses over several days. Premsrirut notes that "most toxicology studies" of drugs also start in rats. "If you can study a drug directly in rats, you're a step ahead."

Ferrets are a mainstay of research on another respiratory disease, influenza, because the flu virus not only infects them, but produces symptoms that mimic the human disease. Infected ferrets even sneeze, readily spreading flu though the air. The animals may not prove as faithful a model for COVID-19, however. The virus does infect them and causes increases in body temperature, Young Ki Choi of Chungbuk National University and colleagues reported online on 6 April in *Cell Host & Microbe*. But it did not replicate to high levels and the ferrets didn't develop other symptoms.



Syrian hamsters are relatively easy to infect with the new coronavirus and develop mild, but easily detected, symptoms.

The team did find evidence that ferrets might mimic one aspect of COVID-19: respiratory transmission. The animals they infected not only spread SARS-CoV-2 to cage mates, but to two of six ferrets in adjoining cages. Although researchers suspect SARS-CoV-2 primarily transmits through relatively large respiratory droplets that quickly fall to surfaces, this finding suggests finer particles, able to drift in the air for longer periods and over longer distances, can also carry infectious virus. "Aerosol infection is not as highly efficient as direct contact, but it's possible," concludes co-author Jae Jung of the University of Southern California.

The animals likely to carry the most weight in assessing potential drugs and vaccines are monkeys. Although they are expensive and difficult to handle, their close genetic relationship to humans often makes monkeys the gate keeper to clinical trials of drugs and vaccines. "This is going to be our near clinical model that we're going to rest heavily on," Roy says. Intense efforts to infect four different monkey species with SARS-CoV-2 began shortly after the isolation of the virus from people. "There's not been an emergent species that leads me to say, 'Oh wow, this is it,'" says Roy, who is testing African greens and rhesus macaques, and has looked closely at infection data from cynomolgus monkeys. (Marmosets are also being examined.)

In a Dutch study of eight cynomolgus monkeys inoculated with SARS-CoV-2, the four oldest ones developed higher levels of the virus in nose and throat swabs than younger animals. None developed symptomatic disease, but autopsies found some lung damage in two of four animals. "This looks like what you see in mild cases of humans," says Bart Haagmans from Erasmus University Medical Center, whose team published its data on 17 March on bioRxiv.

Monkey studies have also begun to explore questions about immune protection. Two rhesus monkeys that recovered from being infected with SARS-CoV-2 at Peking Union Medical College were resistant to reinfection 4 weeks later. The finding provides a hint of good news, as it suggests both natural infections and vaccine-triggered immunity will provide at least some subsequent protection.

Like ferrets, monkeys are being used to address the controversial issue of how much risk people face from aerosol transmission of SARS-CoV-2, which could inform debates about the value of homemade face masks. Roy and, separately, Douglas Reed at the University of Pittsburgh are staging experiments in air chambers that attempt to infect monkeys through this route. Humans who suffer from severe COVID-19 often have underlying diseases, such as hypertension or diabetes, and Roy says researchers may have to find or create monkeys with these comorbidities to develop the most meaningful model.

The list of animal models likely will grow rapidly. A study published online on 8 April by *Science*, for example, reported that the virus can infect cats. Autopsies showed the infection led to "massive" lesions in their nasal passages, trachea, and lungs.

Dave O'Connor of the University of Wisconsin, Madison, who is studying SARS-CoV-2 in cynomolgus monkeys, says the field will ultimately winnow down models. "It might turn out that some models are not really worth pursuing after we do this sort of foundational work, but I just don't think we're there yet. We need to let the data guide us." ■

PHOTO: DEWI ROWLANDS/LABORATORY ANIMAL UNIT/UNIVERSITY OF HONG KONG

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