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April-May 2020

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Anatomy of an Outbreak

The new coronavirus raises questions about how pathogens evolve–and if we're ready to face them

WITH COVERAGE FROM nature

LIZ TORMES

Warfare in Wonderland

In Lewis Carroll's *Through the Looking-Glass,* the Red Queen tells Alice that "it takes all the running you can do, to keep in the same place." This passage inspired the name of one of the principal concepts of evolution: in its broadest sense, the Red Queen hypothesis describes the evolutionary arms race between two species—say, predator and prey—who evolve side by side in response to each other, both vying for survival by adapting to the pressure of coexistence. In the past several weeks of covering the new global coronavirus outbreak, the Red Queen has certainly been running around my mind. Whenever a new virus emerges in the human species, scientists rush to quickly understand its unique structure and, hopefully, devise a vaccine to counteract, or at least contain, it. In this issue's cover story, Simon Makin describes what researchers know so far about the structure of coronaviruses and what tools we may have to disable them (see "How Coronaviruses Cause Infection—from Colds to Deadly Pneumonia"). As case numbers pile up in this country and others, epidemiologists must work swiftly. As the queen says: "If you want to get somewhere else, you must run at least twice as fast."

Elsewhere Nicole Wetsman reports on how social media offers doctors and researchers a new way to share their research findings (see "How Twitter Is Changing Medical Research"). And Heidi Ledford updates readers on the progress of clinical applications of the CRISPR-Cas9 gene-editing complex, some of which are inching closer to real disease treatments (see "Quest to Use CRISPR against Disease Gains Ground"). Curiouser and curiouser.

Andrea Gawrylewski
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Health & Medicine

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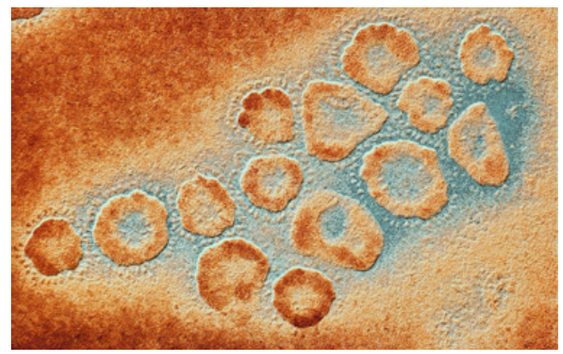

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On the Cover

The new coronavirus raises questions about how pathogens evolve—and if we're ready to face them

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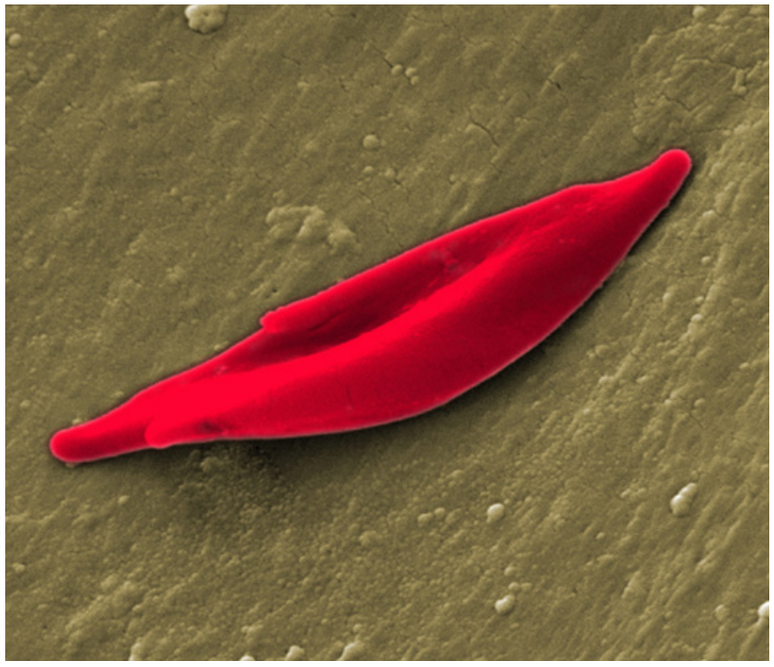

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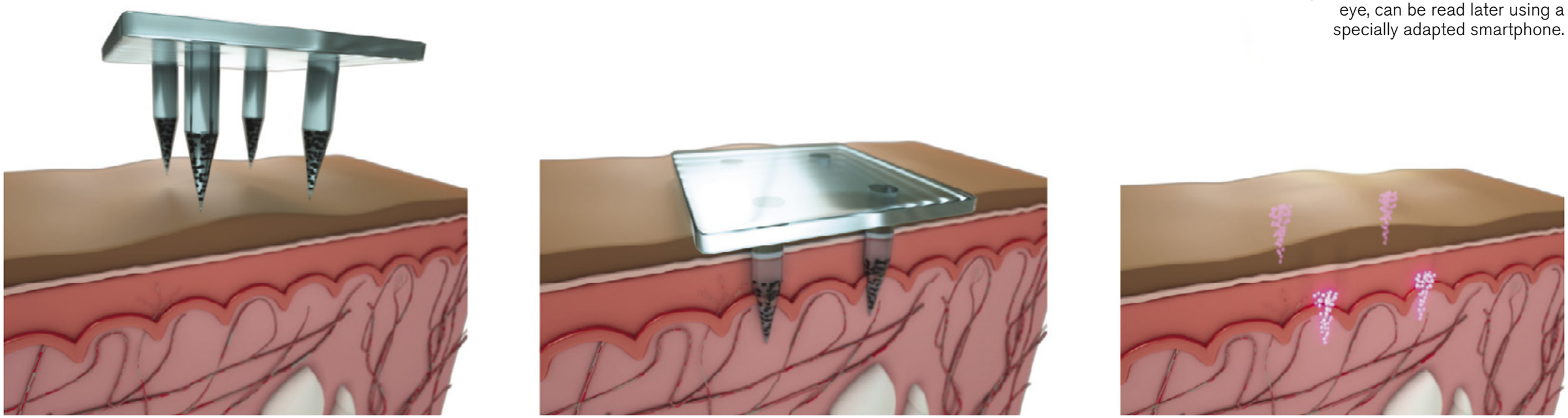


M.I.T. engineers have developed a way to store medical information under the skin, using a quantum dot dye that is delivered, along with a vaccine, by a microneedle patch. The dye, which is invisible to the naked eye, can be read later using a specially adapted smartphone.

Invisible Ink Could Reveal Whether Kids Have Been Vaccinated

The technology embeds immunization records into a child's skin

Keeping track of vaccinations remains a major challenge in the developing world, and even in many developed countries paperwork gets lost and parents forget whether their child is up to date. Now a group of Massachusetts Institute of Technology researchers has developed a novel way to address this problem: embedding the record directly into the skin.

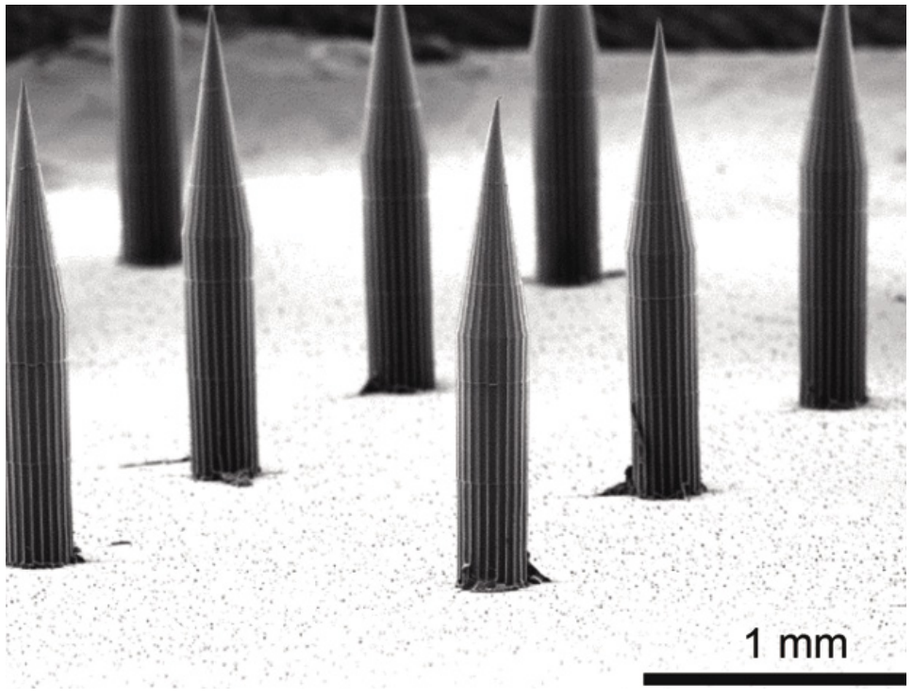
Along with the vaccine, a child would be injected with a bit of dye that is invisible to the naked eye but easily seen with a special cell-phone filter combined with an app that shines near-infrared light onto the skin. The dye would be expected to last up to five years, according to tests on pig and rat skin and human skin in a dish.

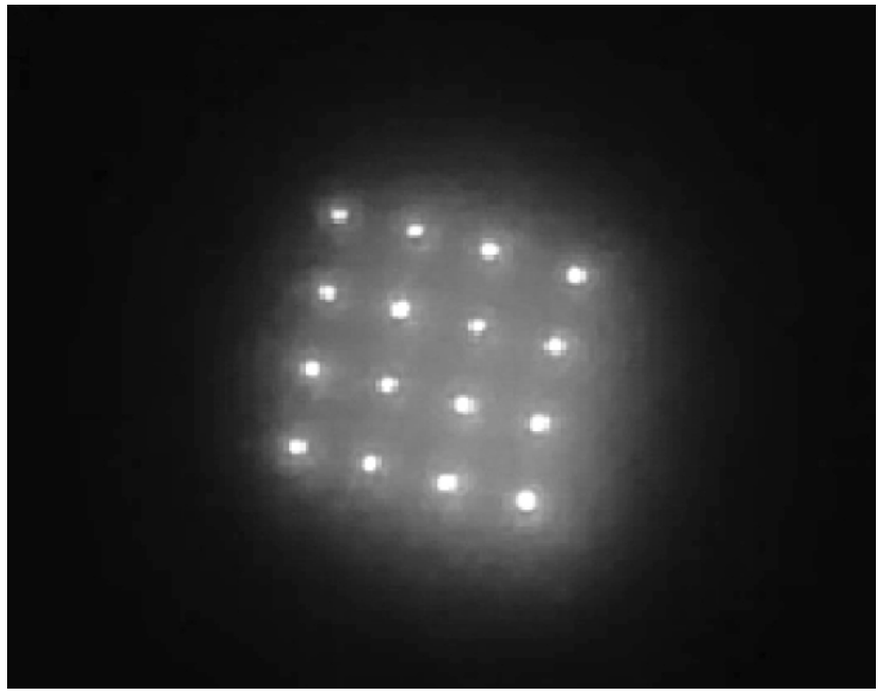
The system—which has not yet been tested in children—would provide quick and easy access to vaccination history, avoid the risk of clerical errors and add little to the cost or risk of the procedure, according to the study, published last December in *Science Translational Medicine*.

"Especially in developing countries where medical records may not be as complete or as accessible, there can be value in having medical information directly associated with a person," says Mark Prausnitz, a bioengineering professor at the Georgia Institute of Technology, who was not involved in the new study. Such a system of recording medical information must be extremely discreet and acceptable to the person whose health information is being recorded and to his or her family, he says. "This, I think, is a pretty interesting way to accomplish those goals."

The research, conducted by M.I.T. bioengineers Robert Langer and Ana Jaklenec and their colleagues, uses a

SECOND BAY STUDIOS





A close-up microscope image of the microneedle array, which could deliver quantum dots into skin (*left*). The quantum dots after being administered in the skin of rodents (*right*).

patch of tiny needles called microneedles to provide an effective vaccination without a teeth-clenching jab. Microneedles are embedded in a Band-Aid-like device that is placed on the skin; a skilled nurse or technician is not required. Vaccines delivered with microneedles also may not need to be refrigerated, reducing both the cost and the difficulty of delivery, Langer and Jaklenec say.

Delivering the dye required the researchers to find something that was safe and that would last long enough to be useful. "That's really the biggest challenge that we overcame in the project," Jaklenec says, adding that the team tested a number of off-the-shelf dyes that could be used in the body but did not find any that endured when exposed to sunlight. The team ended up using a technology called quantum dots, tiny semiconducting crystals that reflect light, which were originally developed to label cells during research. The dye has been shown to be safe in humans.

The approach raises some privacy concerns, says Prausnitz, who helped invent microneedle technology and directs Georgia Tech's Center for Drug Design, Development and Delivery. "There may be other concerns that patients have about being 'tattooed,' carrying around personal medical information on their bodies or other aspects of this unfamiliar approach to storing medical records," he says. "Different people and different cultures will probably feel differently about having an invisible medical tattoo."

When people were still vaccinated for smallpox, which has since been eradicated worldwide, they got a visible scar on their arm from the shot that made it easy to identify who had been vaccinated and who had not, Jaklenec says. "But obviously we didn't want to give people a scar," she says, noting that her team was looking for an identifier that would be invisible to the naked eye. The researchers also wanted to avoid technologies that would raise even more privacy concerns, such as iris scans and databases with names and identifiable data, she says.

The work was funded by the Bill & Melinda Gates Foundation and came about because of a direct request from Microsoft founder and philanthropist Bill Gates himself, who has been supporting efforts to wipe out diseases such as polio and measles across the world, Jaklenec says. "If we don't have good data, it's really difficult to eradicate disease," she says.

The researchers hope to add more detailed information to the dots, such as the date of vaccination. Along with them, the team eventually wants to inject sensors that could also potentially be used to track aspects of health such as insulin levels in diabetics, Jaklenec says.

This approach is likely to be one of many trying to solve the problem of storing individuals' medical information, says Ruchit Nagar, a fourth-year student at Harvard Medical School, who also was not involved in the new study. He runs a company called Khushi Baby that is also trying to create a system for tracking such information, including vaccination history, in the developing world.

Working in the northern Indian state of Rajasthan, Nagar and his team have devised a necklace, resembling one worn locally, that compresses, encrypts and password-protects medical information. The necklace uses the same technology as radio-frequency identification (RFID) chips—such as those employed in retail clothing and athletes' race bibs—and provides health care workers with access to a mother's pregnancy history, her child's growth chart and vaccination history, and suggestions on what vaccinations and other treatments may be needed, he says. But Nagar acknowledges the possible concerns all such technology poses. "Messaging and cultural appropriateness need to be considered," he says.

—Karen Weintraub

Virus Spread by Shrews Linked to Human Deaths from Mysterious Brain Infections

The pathogen has been newly identified in eight cases of encephalitis in Germany over the past 20 years

Bicolored white-toothed shrew in its natural environment

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Borna disease virus 1 (BoDV-1) causes a bizarre and deadly neurological infection in horses, sheep and other domesticated mammals in parts of Germany, Switzerland, Liechtenstein and Austria. Borna disease was named after a city in eastern Germany where it once killed numerous horses in the late 19th century. Infected animals have been known to engage in strange behaviors such as smashing their heads into things and "pipe smoking"—an informal term for when animals are eating hay and suddenly stop chewing mid-mouthful, with the uneaten portion protruding like a pipe. But the disease does not appear to spread between horses; they are thought to acquire it from shrews, which can live in hay and secrete or excrete fluids containing the virus.

About 14 years ago researchers identified the bicolored white-toothed shrew as a reservoir host—an organism in which a virus replicates but does not usually cause illness—for BoDV-1. Horses and sheep are considered "dead-end hosts" that cannot spread the pathogen. For decades, scientists had debated whether the virus is zoonotic, or capable of jumping from animals to humans. Several studies even suggested that it might be present in people with psychiatric disorders such as depression, schizophrenia and bipolar disorder. It was later shown, however, that the viral RNA sequences detected in these studies were likely the result of laboratory contamination, and research on human infections subsided.

But in 2015 a related type of bornavirus found in exotic squirrels was implicated in at least four human deaths. Then, between 2018 and 2019, scientists detected the classical bornavirus, BoDV-1, in five peo-

ple in Germany who suffered serious or fatal encephalitis (brain inflammation caused by infection)—three of whom were recipients of organ transplants and were taking drugs to suppress their immune system. Now, in a study published in January in *Lancet Infectious Diseases*, researchers have reported eight additional cases of BoDV-1 infection in humans who died of encephalitis. The pathogen appears to have flown under the radar for decades, but the researchers say doctors should be considering it a potential cause in such deaths.

"We now have eight more cases, and these provide additional material for a better understanding of the disease," says Martin Beer, head of the Institute of Diagnostic Virology at the Friedrich Loeffler Institute in Germany, who was co-senior author of the new study and also was part of the team that reported the squirrel bornavirus infections. The findings confirm that the virus can infect humans and cause deadly encephalitis. "But the risk is, to our opinion, pretty low," Beer says.

Beer and his colleagues analyzed postmortem brain tissue from 56 patients in southeastern Germany's state of Bavaria between 1999 and 2019. The samples were tested for genetic material from BoDV-1, which the researchers verified by additional testing for antibodies to it. Seven out of nine patients who died of encephalitis of unknown cause at one diagnostic center later tested positive for the virus (one of these cases had been reported previously). An additional two cases with positive tests were also included in the analysis.

The results confirmed that the virus had caused eight new encephalitis cases; two of the patients were immune-compromised individuals who had received organ transplants, and six were not. Because other recipients of organs from the same donor did not test positive for the virus, researchers think the transplant recipients who died from the virus probably acquired it because they were immune-compromised, not from the donor. The patients suffered symptoms including headache, fever and confusion that later progressed to coma and ultimately death.

All of the patients lived in rural areas and worked or spent a lot of time outside. Most had also been around cats, which are known to catch shrews and sometimes present them to their owners. Beer and his team hypothesize that the patients were exposed to BoDV-1 this way or perhaps by inhaling dust containing dried shrew urine. Future research will be needed to determine the exact infection route, he says.

Once in a human or horse host, the virus is thought to cross the blood-brain barrier into the central nervous system, where it triggers the host's immune system to attack brain tissue. "It's not the virus killing the brain cell or nerve tissue," Beer explains. "It's the [host's] own immune system recognizing the infection and starting to kill parts of brain."

There is no known treatment for the disease, but researchers are exploring whether antivirals such as ribavirin—which has been shown to kill a range of bornaviruses in cells grown in a dish and in animal studies—could be effective in treating BoDV-1 infections in humans. Beer and his colleagues have plans to test newer antivirals against the virus in animal studies.

"I think it's an excellent paper," says Norbert Nowotny, a professor of virology at the University of Veterinary Medicine, Vienna, who was not involved in the new study but was part of the group that discovered shrews were a reservoir host for the virus. "This Borna disease is really a strange disease—it's not like a flu," he adds, noting that it does not cause epidemics. "It's a single-animal disease, and it seems to be the same in humans."

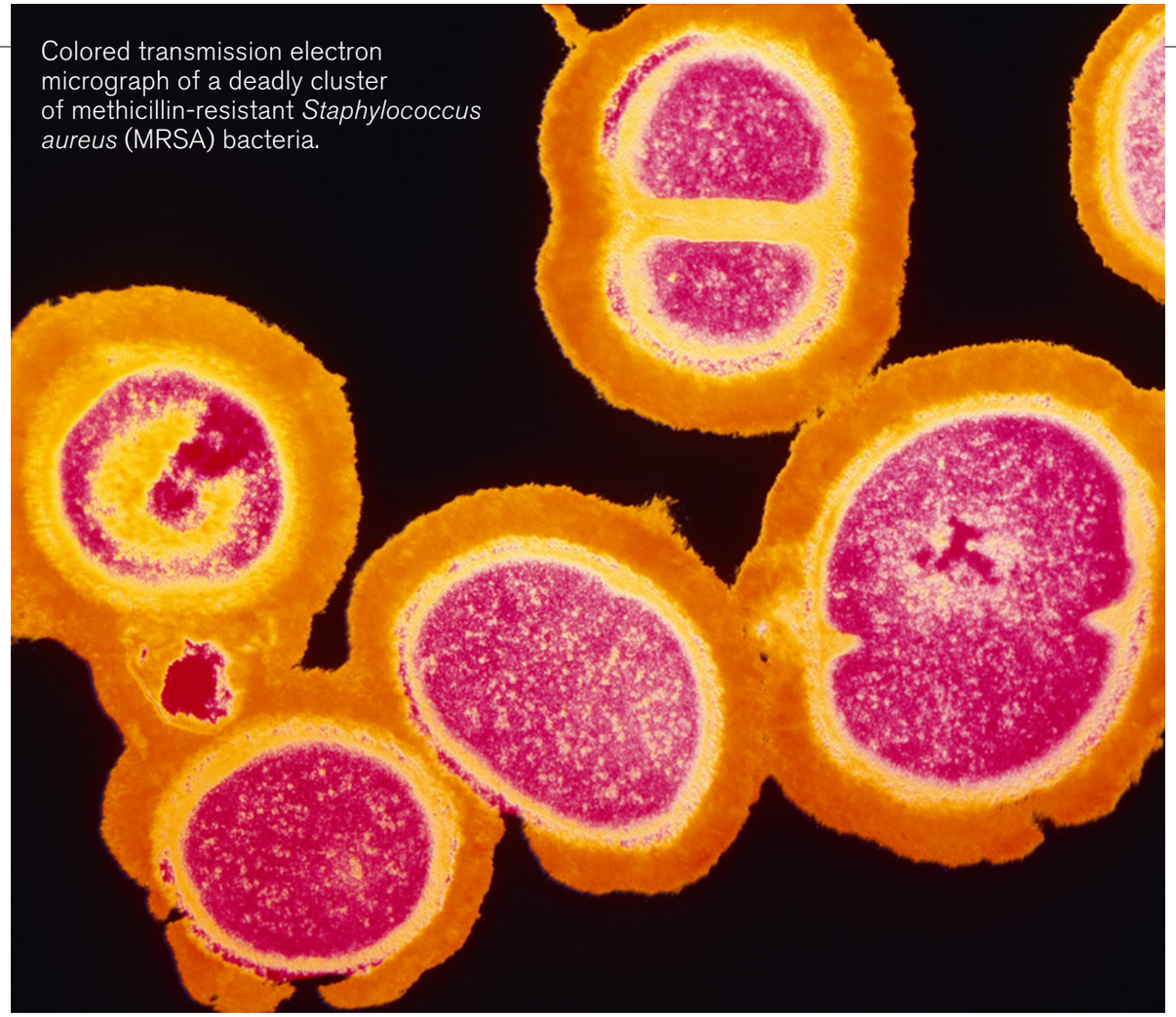
The virus itself is somewhat unusual in that it has a very short genome and makes only a few proteins. It does not seem to infect many individuals—but when it does, it kills them very efficiently. Numerous other zoonotic viruses infect many people but are seldom deadly. Previous research has found that humans and most mammals actually have bornavirus sequences in their genomes, which may help organisms protect themselves against infection, some hypothesize.

Fortunately, the virus does not appear to be transmitted between humans. "I think we are all happy that this is not a virus that can spread easily," Beer says. But in light of these new findings, doctors should consider BoDV-1 as a possible cause of encephalitis in areas where it has been known to infect humans and horses.

—Tanya Lewis

Bacteria "Tolerant" of One Antibiotic Are More Likely to Develop Resistance

Even combination therapies do not prevent such pathogens from becoming resistant



Colored transmission electron micrograph of a deadly cluster of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria.

KARI LOUNATMAA *GETTY IMAGES*

One way to address the growing problem of antibiotic resistance has been to use multiple drugs. Give patients two antibiotics, the thinking goes, and even if the microbes are resistant to one of them, the other will work. But a new study suggests that drug combinations can actually speed the development of resistance.

In a paper published in January in *Science,* Israeli researchers showed that when a patient develops tolerance to a single antibiotic in a combination—meaning it kills bacteria more slowly—outright resistance to the second drug becomes more likely. Previous work by the same team and others had already shown the same effect in a lab dish: they found that slowing the killing rate can lead to resistance such that the bacteria continue to grow even in the presence of an antibiotic. But this was the first study to demonstrate the process in people, according to its senior author Nathalie Balaban, a biophysicist at the Hebrew University of Jerusalem.

The study, although small, reveals a major threat to the way doctors currently think about combination antibiotics, says Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics & Policy in Washington, D.C., who was not involved in the work. "Our entire approach to antibiotics is going to have to be rethought," says Laxminarayan, who is also a senior research scholar at Princeton University. "We can't do this 'give to everybody and kumbaya' [approach], which is what we're following now."

Clinicians tend not to focus on tolerance, because it may not have much impact in the short term. "Their own patients are [probably] going to be treatable," Laxminarayan says, although the killing action of the antibiotic may kick in more slowly. "It's really a public health problem, not a clinical problem" for a single patient.

"We agree that judicious use and proper antimicrobial stewardship is critical to preserving the longevity of our antibiotics," say Andrew Berti, an assistant professor at Wayne State University's Eugene Applebaum College of Pharmacy and Health Sciences, and Elizabeth Hirsch, an assistant professor at the University of Minnesota's College of Pharmacy. Neither Berti nor Hirsch was involved in the study, but they co-wrote a related Perspectives piece in the same issue of *Science.* "However," they say, "in the absence of a rapid, validated means to determine antibiotic tolerance, we continue to see a clear role for combination antibiotic therapy in cases of documented staphylococcal infection, [where such] combinations maintain their ability to suppress resistance development against typical, nontolerant bacteria."

Every year in the U.S. more than 35,000 people die, and more than 2.8 million get sick, from antibiotic-resistant infections, according to

the U.S. Centers for Disease Control and Prevention. The challenge is that tolerance cannot be measured in the clinic, so doctors cannot tell whether a patient has developed it. This will not make much difference in an otherwise healthy person who just needs a little help to fight off an infection, Balaban says. But it could be life-threatening in an already weakened patient with a blood infection.

Balaban and her colleagues at the Hebrew University of Jerusalem and Shaare Zedek Medical Center in Israel looked at the evolution of potentially deadly methicillin-resistant *Staphylococcus aureus* (MRSA) in two patients with blood infections that lasted for more than two weeks even though they were on antibiotics. One patient was first put on the antibiotic vancomycin. After four days rifampicin was added to that person's regimen. Then, from day eight to day 14, vancomycin was replaced with daptomycin.

When the team tested bacteria taken from the patient, the microbes that had developed tolerance against vancomycin were also killed more slowly by daptomycin. And the combination of rifampicin and daptomycin was not any more effective than the single agent.

The researchers also showed that such resistance develops in some other dangerous bacteria and with other antibiotic combinations. They next plan to study whether the effect occurs in more types of bacteria, Balaban says, and to examine antibiotic combinations that could effectively treat life-threatening infections without promoting resistance.

Theoretically, the second drug in a combination is expected to kill any of the microbes left alive by the first antibiotic. But the new study demonstrated that when a patient is already tolerant to the first drug, adding a second one spurs resistance by promoting the reproduction of bacteria that were not killed immediately.

As a patient's serum level of antibiotic drops between daily doses, the bacteria that "went to sleep" in the presence of the drug can reawaken and reproduce enough to evolve resistance, Berti says. Hirsch says the new study's major contribution was finding in patients what had already been seen in the lab. Berti agrees: "It's been assumed for a long time," he says. "This is the first time it's been shown" definitively in patients.

Balaban says the same evolutionary processes involved in the development of antibiotic tolerance and resistance are likely to be at play in cancer as well and might be used to inform treatment. Tumor cells might become tolerant of chemotherapy first and then develop resistance that spreads to other drugs. She does not plan to conduct such research herself, however.

The new study points to the need for a laboratory test to detect whether the bacteria infecting a patient are tolerant of the planned antibiotic treatment before starting therapy, says Bruce Levin, a biology professor at Emory University. Levin, an evolutionary biologist who studies infectious disease and drug treatment and was not involved in the study, adds that he was intrigued and impressed by the results. The question is, he says, "Will this study serve as a warning, [and] will people respond to it? Or will it be just another academic exercise?"

Editor's Note (1/13/20): This article was updated to include additional comments from Andrew Berti and Elizabeth Hirsch on the use of combination antibiotic therapy.

—Karen Weintraub

What's in Kale (or a Pear) That Seems to Lower Alzheimer's Risk?

Particular antioxidants in fruits and vegetables may lower chances of getting the disease

A number of studies in recent years have shown that clean living—exercise, sleep, a Mediterranean diet—lowers one's prospect of being diagnosed with Alzheimer's. Some of these recommendations sound a little like a parent's entreaty to a child to eat the daily apple or finish broccoli left on a plate. What does it really mean, though, to say that eating greens or berries diminishes risk? How much do such changes lower your chances of Alzheimer's? And which specific chemicals help to ward off the most common type of dementia?

A study by researchers at Rush University Medical Center, published in January in *Neurology,* tries to pin down some specifics—and in doing so, it demonstrates the benefits of using dietary measures to stay cognitively intact. The team took 921

RON LEVINE *GETTY IMAGES*

participants without dementia from Rush's Memory and Aging Project, a large ongoing study that began more than 20 years ago. The recruits, who had a mean age of 81, were tracked for an average of six years.

Study members who followed a regimen with the highest flavonol levels—the top fifth—had a 48 percent lower risk of receiving an Alzheimer's diagnosis than those in the bottom quintile. (Flavonols are a class of antioxidant and anti-inflammatory molecules found in foods.) As the study progressed, 28 people in the top flavanol group of 186 study members, or 15 percent, went on to develop Alzheimer's. Meanwhile 54 of the 182 participants in the lowest quintile, or 30 percent, received such a diagnosis. The study's takeaway is that "a healthy diet that contains various fruits and vegetables is critical for continued health—but especially brain health," says Thomas M. Holland of Rush, who led the research.

In the paper, the researchers dug deeper into the issue, analyzing the risk reduction for the four flavonols surveyed: isorhamnetin, kaempferol, myricetin and quercetin. People in the top quintile who ingested the most isorhamnetin-rich foods—pears, olive oil, wine and tomato sauce—achieved a 38 percent risk reduction compared with members in the lowest quintile. Kale, beans, tea, spinach and broccoli were the sources of the most kaempferol, which furnished a 51 percent drop in risk. Tea, wine, kale, oranges and tomatoes provided lots of myricetin, along with a 38 percent lower Alzheimer's incidence. Tomatoes, kale, apples and tea are loaded with quercetin, but no health benefit was registered for that flavonol.

The biochemical composition of flavonols (part of a larger antioxidant class known as flavonoids) appears to enable them to quell inflammation and to scavenge free radicals in the blood and the gut to help prevent cellular damage. "This study adds to our understanding of which elements of a healthy diet may be important in reducing dementia risk," says Keith Fargo, director of scientific programs and outreach at the Alzheimer's Association, who was not involved in the new paper. "At this point," he adds, "people should not put too much stock in specific nutrients—including subsets of flavonols—for reducing dementia risk until more research is done. Rather they should focus on eating an overall healthy diet."

Also, getting your kaempferol from kale may be better than searching online for a supplement that contains the molecule. "There's a multitude of vitamins, minerals, and bioactive substances in individual foods that you may not get if you're taking multiple supplements," Holland says.

The *Neurology* study did not include a control group, so it was not able to establish a cause-and-effect relationship between dietary patterns and lowered risk. Future investigations also need to look at a more diverse group. Most of the new paper's participants were highly motivated, white and well educated, and three quarters were women.

The senior author of the study was Martha Clare Morris, who developed a diet called the Mediterranean–DASH (Dietary Approaches to Stop Hypertension) Intervention for Neurodegenerative Delay, or MIND, which has been linked to lower Alzheimer's risk. Morris is now heading an effort to do a randomized controlled trial to confirm, with hard evidence, whether this diet really does serve as a preventive measure. When the results are in, it might actually be possible to counter jokes about kale with real data.

—*Gary Stix*

Are Human Body Temperatures Cooling Down?

A new study finds that they have dropped on average over the past century and a half

SARINYA PINNGAM GETTY IMAGES

It is one of those facts of life that we learn early and don't forget: normal body temperature is 98.6 degrees Fahrenheit. But a new study in *eLife* argues that that number is outdated.

The figure was probably accurate in 1851, when German doctor Carl Reinhold August Wunderlich found it to be the average armpit temperature of 25,000 patients. Times have changed, though, according to the recent paper: the average American now seems to run more than a degree F lower.

Stanford University researchers looked at data from Civil War soldiers and veterans and from two more recent cohorts to confirm that body temperatures among American men averaged around 98.6 degrees F back then but have steadily fallen over time and that temperatures among women have fallen as well. Their data reveal an average for men and women of 97.5 degrees F.

The study suggests that in the process of altering our surroundings, we have also altered ourselves, says senior author Julie Parsonnet of Stanford. "We've changed in height, weight—and we're colder," she says. "I don't really know what [the new measurements] mean in terms of health, but they're telling us something. They're telling us that we are changing and that what we've done in the last 150 years has made us change in ways we haven't before."

The researchers did not determine the cause of the apparent temperature drop, but Parsonnet thinks it could be a combination of factors, including warmer clothing, indoor temperature controls, a more sedentary way of life and—perhaps most significantly—a decline in infectious diseases. She notes that people today are much less likely to have infections such as tuberculosis, syphilis and gum disease.

In places like the U.S., people also spend more time in what scientists call the thermoneutral zone—an environment of climate-controlled temperatures that make it unnecessary to rev up the metabolic system to stay warm or to cool off, she says. That perpetually 72-degree-F office may feel cold to some, but it does not stress out the human body the way it would to spend the night in a 40-degree-F cave. It is unclear whether those who live closer to the way people did in the 1800s—with more infection or less climate control—have higher body temperatures.

Research on the Tsimané, indigenous people who live in lowland Bolivia, suggests that infections can boost average body temperature. A 2016 paper showed that responses to infection accounted for about 10 percent of resting metabolism in that population and that lower metabolism was associated with slightly lower body temperature, says Michael Gurven, an anthropologist at the University of California, Santa Barbara, who conducted that study but was not involved in the new one. Yet even in healthy members of the Tsimané population, temperatures appear to have dropped between 2004 and 2018, he adds—a phenomenon he plans to investigate further.

Parsonnet says she suspects that it might be healthier to have a lower

Goodbye, 98.6

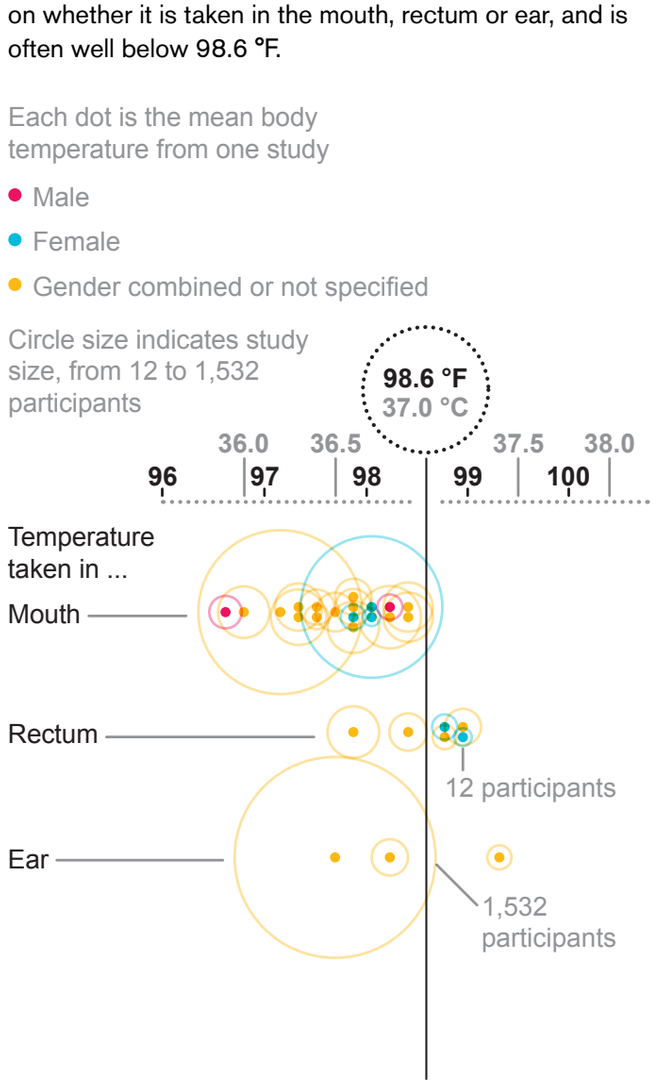
Healthy body temps are surprisingly lower

By Mark Fischetti | Graphic by Nadieh Bremer

Normal body temperature is 98.6 degrees Fahrenheit, right? Not so. There is no baseline for humans Ⓐ, and even if there were, it would be closer to 97.7 °F. Temperature also varies across the day, peaking in late afternoon and bottoming out in early morning Ⓑ. It is slightly higher for women than for men as well Ⓒ. For two decades research has debunked the benchmark, set way back in 1868, yet it persists. One important ramification, says Jonathan S. Hausmann, a rheumatologist at Boston Children's Hospital, who led the latest study, is to redefine fever. Most doctors use 100.4 °F or higher, but if "normal" is lower, then the fever threshold should be, too. It also should vary with the daily pattern and be tailored to each individual, Hausmann says: "A child at 99.0 °F at 4 A.M. may be highly abnormal but at 4 P.M. could be within normal limits."

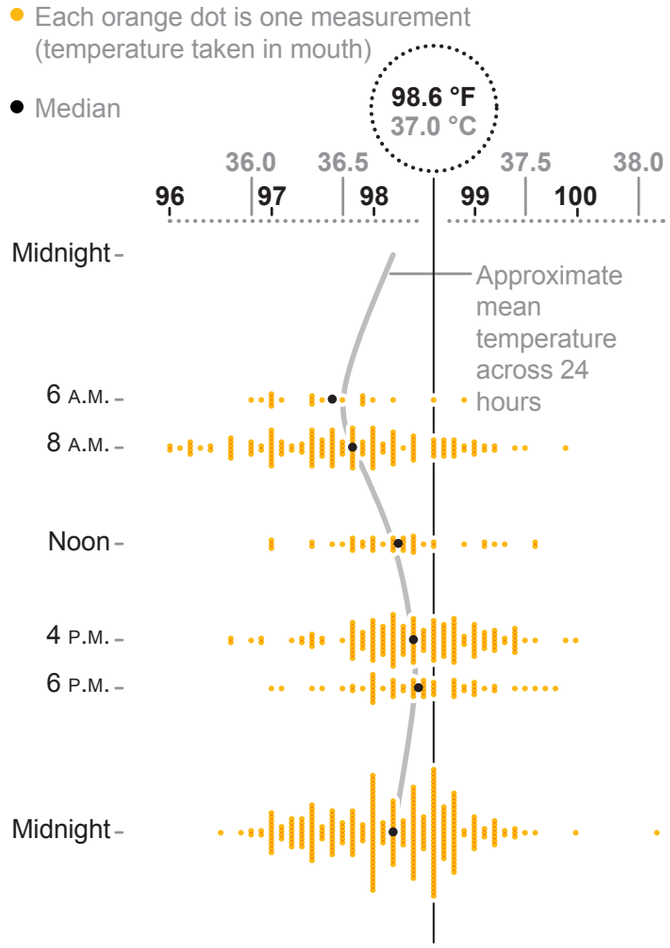
Ⓐ Less Than 98.6

A 2002 analysis of 20 studies showed that mean body temperature in healthy women and men varies, depending on whether it is taken in the mouth, rectum or ear, and is often well below 98.6 °F.



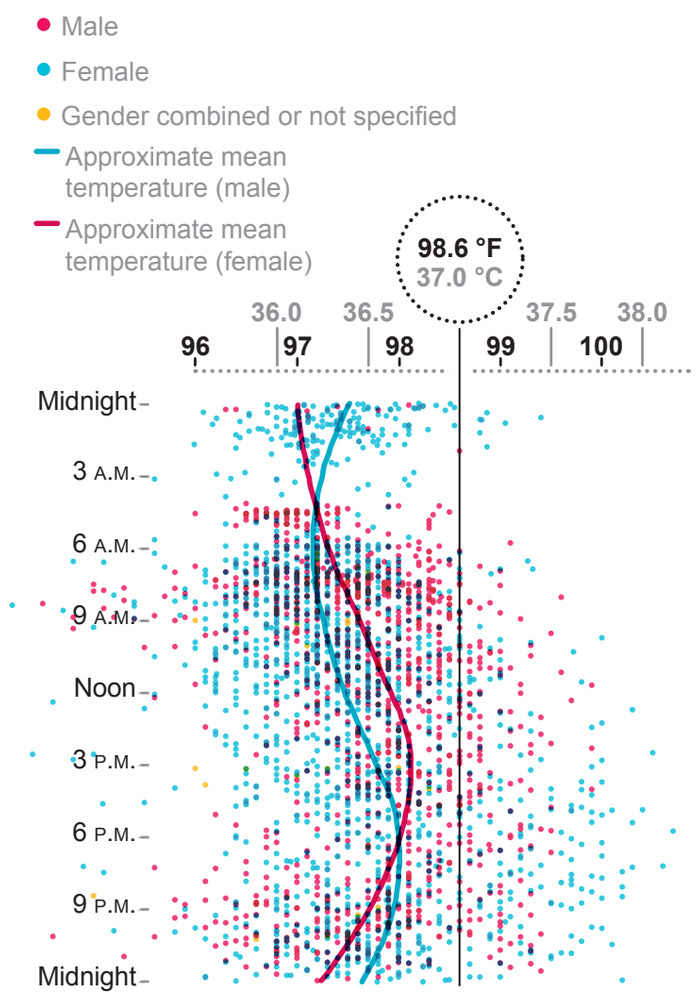
Ⓑ Daily Cycle

A landmark investigation in 1992 found that temperature for 148 men and women hit a low each day of about 97.5 °F around 6 A.M. and peaked at about 98.4 °F between 4 and 6 P.M. It defined the upper limit of the normal range as fever: 98.9 °F at 6 A.M. and 99.9 °F at 4 P.M.



Ⓒ Women and Men

In the newest study, published in August 2018, 329 people took their temperatures, logged on smartphones. The overall mean was 97.7 °F. Women were 0.2 °F higher than men, on average. Fever was found to be 99.5 °F or above. Temperatures varied across the day. They also decreased, on average, with rising age (*not shown*).



R.I.P.

German physician Carl Wunderlich put the mercury thermometer and temperature charts into widespread clinical use. His 1868 book set normal body temperature at 37.0 degrees Celsius, or 98.6 °F. Time to let it go.

SOURCES: "NORMAL ORAL, RECTAL, TYMPANIC AND AXILLARY BODY TEMPERATURE IN ADULT MEN AND WOMEN: A SYSTEMATIC LITERATURE REVIEW," BY MÄRTHA SUNDLEVANDER ET AL., IN *SCANDINAVIAN JOURNAL OF CARING SCIENCES,* VOL. 16, NO. 2; JUNE 2002 (A); "A CRITICAL APPRAISAL OF 98.6 °F, THE UPPER LIMIT OF THE NORMAL BODY TEMPERATURE, AND OTHER LEGACIES OF CARL REINHOLD AUGUST WUNDERLICH," BY PHILIP A. MACKOWIAK ET AL., IN *JAMA,* VOL. 268, NO. 12; SEPTEMBER 23–30, 1992 (B); "USING SMARTPHONE CROWDSOURCING TO REDEFINE NORMAL AND FEBRILE TEMPERATURES IN ADULTS: RESULTS FROM THE FEVERPRINTS STUDY," BY JONATHAN S. HAUSMANN ET AL., IN *JOURNAL OF GENERAL INTERNAL MEDICINE.* PUBLISHED ONLINE AUGUST 13, 2018 (C)

metabolism and body temperature. And she hopes to explore that connection more in the future.

For the *eLife* study, she and her colleagues compared temperatures from three different data sets: a total of 83,900 measurements from the Union Army Veterans of the Civil War (UAVCW) cohort collected between 1862 and 1930; 15,301 measurements from the National Health and Nutrition Examination Survey I (NHANES I) collected between 1971 and 1975; and 578,222 measurements from the Stanford Translational Research Integrated Database Environment (STRIDE) collected between 2007 and 2017. Figures for women were not available from the earliest data set but were collected from the two later cohorts, and the research showed that body temperature for men and women decreased steadily across the time periods.

Philip Mackowiak, an emeritus professor of medicine at the University of Maryland School of Medicine, who was not involved in the new study, says data from as far back as the Civil War are inherently suspect. "That's not to say that what [the new study] found is not valid. It could be, but you just don't know," he says, because there are so many variables that could not be controlled for in the data set, such as whether soldiers and veterans were healthy when tested, where the thermometer was placed and what kind of instrument was used.

Even Wunderlich's established 1851 result is questionable, Mackowiak says, because although he had a large database of patients, it is hard to know whether he measured temperature consistently or how he analyzed such a volume of information long before the invention of computers. And "the body is composed of a whole host of temperatures," Mackowiak adds. The liver is the hottest part, and the surface of the skin is the coldest. Plus, he says, "there's no 'normal' temperature; there's a range of temperatures," with people running hotter later in the day than they do in the morning. Women also have higher temperatures on average than men, in part because their temperatures rise with ovulation.

Parsonnet agrees that the Civil War data set has some limitations, such as where caregivers took the temperatures and whether they were careful or simply filled in 98.6 degrees F because that is what they knew normal temperature was supposed to be. Those concerns were tempered, she says, by the fact that she and her team found a similar annual drop in temperature between the 1970s cohort and the current one. The effect was still present when they looked at soldiers' and veterans' year of birth rather than when the temperature was obtained, suggesting that the type of thermometer or the caregiver's attitude could not explain the change. And within the data set, the researchers found the expected variation by age, weight and height, suggesting that the values were not random.

"We've changed in height, weight—and we're colder."
—Julie Parsonnet

Even with the data's limitations, the findings are compelling, according to Frank Rühli, founding chair and director of the Institute of Evolutionary Medicine at the University of Zurich, who says he reviewed the paper for *eLife* but was not involved in the research. "Human body temperature data going back that far—roughly 150 years—is very interesting," he says. "It allows us to see short-term alterations of physiological traits in humans, which is quite rare."

All the experts agree on one thing: a fever is still a fever. Lowering the average for normal body temperature does not mean that the standard for a fever—generally considered to be higher than 100 degrees F for adults—should be changed, Mackowiak says. "Temperature can be helpful in determining whether or not you're ill and, based on its level, how ill you might be," he says. For patients, a bacterial infection plus a lower-than-normal temperature could be an even more ominous sign than one higher than normal, he says. A rise or fall in temperature can also indicate whether you are getting better or how you are responding to medication, he adds, though "how you feel is the most important thing."

The new study probably should not change the definition of fever, Rühli says. "But the variety of what is looked at as being normal should probably be adjusted."

— Karen Weintraub

How Coronaviruses Cause Infection—from Colds to Deadly Pneumonia

The outbreak of a novel coronavirus raises questions about how such pathogens evolve and what makes infections mild or severe

By Simon Makin

GETTY IMAGES

Simon Makin is a freelance science writer based in London.

THE 2019 NOVEL CORONAVIRUS (2019-nCoV)

behind the ongoing outbreak—which the World Health Organization has declared an international public health emergency—was named after the family of viruses it belongs to. The term "coronavirus" may have initially been unfamiliar to many, but most everyone has encountered milder forms of such viruses, of which four strains cause about a fifth of common cold cases. Other types cause diseases that are endemic in certain animal populations. But until less than two decades ago, all known human varieties caused illness so mild that coronavirus research was something of a backwater.

That all changed in 2003 when the pathogen behind the SARS (severe acute respiratory syndrome) outbreak in China was identified as a coronavirus. "Everybody in the field was shocked," says microbiologist Susan Weiss of the University of Pennsylvania. "People started really caring about this group of viruses." That outbreak is believed to have started when a coronavirus jumped from animals—most likely civet cats—to humans, resulting in a type of disease called a zoonosis. These viruses' propensity for such jumps was underlined in 2012 when a different virus jumped from camels to humans, causing MERS (Middle East respiratory syndrome). That illness has killed 858 people to date, primarily in Saudi Arabia, representing approximately 34 percent of those infected.

SARS, MERS and the new coronavirus almost certainly all originated in bats. The most recent analysis of the 2019-nCoV genome found that it shares 96 percent of its RNA with a coronavirus previously identified in a specific bat species in China. "These viruses have been floating around in bats for a long time" without sickening the animals, says microbiologist Stanley Perlman of the University of Iowa. But there were no bats being sold at the animal market in Wuhan, China, where the current outbreak is thought to have begun, suggesting that an intermediate host species was likely involved. This situation seems to be a common feature of these outbreaks. Such hosts may increase the viruses' genetic diversity by facilitating more or different mutations.

But what is a coronavirus? What determines whether, when and how it jumps to humans and how infectious it will be? And what makes the difference between a case of the sniffles and a deadly disease? In the years since these viruses first emerged as a severe global health threat, researchers have been studying their molecular biology in an effort to answer such questions.

ANATOMY OF A CORONAVIRUS

Coronaviruses are enveloped, single-stranded RNA viruses, which means that their genome consists of a strand of RNA (rather than DNA) and that each viral particle is wrapped in a protein "envelope." Viruses all do basically the same thing: invade a cell and co-opt some of its components to make many copies of themselves, which then infect other cells. But RNA replication typically lacks the error-correction mechanisms cells employ when copying DNA, so RNA viruses make mistakes during replication. Coronaviruses have the longest genomes of any RNA virus—consisting of 30,000 letters, or bases—and the more material a pathogen copies, the more opportunities there are for mistakes. The upshot is that these viruses mutate very rapidly. Some of these mutations may confer new properties, such as the ability to infect new cell types—or even new species.

A coronavirus particle consists of four structural proteins: nucleocapsid, envelope, membrane and spike. The nucleocapsid forms the genetic core, encapsulated in a ball formed by the envelope and membrane proteins. The spike protein forms club-shaped protrusions that stick out all over the ball, making it resemble a crown or the sun's corona—hence the name. These protrusions bind to receptors on host cells, determining the cell types—and thus the range of species—that the virus can infect.

The major difference between coronaviruses that cause a cold and those that cause a severe illness is that the former primarily infect the upper respiratory tract (the nose and throat), whereas the latter thrive in the lower respiratory tract (the lungs) and can lead to pneumonia. The SARS virus binds to a receptor called ACE2, and MERS binds to one called DPP4—both are found in lung cells, among other places. Differences in the distribution of

these receptors in tissues and organs may account for differences between the two diseases, such as the fact that MERS is deadlier than SARS and features more prominent gastrointestinal symptoms. MERS is not hugely infectious, however, which may also be a receptor-related trait. "DPP4 is expressed [highly] in the lower bronchi [airways leading into the lungs], so you have to have a large number of viruses coming in, because our airways are very good at filtering out pathogens," says virologist Christine Tait-Burkard of the University of Edinburgh. "You need prolonged, intense exposure [to reach the lungs], which is why we see people who work closely with camels getting sick."

Conversely, because pathogens can get in and out of the upper airways more readily, viruses that replicate there are more infectious. In addition, "the ability to replicate in different temperatures makes a big difference, because the upper respiratory tract is cooler," Tait-Burkard says. "If the virus is more stable at those temperatures, it doesn't go to the lower respiratory tract." The lower airways are also a more biochemically and immunologically hostile environment, she adds. Analysis of 2019-nCoV strongly suggests that the new virus, like SARS, uses ACE2 to gain entry to cells. This observation would fit with the fact that it appears, so far, to be less deadly than MERS (the current estimated mortality rate for the new coronavirus is about 2 percent, but that figure may change as the outbreak unfolds and more cases are detected).

The picture quickly becomes complex, though, because viruses that use the same receptor can result in drastically different illnesses. One human coronavirus called NL63 binds to the same receptor as SARS but only causes upper respiratory infections, whereas SARS primarily infects the lower respiratory tract. "Why that is, we don't know," Perlman says. Another curiosity is that the ACE2 receptor is prevalent in the heart, but SARS does not infect heart cells. "That was a clear indication that other receptors, or co-receptors, are also involved," says molecular biologist Burtram Fielding of the University of the Western Cape in South Africa. The virus binding to a receptor is only the first step in the cell-entry process. When a virus binds to a host cell, the two start morphing together, and other viral proteins may bind to other receptors. "For the efficiency of entry, it's not just the one main receptor," Fielding says. "There could be others as well."

IMMUNE SYSTEM ARMS RACE

Another important feature of coronaviruses is their "accessory" proteins, which appear to be involved in evading the host's innate immune response—the body's front line of defense. The response is initiated when a cell detects an invader and releases proteins called interferons, which interfere with the pathogen's replication. The interferons trigger cascades of antiviral activity, from shutting down host protein synthesis to inducing cell death. Unfortunately, most of these processes are also bad for the host. "A lot of the disease that's caused is actually the immune reaction—inflammation—and destructive things induced by viruses," Weiss says. "That will also determine how virulent a virus is: how much of a destructive immune response does it induce, as opposed to just a protective one?" This aspect is also why underlying medical conditions are so important. Most of the people who have died from the new coronavirus so far "had comorbidities, like autoimmune diseases, or secondary infections, which can become much more prevalent once our innate immune systems are busy fighting a virus," Tait-Burkard says. "That's why the important thing is to treat people for comorbidities and give them antibiotics to stop bacterial infections taking hold."

Of course, the immune response's purpose is to eliminate invaders, so viruses possess countermeasures. This trait seems to be what differs most among various coronaviruses. "These viruses are closely related, but they have different accessory proteins," Weiss says, adding that they "have evolved to shut down various aspects of that [innate immune] response." Some researchers think bats harbor coronaviruses because they do not mount the intense immune response humans do. "A lot of the signaling molecules that alert our immune system are suppressed in bats, so they don't get sick," Tait-Burkard says. Rather than reacting, bats maintain a constant low-level response, which may contribute to the viruses' evolution. "[Bats] have a constant expression of interferons, which selects for viruses that are good at evading that response," Tait-Burkard says. "So bats are very good selection vessels for viruses that are very good at hiding."

Accessory proteins are far from fully understood, however. "They can be taken out of some viruses without any effect on the ability of the virus to grow," Perlman says. "You would think: if you had a protein that was key for countering the immune response, if you took it out, the immune response would win—and it's not necessarily so." Some researchers believe accessory proteins influence how deadly coronaviruses are. There have been studies with SARS in which removing an accessory protein did not change the virus's replication efficiency but did make it less pathogenic. "Lots of virus would still be made, but it seemed to be less harmful," Fielding says.

Coronaviruses do possess some ability to correct genetic errors, but it neglects certain regions of their genome, Tait-Burkard says. Consequently, two sections in particular are especially prone to mutations: those that encode the spike protein, and accessory protein regions. "In those two areas, coronaviruses allow a lot of mistakes, which drives their evolution, because they manage to bind to new receptors and evade the immune response of new systems," Tait-Burkard says, "which is why coronaviruses are so good at jumping from species to species."

Related Video

How Twitter Is Changing Medical Research

From online journal clubs to "tweetorials" to conference updates, social media is changing the dissemination and discussion of biomedicine

By Nicole Wetsman

GETTY IMAGES

Nicole Wetsman is based in New York.

ESTHER CHOO ONLY HAD A FEW THOUSAND FOLLOWERS ON TWITTER before August 2017. Choo, an emergency physician at the Oregon Health & Science University, interacted mostly with other doctors. But when she tweeted one day about the racism she had endured while practicing medicine, her posts went viral—and her follower count shot up to 20,000 almost overnight. Now she has nearly 80,000 followers.

"The professional benefits have been so concrete," Choo says. Twitter, for her, has helped her meet new professional colleagues and friends and has offered opportunities for advocacy around racial and gender equity in medicine. "It's hard to imagine what my career would be like without it."

As a high-profile physician on the platform, Choo (@choo_ek) is an outlier in the medical community in terms of her number of followers—but she is part of a large and growing community of doctors and scientists who use Twitter as part of their professional lives. A *Nature* survey conducted in 2014 found that 13 percent of scientists use Twitter, and in 2017 an analysis published in *PLoS One* identified over 45,000 scientists with accounts.

Most scientists and physicians do not reach as wide an audience as Choo does, but they find that it has been helpful for their careers. "Twitter lowers the boundaries of our institutional silos," says Ankeet Udani (@ankeetudani), an anesthesiologist and medical-education specialist at the Duke University School of Medicine, who started a Twitter-based journal club for residents. It also helps level the scientific playing field, says Janet Han (@netta_doc), a cardiologist with the Veterans Affairs Greater Los Angeles Healthcare System and the University of California, Los Angeles, and an author on papers about social media in medicine. "Anybody can be on Twitter," she says, from first-year students to department chairs. "Anyone can interact with anyone."

The platform is also fundamentally reshaping the way scientists and academic physicians can discover, discuss and share research. It is not an extracurricular endeavor to those who participate—it is a critical communication tool, says Vinay Prasad (@VPrasadMDMPH), a hematologist-oncologist at Oregon Health & Science University and an active Twitter user with over 30,000 followers. But that change comes with growing pains, and everyone from individuals to major institutions is struggling to figure out the best way to incorporate social media into traditional metrics around achievements. "It's probably one of the most disruptive—and net beneficial—things that has happened in academic medicine," Prasad says.

IMMEDIATE ANALYSIS

Before Twitter, researchers had limited ways to respond to and critique new research in their field. They could write a letter to the editor or an opinion piece in a journal, but that response would be published only if editors of that journal agreed to it. Even if it was published, it would often not appear for weeks. They could conduct their own experiments and publish their own papers, but that avenue is also subject to the same gatekeeping and time restrictions. Blogs allow self-publishing, but it is hard to direct people to them, and the PubMed Commons—which offered a way for researchers to comment directly on articles—never caught on and was discontinued in 2018.

Twitter sidesteps those roadblocks and allows conversations about new papers to happen immediately and publicly, says Jordan Gauthier (@drjgauthier), a fellow at the Fred Hutchinson Cancer Research Center. "On the day of publication, people can react to it," says Gauthier, an active Twitter user with around 2,000 followers.

Comments on Twitter remove the journal from the equation, allow anyone to discuss scholarship and have high visibility, Prasad says: "It's a tremendous democratization of critique of science." The open platform allows for the possibility that some of the criticism or comments might be inaccurate, he adds. "But I trust that the community is smart enough to draw attention to what is accurate. Inaccurate comments don't get the same retweets."

Sometimes feedback given on Twitter can be more pointed and critical than what might be given in person

or in a formal op-ed. "You can see sharks gathering around a paper to tear it apart," Gauthier says. But while they can bite, the trend might help push the quality of research. "I think about it—am I going to get panned by one of the statisticians online?" he says. "Maybe it's driving excellence and improving methods and asking people to think about what the community in the field thinks, rather than just in your own office."

GOING CLUBBING

Online discussion of papers is sometimes facilitated by Twitter journal clubs. Journal clubs, where researchers get together and critically examine new papers or pieces of literature, are important forums for the exchange of ideas and continuing education. But they traditionally happen in person, and participants are usually limited by location. On Twitter, however, journal clubs can expand beyond those boundaries. Udani, for example, started one for anesthesia residents. Anesthesiologists are often isolated, but using Twitter to talk about papers exposes them to approaches from all over the world. "It's a change to the traditional journal club, which is a bit outdated," he says.

A formal analysis of the educational potential of Twitter journal clubs, centered on a medical-radiation journal club, concluded that the flexibility and accessibility of the digital environment offer benefits that in-person clubs do not—including the opportunity for more people to observe without pressure to participate, global engagement and fewer hierarchies based on seniority. In this particular journal club—the #MedRadJClub meeting—one hour of conversation could have up to 245 participants and 4,559 tweets, the analysis showed.

Twitter can offer a second chance for papers that might not have been accepted in high-impact journals, says Sharonne Hayes (@SharonneHayes), cardiologist and founder of the Women's Heart Clinic at the Mayo Clinic in Rochester, Minnesota. She was the senior author on a 2017 paper that found, for the first time, that female doctors were significantly less likely to be introduced with the professional title "Doctor" than were their male colleagues during grand rounds, when clinicians describe patient cases to other physicians—male physicians introduced their female colleagues using formal titles only around half the time. The team submitted their results to three high-impact journals but were rejected.

"The main sense I got from reviewers was that they didn't think [the findings] were actually a thing," Hayes says. The paper was eventually published in a lower-impact women's health journal, but she pushed the paper out on social media and wrote a blog post describing the findings. That helped the paper reach a wider audience even out of a less widely read journal. "As a result, my co-authors have been quoted in *Time* and the *Washington Post*."

The scientific community is still trying to figure out how to integrate social media into traditional benchmarks of success. Hayes herself says that the number of retweets and likes a paper gets should not be a surrogate for the value of the science itself.

UPENDING POWER STRUCTURES

Social media offers an alternative to traditional power structures in science and research, which give high-impact journals, tenured professors and prestigious institutions the most weight. On Twitter, people who do not have tenure, who have more limited publications to their name or who are early in their career have opportunities to demonstrate their expertise. But displays of knowledge on social media, rather than in traditional forums such as journals, are sometimes criticized as less relevant or rigorous. In 2014 a researcher created a metric called the "Kardashian index" to measure scientists' Twitter followings against the number of citations their papers receive—with the implication that some had Twitter "celebrity" status that was not grounded in academic success and therefore was not justified.

The index was broadly criticized, including by those who took issue with the idea that citations are the most important metric of scientific expertise—which penalizes junior researchers, for example, who will automatically have a lower citation count. "It's critical of people who seek to communicate more broadly, as if that's a bad thing," Prasad says.

Choo says that mentality has faded within the scientific community. "A few years ago it was a very different landscape," she says. "You don't hear much anymore that you're wasting your time on Twitter and should be writing a paper."

Some institutions are starting to consider social media activity in hiring and promotion decisions, which is a positive step, says Eric Topol (@EricTopol), a cardiologist and geneticist at the Scripps Research Institute and a high-profile figure (with over 177,000 followers) in scientific Twitter. "Increasingly, this is going to be the way the science community does exchange ideas, and it complements the typical story of a person's citations," he says.

However, it should be included in only a small way, says Hayes. "Being popular should not be the reason someone becomes a full professor." Organizations have to grapple with how much weight they give social media use and how they determine what types of usage are relevant to a person's scientific work. "We need to systematize the way we assess validity," Hayes says. "It's still a bit of a Wild West out there."

Choo did not initially think that social media should be incorporated into career-advancement decisions, but she's been won over. "I was sold on the quality and rigor of some of the educational information people are putting out on social media. People do tweetorials, which are really rigorous. It's incredible medical education." Choo says, however, that rigorous, quantitative measures need to be developed to assess people's social media use.

ESTABLISHING A PRESENCE

With so many conversations about science and medicine happening on Twitter, people who do not use it at all are missing out on an important forum for conversations about science and medicine, Hayes says. They do not have to be as active as Prasad or Choo—or even tweet at all—but they should keep an eye on the discussion. "I think it has reached the point where academic physicians for sure should have a presence, if nothing else, just so they can see what's going on. It's like reading journals," she says. "You can't put your head in the sand. It's another source of information."

People who resist often have common concerns, including the brevity of tweets and the time it takes away from other work. Reshma Jagsi (@reshmajagsi), deputy chair in the department of radiation oncology at the University of Michigan, shared many of those concerns before she started using Twitter this summer. "I was a Twitter resister," she says. She saw her concerns upended quickly, noting that threading tweets and linking out to articles allow for robust conversations.

Social media can eat up a lot of time, but it is possible to use it productively and in moderation. Good science, Choo says, often takes time and space, so time management is key. "Some days I can get really caught up in it," she says. "I definitely do think you need safeguards in place to make sure you're staying productive."

Sorting through the volume of information on Twitter and identifying the best ways to use it can take time as well. Ignoring it entirely is not the right solution to that problem, however, and it is possible to see a slice of the information even if someone cannot see everything, Jagsi says. "The sorting of the wheat from the chaff is, so far, worth it."

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QUEST TO USE CRISPR AGAINST DISEASE GAINS GROUND

As the first clinical trial results trickle in, researchers look ahead to more sophisticated medical applications for genome editing

By Heidi Ledford

A scanning electron microscope image of a sickle-cell red blood cell.

GETTY IMAGES

The prospect of using the popular genome-editing tool CRISPR to treat a host of diseases in people is moving closer to reality.

Medical applications of CRISPR–Cas9 had a banner year in 2019. The first results trickled in from trials testing the tool in people, and more trials launched. In the coming years researchers will be looking ahead to more sophisticated applications of CRISPR genome editing that could lay the foundation for treating an array of diseases from blood disorders to hereditary blindness.

But although the results of clinical trials of CRISPR genome editing so far have been promising, researchers say that it is still too soon to know whether the technique will be safe or effective in the clinic.

"There's been a lot of appropriate caution in applying this to treating people," says Edward Stadtmauer, an oncologist at the University of Pennsylvania in Philadelphia. "But I think we're starting to see some of the results of that work."

It has been only seven years since researchers discovered that a molecular defense system called CRISPR–Cas9, which microbes use to fend off viruses and other invaders, could be harnessed to rewrite human genes.

Since then gene editing has attracted attention for its potential to modify embryos—an application that is ethically and legally fraught if those embryos are destined to become human beings. But in parallel, scientists have been testing CRISPR's much less controversial ability to disable or correct problematic genes in other cells in order to treat a host of diseases.

In 2016 Chinese researchers announced that they had treated the first person with a CRISPR–Cas9 therapy designed to fight cancer. In cells extracted from a participant's blood, the researchers disabled the gene that codes for a protein called PD-1, which holds the immune system in check but can shield cancer cells in the process. The scientists then reinjected the cells.

By 2019 the U.S. government's clinicaltrials.gov database listed more than a dozen active studies testing CRISPR–Cas9 as a treatment for a range of diseases from cancer to HIV and blood disorders.

So far too few people have been treated in these trials for any firm conclusions to be drawn about the safety of CRISPR–Cas9 therapies or how well they work. Preliminary results from two trials—one in which gene-edited blood cells were transplanted into a man to treat HIV infection and one in which they were transplanted into three people to treat some forms of cancer—showed no signs of clinical improvement.

SIGNS OF PROGRESS

In both cases the transplanted cells flourished in the bone marrow of recipients without any serious safety concerns, but they did not produce a clear medical benefit. In the man treated for HIV, the researchers attempted to use CRISPR to disable a protein that many strains of HIV use to enter cells. But only 5 percent of the transplanted cells were edited—not enough to cure disease, the researchers reported in September. The study has been placed on hold while researchers explore ways to boost that percentage, says Hongkui Deng, a stem-cell researcher at Peking University in Beijing and a lead author of the work.

There are early hints that another trial might meet with more success. CRISPR Therapeutics in Cambridge, Mass., and Vertex Pharmaceuticals in Boston, Mass., have treated two people with the genetic disorders sickle-cell anemia and β-thalassemia. Both deplete oxygen-carrying hemoglobin molecules in the blood; the idea is to use CRISPR to disable a gene that otherwise shuts off production of another form of hemoglobin. Early results suggest that the treatment might have eased some symptoms of the disorders, but the participants will need to be followed for a longer period to be sure.

Other researchers are already itching to move beyond editing cells in a dish. The challenge is in finding ways to transport the gene-editing machinery to where it is

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Heidi Ledford works for *Nature* magazine.

needed in the body, says John Leonard, chief executive of Intellia Therapeutics, a biotechnology company in Cambridge, Mass., that is focused on CRISPR–Cas9 genome editing. "The delivery approach is so important."

Last July the pharmaceutical companies Editas Medicine in Cambridge, Mass., and Allergan in Dublin launched a trial to treat the genetic disorder Leber congenital amaurosis 10, which can cause blindness, by editing eye cells. Researchers will inject into the eye a virus containing DNA that encodes the CRISPR genome-editing machinery, bypassing the need to guide those tools through the bloodstream to the specific tissues. The virus will be responsible for carrying the genome-editing tools into cells. It is the first trial to attempt CRISPR–Cas9 gene editing inside the body, and early results could be reported this year.

That would be a landmark moment for the field and could pave the way for future trials targeting other organs, says Charles Gersbach, a bioengineer at Duke University in Durham, N.C. But he and others say that they hope researchers will eventually move away from using viruses to shuttle genome-editing machinery into cells. Deactivated viruses can still sometimes provoke immune responses and can carry only a limited amount of DNA.

"Can you imagine a future without gene editing?"
—John Leonard

SHRINK TO FIT

What's more, some gene-editing tools are currently too large to fit inside commonly used gene-therapy viruses, says chemical biologist Andrew Anzalone at the Broad Institute of M.I.T. and Harvard in Cambridge, Mass. These include the souped-up CRISPR systems called prime editors that were first reported in late 2019 and which might prove to be more precise and controllable than CRISPR–Cas9.

Intellia is looking for a way around the viruses. The company has partnered with Swiss pharmaceutical giant Novartis to develop fatty nanoparticles that can protect genome-editing molecules as they travel through the bloodstream but also can pass through the membranes of target cells.

These particles tend to accumulate in the liver, and researchers are working to develop particles that infiltrate other tissues, such as muscle or the brain. But for now Intellia will focus on liver diseases, says Leonard, and the company plans to launch its first trial of the technology this year. "It's crawl before you walk, so to speak," he says.

None of the technologies currently being tested is what researchers envision for the long-term applications of genome editing, says Gersbach. "The approaches that people are taking are the things that we can do today," he says, "but not what we would do if we could design the ideal drug."

Leonard says that when he meets with investors, they often demand to know what medical advances will be made in the next six months. "We do our best to describe that, but I always end it by saying, 'Can you imagine a future without gene editing?'" he says. "I have yet to meet the person who says yes."

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Seth Berkley is CEO of Gavi, the Vaccine Alliance.

PUBLIC HEALTH

Novel Coronavirus Is a Reminder: The Best Defense against a New Viral Outbreak Is Early Detection

Infectious disease surveillance networks already exist, but they can be highly porous

Visitors to the Temple of Heaven, Beijing, during the outbreak in January 2020.

KEVIN FRAYER *GETTY IMAGES*

The current outbreak of a new coronavirus, 2019-nCoV, has quickly escalated to become a serious global problem that has now been declared a Public Health Emergency of International Concern by the World Health Organization. As of this writing the disease has spread to more than 100 countries, including more than 300 confirmed cases in the U.S.

But in some ways, outbreaks such as this should come as no surprise. Deforestation and the sale of live wild animals or bushmeat, such as bats and monkeys, make the emergence of new viruses inevitable, and population growth, dense urbaniza-

tion and human migration make their spread easier. What is surprising is that, although we are better able to respond to such threats than ever before, we are still not fully prepared.

Screening at airports is likely to be of limited use in preventing its further spread, but we now at least have the ability to rapidly identify and genetically sequence new pathogens, to help minimize the time it takes to develop treatments and vaccines. We also have mechanisms in place, such as through the Coalition for Epidemic Preparedness and Innovation and Gavi, the Vaccine Alliance, to help stimulate the development of vaccines and make them available quickly once we have them. But despite this, our ability to swiftly detect threats in the first place is seriously wanting, and that is worrying.

Infectious disease knows no borders, so when it comes to controlling outbreaks, timing is everything. The speed with which this outbreak was identified and communicated and the fact that 2019-nCoV has been genetically sequenced are positive steps, and there is more than one vaccine now already in development. But even though vaccines for coronaviruses are far simpler to develop than those for diseases such as malaria and HIV, it will still be months before the first clinical trials take place and at least a year before a vaccine could possibly be available for use. As context, the Ebola vaccine Ervebo, which is now being used in the Democratic Republic of the Congo, is one of the fastest vaccines to get regulatory approval, and that took five years. That is why it is so important to detect threats as early as possible, before they spread, and why good disease surveillance is so important.

There are no guaranteed solutions to ensure infectious diseases are always detected early, before they reach densely populated areas.

Infectious disease surveillance networks already exist across the globe to do precisely this. They can, however, be highly porous and of varying effectiveness. In some ways we are lucky that 2019-nCoV emerged in China, where there exists a strong public health system. During the West Africa Ebola epidemic, it took three months before the very first case, patient zero, was confirmed by a laboratory, because that community was outside of an efficient disease surveillance network. Also, new threats are more common than perhaps most people realize. Since 1940 more than 330 emerging infectious diseases have been identified. If deforestation and the unregulated sale of bushmeat continue, then we should expect to see more.

Deforestation runs the risk of exposing humanity to as yet unencountered viruses—often through contact with wild animals such as bats, exotic canine species and monkeys or with vectors such as mosquitoes—increasing the risk of outbreaks of both new and existing diseases. Indeed, genetic analysis of 2019-nCoV suggests that it most likely came from a bat.

With 2019-nCoV, the third new severe outbreak of novel coronaviruses in the past two decades, we still do not have enough information to know how virulent it is—but with a rising death toll, we have to be worried. We also do not know how easily it can be transmitted from human to human, although we now have confirmation that this is occurring.

Nor do we know exactly where it originated. It is possible that the first transmission of the virus from animal to human took place at a market in Wuhan where live wild animals were sold. But if other people were infected in rural areas before the infected animal was brought to market, that means that with good surveillance it might have been possible to detect the threat before it reached densely populated areas.

There are no guaranteed solutions to ensure that infectious diseases are always detected early, before they reach densely populated areas. But we do have one cost-effective way of widening the net: increased government investment in primary health care, particularly in lower-income countries. Primary health care is typically the first point of contact people have with medical and health services when they get sick and so is ideal for early detection of diseases. But in many parts of the world it is still very limited or even nonexistent. Even in middle-income countries, where health care provision can be relatively good, there can exist large clusters of communities that are missing out. When it comes to new emerging

infectious diseases, people in rural areas, those close to forests and those consuming bushmeat are our biggest concern, because these are essentially our underserved blind spots.

National immunization programs can help change that. With 90 percent of the world's children now receiving at least one routine vaccination, childhood immunization already has a larger reach than any other medical intervention. In addition to this, immunization provides an impetus for other vital health components that not only are essential to vaccination but can help strengthen primary health care.

These include supply chains, trained health workers, data systems and, crucially, disease surveillance and in some cases basic laboratory testing. Extending routine immunization systems to that last 10 percent not only will make those communities healthier and save lives but also will put in place the basics of a health care warning system.

No matter how we achieve it, primary health care must be strengthened at a global level to reach every community if we are to widen the surveillance and response net and be fully prepared for these kinds of outbreaks. Until we have a resilient and universal primary health care system, we will be leaving some communities out. And when the next emerging infectious disease strikes, that may simply not be enough.

Related Video

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MENTAL HEALTH

Doctors and Suicide

The rate among students, residents and physicians is significantly higher than the average—but so-called wellness initiatives can help

"First, do no harm," is what medical students in the U.S. declare when they take the Hippocratic oath at the white-coat ceremony symbolizing their entry into the medical profession. It refers to the patients they will be taking care of. But perhaps it should also refer to themselves.

As a psychologist embedded in the department of pediatrics at a major medical center, I have worked closely with pediatric residents since 1995. In addition to meeting with first-year residents during the first week of orientation, I facilitate a monthly support group where residents have protected time to share concerns in a nonthreatening, confidential environment.

These monthly groups have spurred many positive changes, including trying to ensure that rotations with the most demanding schedules are now staggered with rotations that have less demanding schedules.

Yet many health care professionals do not often discuss a major occupational hazard in medical training: the high suicide rate among medical students, residents and physicians.

The rates of death by suicide in the general public in the U.S. are increasing. The National Institute of Mental Health reported in 2017 that suicide was the 10th leading cause of death for males and the 14th for females. It was the second leading cause of death for young people aged 10 to 34, a common age bracket for medical students and residents.

Compared with those among the general population, however, the rates of death by suicide are much higher in physicians, especially physicians who are women. In the U.S. an estimated 300 to 400 medical students, residents and practicing physicians die by suicide annually. Physician deaths impact not only the families and friends of the doctors who end their lives but also thousands of patients, nurses, support staff and others.

In January 2019 the Accreditation Council for Graduate Medical Education sent out an e-com-

munication to members wishing everyone a "joyous, happy and healthy New Year." The note also included a reminder that the third quarter of the academic year, beginning in January, is the second highest period of risk for resident and fellow suicide.

For 2020, the third quarter for the academic year begins shortly. Recognizing that physicians are at increased risk for burnout and depression, the council introduced new standards and, in their updated Common Program Requirements, defined "well-being" of physicians to include that they "retain the joy in medicine while managing their own real-life stresses."

The ACGME guide states: "Residents and faculty members are at risk for burnout and depression. Programs, in partnership with their Sponsoring Institutions, have the same responsibility to address well-being as other aspects of resident competence."

Historically there have been many mixed messages in residency training, noting that it is insufficient to provide a wellness curriculum without including, as I wrote about the problem in 1992, "the larger working environment … involving the hospital and/or training programs, and the constantly changing health care system."

Medical schools, residency training programs and hospitals throughout the country are implementing "wellness initiatives" of varying degrees. And many medically affiliated organizations have programs dedicated to addressing wellness, such as the American Medical Association's Steps Forward: Preventing Physician Burnout, the Mayo Clinic's Program on Physician Well-Being, Stanford's WellMD, and the Pediatric Resident Burnout-Resilience Study Consortium.

Indeed, many of the concerns and challenges of residency—debt, moving to a new location, time management, impostor syndrome—have not changed over the past two decades. Many concerns have intensified, however, such as the demands of electronic record keeping, the increased burden of non-MD chores such as insurance pre-authorizations, and the intrusion of 24-7 access.

The American Academy of Pediatrics emphasizes the need to address the social-emotional lives of physicians, as well as the need to help them sustain their work-life balance and avoid burnout. In 2015 six institutions founded the 2016–2019 Pediatric Resident Burnout-Resilience Study Consortium.

The World Health Organization defines burnout as an "occupational phenomenon." According to the WHO, burnout is a "syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed" and refers specifically to the occupational or workplace context and not to experiences in other [personal] areas of life."

Some leading institutions are addressing and recognizing the need to address the issues of burnout and work-life balance at the institutional level. In 2017, moving from the Mayo Clinic to Stanford Medicine, physician Tait Shanafelt became the first chief wellness officer at a U.S. academic medical center. At my own institution, in December 2018, physician Bryant Adibe moved to Rush University Medical Center as its first chief wellness officer.

To reduce rates of burnout at Rush University Children's Hospital, a four-week wellness rotation was launched in 2017 for the second year of training. Many were skeptical about this four-week rotation, yet the most salient component of this rotation provides residents with the time to schedule appointments with their own health care providers, in addition to covering their peers, so that they too may schedule health care appointments. Residents are also encouraged to eat healthy meals, exercise, check in with the staff psychologist, catch up on sleep and socialize with friends and family.

Prior to the launch of the four-week wellness rotation in 2017, the burnout rate reported by Rush's second-year pediatric and internal medicine/pediatric, or med/peds, residents was 80 percent. In 2018 residents reported that rates of burnout fell from 80 percent to 30 percent, and they remained there in 2019.

To be sure, a four-week wellness rotation is not the answer to the epidemic of physician burnout, depression and suicide. But it is a start.

Burnout is a symptom; it is not the problem. Medical students and physicians need time to engage in self-care activities and seek mental health assistance without jeopardizing their license, reputation and ability to practice medicine.

Yes, residents learn that to be ethical doctors, they must first do no harm. They can also learn to first help themselves.

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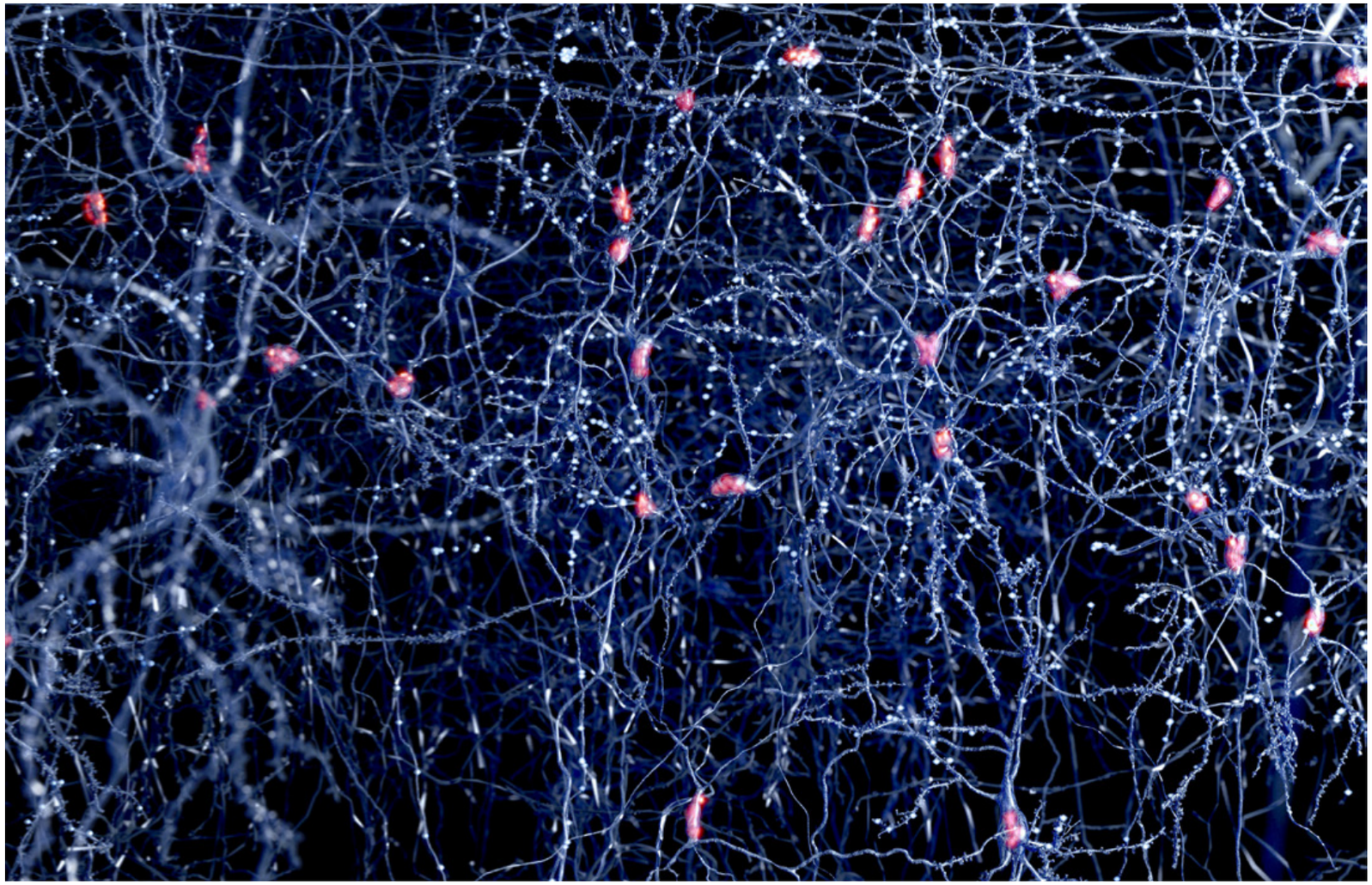
THE BODY

Calling an Illness "Psychosomatic" Doesn't Mean It's Imaginary

Recent experiments have begun mapping the neuronal connections between mind and body like never before



JUAN GARTNER *GETTY IMAGES*

Placebo effects, exercise highs, getting sick when you're stressed out—the popular press and the scientific literature alike are replete with examples of how the mind or mental processes influence our health and well-being. This "mind-body connection" is essential for normal organ function and also is viewed as the basis for psychosomatic disorders. Yet the concept that our thoughts can influence the function of a variety of organ systems is often viewed with some skepticism, in part because it has lacked a firm biological basis.

That's changing. We are now starting to provide the scientific evidence to reveal the important dynamic between our brains and our bodies. And in the process we are learning how the brains of primates are different from those of other animals—a reality that has important implications for research into the causes and treatment of neurological disorders.

The connection between the central nervous system and internal organs is mediated by sympathetic (fight-or-flight) and parasympathetic (rest and digest) subdivisions of the autonomic nervous system. We know a great deal about the neural connections that link autonomic output from centers in the brain stem and spinal cord to specific organs.

Yet the neural circuits that link higher brain function and central sites, such as the cerebral cortex, to autonomic output and organ function have not been clearly defined. That's because

most conventional tracers are capable of defining only the direct inputs to and outputs from an organ and not the background web of connections that provide indirect, but meaningful, neural signals.

Our research team has overcome this challenge by using neurotropic viruses, which specifically target neurons, as transneuronal tracers. In the *Proceedings of the National Academy of Sciences* we recently described using a rabies virus tracer to reveal the areas of the cerebral cortex that influence the adrenal medulla of the monkey and rat, as well as rabies transport from the kidney in the rat.

In our nonhuman primate studies we injected the rabies tracer into the adrenal medulla, a gland at the top of the kidney, and tracked its path back to brain regions involved in movement, cognition and mood. These cortical areas represent key nodes in a "stress and depression connectome." In the rat, descending influences over the adrenal medulla, as well as the kidney, originate largely from cortical motor areas. In fact, the cortical areas that are the major source of cognitive control in the monkey appear to be absent in the rat. Thus the mind-body connection in primates is more widespread and complex than that in rats.

These observations provide a new perspective on the neuroanatomical organization of the cortical influences over the sympathetic nervous system. The power of transneuronal tracing with rabies virus is that it reveals the entire extent of the cortical influence over this system. In this way it identifies the potential origins of the elusive "central commands" from the cerebral cortex.

This general experimental paradigm is one that can be applied to reveal multisynaptic circuits in a wide variety of networks. For example, rabies tracer injections into limb muscles can reveal the networks involved in the voluntary control of movement; tracer injections into laryngeal muscles can reveal the central circuits responsible for vocalization; tracer injections into the heart and stomach can reveal circuits responsible for the central control over the cardiovascular and gastrointestinal systems; and tracer injections into the spleen can reveal the central neural circuits that influence immune function.

The adrenal medulla can be considered as our "first responder" in situations requiring fight or flight. Thus one might expect the input to it to be highly conserved across species. Indeed, the cortical motor areas are a major source of input to the adrenal medulla in both the rat and the monkey. But here the similarities end. The primary motor cortex, the primary somatosensory cortex and a single secondary motor area account for about 93 percent of the cortical input to the adrenal medulla in the rat. In contrast, the monkey's adrenal medulla receives input not only from cortical motor areas (about 53 percent) but also from cortical areas involved in cognition and affect (about 35 percent).

Furthermore, in the monkey the adrenal medulla receives substantial input from motor areas on the medial wall of the hemisphere that don't exist in the rat. Thus the monkey's adrenal medulla is the target of output from a broader set of cortical areas and is influenced by a more diverse set of behaviors. Each network found in the monkey has a human equivalent. Taken together, these observations suggest that nonhuman primate models are essential for examining the influences of higher-order aspects of movement, cognition and mood on sympathetic function.

Modern medicine has generally viewed the concept of psychosomatic disease with suspicion. This attitude is partly the result of a lack of information about the neural networks that connect the "mind," conceptually associated with the cerebral cortex, with autonomic and endocrine systems that regulate internal organs. As a consequence, some definitions of psychosomatic disorders include dismissive descriptions such as "all in the mind," "irrational" or "subconscious."

Our findings should correct this perspective because they provide a concrete neural substrate for cortical areas involved in movement, cognition and affect to influence a major sympathetic effector, the adrenal medulla. We suggest the adoption of the view reflected in the dialogue at the end of *Harry Potter and the Deathly Hallows,* where Harry says, "Tell me one last thing, is this real? Or has this been happening inside my head?" Professor Dumbledore replies, "Of course it is happening inside your head, Harry, but why on earth should that mean that it is not real?"

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