



Illustration by Ana Miminoshvili

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# CAN WE PREDICT WHICH VIRUSES WILL SPREAD FROM ANIMALS TO HUMANS?

*COVID, monkeypox, Ebola, and SARS all originated in animals. Some researchers think we can predict what's next, while others believe it's an impossible task.*

By Matthew Hutson

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**T**he natural world is a reservoir of plagues. At any moment, untold numbers of viruses circulate among animals. Inevitably, some will cross the species barrier, infecting

people and making them sick. Scientists call such an event a “zoonotic spillover.” No one knows how often such spillovers happen—presumably, animal viruses are always establishing footholds that our immune systems destroy. We notice, though, when the viruses propagate. Today, countries around the world are seeing cases of monkeypox, a milder relative of smallpox. Just like COVID-19, the disease originated in other animals. It was seen first in monkeys, in 1958, before being detected in a boy, in 1970. Other recent spillovers have caused diseases including Ebola, flu, Lassa, Marburg, MERS, Nipah, SARS, and Zika.

Dawn Zimmerman, a fifty-one-year-old wildlife veterinarian formerly at the Smithsonian Global Health Program, has spent years studying zoonotic viruses in wildlife in Turkana county, Kenya. On one trip in 2017, she visited an area in the northwest called No Man’s Land. “It’s because no one owns it,” she told me. “People are always fighting over that land.” On a field day, her team might gather early in the morning to drive into the bush, sometimes accompanied by armed guards. They would check rodent traps set the night before, taking oral and rectal swabs from any animal they found, and follow troops of baboons, picking up droppings and sampling them. Occasionally, they would set a trap for a baboon—a cage that closes when a primate pulls on an ear of maize tied to a string—to facilitate sampling. In the evening, they’d use mist nets on riverbanks to catch the bats that emerged after dusk.

Sometimes the team took samples from camels—livestock animals that are known to be “viral reservoirs,” or sources of possible spillover. In one town, a woman named Ester was in charge of the livestock; after having tea in Ester’s house, Zimmerman’s team went out to meet the animals, bringing along medicine for them as a thank-you. They hadn’t brought enough, and an owner pointed what looked like an AK-47 at them. “She just put her finger up, and she’s, like, ‘No!’ ” Zimmerman recalled, of Ester. “And he put his gun away.” To access a different site, they had to cross a river. “The first thing I asked is, ‘Are there crocodiles in this river?’ And they said, ‘No, no, totally hunted out, no problem,’ ” Zimmerman told me. The researchers crossed as part of a large crowd, with Zimmerman immersed to her chest. That night, while they were setting up their bat nets, they saw two pairs of crocodile eyes shining in the water.

While sampling, researchers like Zimmerman wear N95 respirators, rubber boots, one or

two pairs of gloves, and Tyvek suits—a getup that can become unbearable in the heat. They lug around a container of liquid nitrogen for storing their samples until they can be frozen and sent to a lab, where researchers will screen them for viruses, then sequence the viruses' genes to determine if they're known or novel. In another lab, further analyses might attempt to predict the risk that any novel viruses pose to people. For several years, Zimmerman's data made its way to PREDICT, a program run by the United States Agency for International Development (U.S.A.I.D.) aimed at predicting, preventing, and containing emerging infectious diseases. From 2009 to 2020, PREDICT's researchers collected samples from a hundred and sixty thousand animals and people in about thirty countries, and discovered almost a thousand new viruses. It's since been replaced by DEEP-VZN (Discovery & Exploration of Emerging Pathogens—Viral Zoonoses), a five-year program, also funded by U.S.A.I.D., which will spend a hundred and twenty-five million dollars to find new viruses in animals around the world. DEEP-VZN will focus in particular on coronaviruses, filoviruses, and paramyxoviruses—the three viral families that include SARS-CoV-2, Ebola, and measles. (U.S.A.I.D. has also launched a hundred-million-dollar effort called STOP Spillover, aimed at preventing and catching spillovers, based on knowledge gained from viral surveillance.) “It will be a defining characteristic of this century, these zoonotic spillovers,” Dennis Carroll, the infectious-disease specialist who founded PREDICT, told me. Today, Carroll runs the Global Virome Project (G.V.P.), another successor to PREDICT.

Vast amounts of money are flowing to these initiatives, under the theory that understanding what's out there, where it lies, and how it might jump to humans will help us stop spillovers and respond to them more effectively when they happen. Implicit in such efforts is an idea about how spillovers work. They are like ticking time bombs: spot them soon enough, and we might defuse them. But some scientists see money spent on spillover prediction as money misspent. Spillovers happen, they say, but predicting them is beyond our current or foreseeable abilities. Pandemics, in this view, are a bit like avalanches: we know that somewhere on a slope a small crack will open and spread, snowballing into something monstrous, and we know that this is more likely to happen in certain areas and under certain conditions—and yet we can't forecast precisely when or where. Just as avalanches emerge from an accumulation of complex mechanical and meteorological processes, so pandemics happen when a knotted interplay of molecular, physiological,

ecological, social, and economic conditions converge. They will always surprise us.

It could be that, instead of surveying wildlife, we are better off monitoring people and catching outbreaks early, after spillover has occurred. Richard Ebright, a microbiologist at Rutgers University who studies infectious disease, has emerged as a major critic of the prediction approach, and believes that wildlife monitoring could actually increase the risk of an outbreak. “The possibility that SARS-CoV-2 entered humans as a direct result of the activities of PREDICT—during field collection of bats and bat excreta, or during laboratory characterization of bats, bat excreta, or bat viruses—cannot be excluded,” he told me. As for whether the Global Virome Project will improve on PREDICT’s efforts, he said, “expanding a program that at best was an expensive failure would be frank insanity. One could not possibly invest research funding less wisely.”

James Bangura joined PREDICT after an Ebola outbreak in Sierra Leone, in 2014. “It was horrifying,” he said, of the virus’s toll. Bangura lost three friends and colleagues to Ebola. As a surveillance lead for the country’s Ministry of Health and Sanitation, he monitored the spread of the virus, winning a Presidential medal for his work. The next year, PREDICT started operations in Sierra Leone, and he signed on soon after.

Bangura’s team, like Zimmerman’s, looked for spillover-ready viruses in bats, rodents, and nonhuman primates, taking samples from forty to eighty animals during a typical two-week trip. In 2016, they discovered a new kind of Ebola virus that was hiding not in caves or forests but in people’s homes: four bats in three small villages within a dozen miles of one another, in the Bombali district of Sierra Leone, were found to be hosts for what would eventually be called *Bombali ebolavirus*. Whether it will sicken people, or travel between them, remains uncertain—there are no known cases of human infection. “Seeing a new kind of Ebola was a huge fulfillment for me in my career,” Bangura said. After the discovery, “the energy was there: ‘O.K., let’s look for more viruses.’” In 2020, Bangura’s team reported the first discovery of Marburg virus in bats in West Africa. Including the current outbreak, there have been fifteen recorded spillovers of Marburg; the largest, which occurred in Angola, in 2004-05, killed ninety per cent of the two hundred and fifty-two people known to have been infected. After both of Bangura’s discoveries, PREDICT mounted a public-information campaign on the dangers of interaction with bats, and increased animal-sampling for viruses—measures meant to prevent spillovers from

occurring.

PREDICT has created a hot-spot map indicating where zoonoses, including coronavirus spillovers, are likely to occur. (Other groups, including researchers at Oxford and EcoHealth Alliance, an N.G.O. that studies emerging infectious diseases, have created similar maps for other viruses.) These maps extrapolate from past spillover events and ecological factors associated with them. One thing they look at is the distribution of animal species. Bats are a logical place to look if you want to predict spillovers. SARS-CoV-2 almost certainly came from bats—perhaps reaching humans through an intermediary animal, such as a pangolin—as did the coronaviruses that cause SARS and MERS. “Bats, for some reason, seem to be really good hosts for coronavirus,” Timothy Sheahan, a virologist at the University of North Carolina, told me. Some researchers have suggested that, in order to help their bodies cope with the stresses of flight, the animals have evolved to suppress inflammation, which makes it easier for them to tolerate viral infections without developing disease. Tracey Goldstein, a comparative pathologist at the University of California, Davis, School of Veterinary Medicine who served as PREDICT’s lab director, said that the project’s surveyors tended to find a few new coronaviruses inside each species of bat they surveyed.

There are more than fourteen hundred species of bat. They make up a fifth of the mammalian kingdom and, in total, they likely host thousands of coronaviruses, some of which have spillover potential. “Bats are way more common than people realize,” Christine Johnson, an epidemiologist at U.C. Davis and the director of PREDICT from January to September of 2020, told me. “They’re kind of like rodents. They live amongst us.” Bats nest in houses, churches, and restaurants; they eat fruit, leaving behind saliva-coated scraps for other animals to find; they urinate in palm sap and are consumed for food or medicine. We read about bats in Asia and elsewhere, but they live in Europe and North America, too: in 2009, a new coronavirus was found in bats in an abandoned railroad tunnel in Maryland.

Usually, scientists work backward, starting with infected people and then searching for the animal origins of the virus that has sickened them. The first case of MERS was uncovered in 2012, when a man in Saudi Arabia died of a sudden and mysterious respiratory disease after testing negative for flu and other common infections; the Ministry of Health asked Ian Lipkin, a virologist at Columbia University, to investigate the virus they had found

Ian Lipkin, a virologist at Columbia University, to investigate the virus they had found. Lipkin, in turn, called Jonathan Epstein, a veterinarian and disease ecologist at EcoHealth Alliance. Epstein, Lipkin, and their teams travelled to Saudi Arabia, arriving in the town where the man had lived. They asked people where to look for bats. Eventually, someone suggested that they visit some nearby ruins—decayed sandstone buildings with underground rooms.

Epstein's team donned respirators, then began exploring. "It was like being in an archeological site," Epstein told me. In some buildings, they found the mummified remains of bats; they stumbled across a camel skeleton in the sand. Most rooms had only a few bats, but after a couple of days they entered a chamber where hundreds lived; they put on Tyvek suits and helmets over their masks before entering. "That was like a jackpot," Epstein said. He set up a harp trap—a vertical frame with wires too thin to be sensed with echolocation—and bats started flying into it, falling into a canvas pocket. In just ten or twenty minutes, Epstein caught fifty. He also visited the house of the man who'd died, sampling his camels, sheep, and goats. A bat from ruins nearby turned out to have a piece of the new virus's genome in its feces. Lipkin's team, and other researchers, found the virus in camels, suggesting a path from bats to camels to humans. The disease went on to kill nearly nine hundred people—more than a third of those infected.

The story illustrates both the promise and the difficulty of spillover prediction. If MERS had been on epidemiologists' radar sooner, some of those deaths might have been avoided. (Later, it was found that a cluster of MERS cases had appeared in Jordan months earlier.) And yet you'd have to have found the camels—or the bats—to have found MERS in time. And you'd have to have guessed that MERS was especially risky. For prediction to work, it's not a matter of finding a needle in a haystack; you're looking for the sharpest piece of hay, and you don't know what continent the haystack is on.

**A**mong infectious-disease specialists, there's a widespread consensus that the likelihood of spillovers is increasing. A lot of practices around the world, such as changes in travel and land use, elevate the risk of viruses crossing the species barrier and spreading. "Getting a granular insight, understanding those hot spots, is the stuff that will allow you to prevent the preventable," Carroll, the PREDICT and G.V.P. founder, told me. Before PREDICT, Carroll said, it was unclear whether spillover prediction could work. Was it possible for researchers to find viruses? To characterize a virus's risk based on its genome?

possible for researchers to find viruses. To characterize a virus's risk based on its genome: To understand the impact of human behavior and its contributions to spillovers? PREDICT, he argued, had been a successful "proof of concept" for bigger efforts, such the Global Virome Project.

And yet efforts that attempt to identify spillover candidates before they strike face a host of challenges. One is scale. During the first phase of operation, PREDICT discovered about a hundred viruses. In a 2018 paper published in *Science*, Carroll and his co-authors estimated that there are 1.7 million unknown viruses still out there, roughly half of them with the capacity to infect people. At great expense, spillover prediction may be capable of identifying only a small proportion of the threats we face. Carroll and his collaborators have estimated that, by spending about a billion dollars in a ten-year period and leveraging surveillance and lab capacities that have already been built in dozens of countries, it may be possible to find about seventy per cent of the viruses that remain undiscovered. "It is an audacious goal but more than doable," Carroll said.

In an ideal world, viruses would be predictable. We would discover a new one in some wild animal, analyze it in a lab, determine its pandemic potential, and then test the effectiveness of available vaccines or antibodies before it spills over. But looking at a virus in a lab will tell you only so much. Even if it appears to have all the right pieces to invade a human cell, that's only part of the picture, Mark Denison, the director of the Division of Pediatric Infectious Diseases at Vanderbilt University Medical Center, told me. To cause infectious disease, the virus must overcome tissue barriers, and, without killing its hosts, make them both sick and contagious. It must also be stable enough on surfaces, or in the air, to be transmitted. "They don't 'jump,'" Denison said, of zoonotic viruses. "I don't call it a 'jump.' It's more like a twenty-six-mile-long high hurdle." Success isn't guaranteed until the finish line is crossed.

In a study of two hundred and three human viruses, Jemma Geoghegan, an evolutionary biologist and virologist at the University of Otago, in New Zealand, found that the half which were transmittable from human to human shared a few traits. In general, they didn't kill their hosts, but led to long-term infections; their usual mode of transmission from animal to humans was by means other than through vectors such as mosquitos; and they had "nonsegmented" genomes that were easier to replicate. But many viruses check those boxes without causing pandemics, and some of those traits aren't measurable until a virus has already spread. Carroll has pointed to a virus's history of adapting to new host species

has already spread. Carron has pointed to a virus's history of adapting to new host species as a warning sign of its potential ability to adapt to us. But many viruses can jump hosts; moreover, Geoghegan has written, "evolutionary and epidemiological time scales should not simply be assumed to be equivalent." It may have taken a virus millions of years to cross from one species to another. That doesn't mean it will infect humans in the next few decades.

Some researchers hope that sophisticated machine-learning algorithms will reveal hidden patterns in the data collected on viruses. In a study published last year, a team at the University of Glasgow used the genomes of hundreds of viral species to train a neural network to predict a virus's ability to infect humans. By one measure, its performance was 0.77, where 1.0 is perfect. This is an impressive result—and yet it might not be impressive enough, if there are more than a million viruses to sift through. (The algorithm also did not predict pandemic potential.) Other A.I. models have predicted which host species are more likely to carry novel viruses of interest; they can help focus the work of animal surveillance. But the scope is still wide, and we're still left to make predictions about individual viruses.

A central issue with machine learning is that it works best when furnished with big data. We have only a few documented spillover events from which to learn. Even uneventful transmission to humans is relatively rare. A recent study looked for coronavirus antibodies in a couple of hundred people living within a few miles of some caves that hosted bat colonies in China. Nearly all of these "high risk" participants had been in contact with livestock or wild animals. Only six carried antibodies. Of roughly two hundred human viruses we know of with a zoonotic origin, only half spread between people, and many don't cause serious illness. Efforts such as G.V.P. hope to surface hundreds of thousands of new viruses, but characterizing them could take decades, during which mutations may render the data outdated.

Pandemics depend on more than just a dangerous pathogen. They also require a permissive ecology, in which the right animals (including people) brush up against one another in the right ways. Geoghegan cites canine influenza, or C.I.V., as an example of a virus that spreads widely, but only in the right circumstances. "C.I.V. clearly possesses all the genetic characteristics necessary to spread in dogs," she has written. And so it spreads—but only in shelters. Outside of them, dogs are not as densely packed. These sorts of ecological factors



can have counterintuitive effects. Rich biodiversity has been called a risk factor for spillover; the idea is that many species are intermingling, sharing viruses. But some evidence points to a “dilution effect,” in which the variety of creatures present, each in smaller numbers, actually decreases the likelihood of species-jumping. It’s also possible that our preconceptions about different species are wrong. Bats are certainly good hosts for viruses. But a paper published in 2020, in *Proceedings of the National Academy of Sciences*, found that, among mammals and birds, no individual taxonomic order is better than any other at infecting humans, averaged across species in that order. One reason bats infect us disproportionately is that there are so many species of bat; a given bat species is, on average, no more dangerous than a given species of horse or kangaroo.

Kristian Andersen, an infectious-disease researcher at the Scripps Research Institute, is one of many researchers who question the promises made by people such as Carroll and Peter Daszak, the president of EcoHealth Alliance. “It’s all these big words,” Andersen told me. He argued that, while a project like PREDICT may quicken our response to outbreaks, it can’t prevent them. Researchers have been sequencing coronaviruses in China and elsewhere for a decade, he noted; well before the COVID-19 pandemic, they sequenced a virus that was 96.2-per-cent identical to SARS-CoV-2. “If they really could predict the next pandemic and prevent it,” that would have been “the time to shine,” he said. In reality, a large gap separates identifying a spillover-ready virus from issuing guidance about its imminent spillover. Even hot-spot maps may not be useful. “While you can certainly do these kinds of risk maps, the confidence intervals are going to be so wide, because, inherently, pandemics are extremely unpredictable,” he said. We worry about bat caves in China, then “all of a sudden it’s pig farms in Mexico.” Mexico and Saudi Arabia—countries that don’t feature the largest hot spots in a map of spillover risk generated by EcoHealth Alliance—gave us, respectively, swine flu and MERS.

One thing we can say for sure is that there will be another pandemic—and another, and another. “It’s fundamentally a consequence of population pressure,” Carroll said. “We think the world we’re living in right now, eight billion people, is the norm, but it’s not. It is a phenomenal transformation of our footprint in the last century.” Epstein, the MERS investigator, said, “We have to focus on people as the culprit. It’s not wildlife’s fault for carrying these viruses but, rather, it’s the things we’re doing that put us into more

contact with wildlife.” We’re in avalanche country, tromping around on the mountain.

In 2018, PREDICT developed a picture book in several languages called “Living Safely with Bats.” It advised readers to avoid contact with the animals and their excrement, to cover food and water, and to close up holes in one’s home; the Asian edition included sections on protecting oneself in caves and when farming bat guano for fertilizer. In Kenya, Zimmerman held town halls where she educated community leaders about these risks. (She’s seen bat droppings on supplies and medicine bottles in a clinic.) And yet experts also implore people not to kill bats, in part because the animals are an important part of the ecosystem—they pollinate plants, disperse seeds, and eat disease-carrying insects—and because killing them can increase risk. In 2007, four workers at Kitaka mine, in southern Uganda, contracted Marburg, and one died. The mine contained around a hundred thousand bats, and the miners killed nearly all of them before sealing the entrances with sticks and plastic. But, when the mine reopened, the bat population rebounded, with more than twice the rate of Marburg infection as before. The town of Ibanda, a dozen miles away, subsequently suffered the worst outbreak of Marburg in Ugandan history, with fifteen confirmed cases; the victims were infected with a strain nearly identical to the one in the Kitaka mine, suggesting that the miners’ efforts had backfired.

In many places, people don’t have a choice in their interactions with animals. Kenya is facing an extended drought. On one trip several years ago, Zimmerman saw calves dying of starvation by the side of the road, and learned of a man who had lost his last cow, then killed his family and himself. “So it’s that desperation,” she said. “They say, ‘Yes, during droughts, we will kill baboons and eat them, because we have nothing to eat.’” The solution to such a problem, she proposed, might be livestock insurance. Bangura asks people in Sierra Leone not to eat bushmeat, but many “don’t have alternatives,” he said; he’s therefore begun advising the government on policies to promote poultry and livestock farming. He’s also recommended that villagers whose only water sources are in caves look for new ones. Knowing of hot spots is helpful in these efforts, because they indicate where these sorts of interventions might be most needed.

Wildlife markets have been flagged as a source of spillover danger. “I’ve been in them in many places around the world,” Tracey Goldstein, the PREDICT lab director, said. “They’re not the most sanitary places. You’ve got live animals and dead animals and wild animals and domestic animals, all in really close confinement, not necessarily in great

animals and domestic animals, all in really close confinement, not necessarily in great conditions . . . they're stressed, probably shedding viruses. . . . And then you've got cages of different animals on top of each other, so urine and feces flowing down, and people handling them . . . and there's not really a good way for them to wash hands or do anything cleanly." In February of 2020, China banned wildlife trade for consumption. But "you're not going to get rid of markets," Goldstein said. She favors policies that aim for incremental improvements. "Figure out ways not to have live and dead animals in the same place. Keep your wildlife separate from your domestic animals. Have places to wash hands and wash down cages. It's not perfect, but you have to do something to try to improve the biosecurity of these places. Otherwise we're going to continue to have these sorts of events occur." Spillover-prediction initiatives can be useful in this context, too, even if they are imprecise: if researchers suspect that certain species present more risk, or are riskier at certain times of year, they can focus their efforts.

The biggest factor driving epidemic trends is land-use change, Epstein said—especially increases in deforestation, agriculture, and urbanization. James Hassell, a wildlife veterinarian and an epidemiologist at the Smithsonian's Global Health Program, cited extraction, tourism, and the bushmeat trade as additional factors. In East Africa, he said, growing cities are a "crucible" for interactions between humans, livestock, pets, and wild animals. Hassell grew up just outside London, and, at the beginning of his career, he told me, he was "amazed at the sheer diversity of wildlife that lives in urban settings in the tropics." He recalled visiting a cave by a river flowing through a large urban settlement. Sewage from the slum above dripped down into the cave, which was filled with bats. "I think that was the most extraordinary interface I've come across, with all kinds of implications for potential disease transfer," he said. Hassell asked me not to share the cave's location, lest policymakers seal it off, forcing the bats to roost in people's homes.

Zimmerman said that, in the field, "you get this holistic view of nature." Researchers speak of a "one health" perspective, which connects people, wildlife, and the environment. It makes her think about what she could do better—eat less red meat, use less plastic, rely less on pesticides. ("And then you're, like, 'I want all the things from the store,'" she said.) It's possible to adopt a similar perspective about pandemic prediction and preparation—a vast endeavor in which the parts are connected, too. During the pandemic, while isolated at home, Zimmerman—who now teaches epidemiology at Yale, among

other appointments—wrote grant proposals for future trips and phoned with Kenya’s country coordinator for PREDICT, Joseph Kamau. She helped train researchers and technicians at his lab, which pivoted to become a COVID-19 testing center. “It kind of comes full circle,” she said. “Now there’s an actual pandemic, where he’s using all that knowledge and expertise, and he’s recognized in his country as the authority on ‘one health.’ ”

Wildlife surveillance may not pinpoint the next viral threat, and it may be hard to show that it’s the best use of resources. It could be true, as researchers including Elbright, the Rutgers biologist, argue, that virus hunting puts people at risk of infection from wildlife, brings dangerous viruses into labs, and leads to publications about them that evildoers might use. But that doesn’t mean it’s a waste or a mistake. A sampling of what’s out there may help researchers develop broad-spectrum drugs or vaccines that target not just a single virus but a family of related viruses; such treatments might build a foundation for future pandemic responses. Goldstein, of U.C. Davis, said that drug companies are now including *Bombali ebolavirus* in their set of *Ebolavirus* targets. Jonathan Towner, who leads the virus-host-ecology section at the Centers for Disease Control and Prevention, also noted that, once an outbreak has happened, a virus can more easily be tracked to its source if it is already in a database of potential threats. Meanwhile, efforts such as those undertaken by PREDICT, G.V.P., EcoHealth Alliance, and the Smithsonian include valuable outreach and equip local labs to catch outbreaks in wildlife and domestic animals early. At the very least, failed attempts to predict or stop spillovers paint a picture of our ignorance, populating our heat maps with dragons. Knowledge of the limitations of knowledge is knowledge all the same.

“We can speak with better forecasting abilities as to where these viruses may emerge, based on hot-spot maps,” Carroll said. “And we can speak with greater authority as to what are the human behaviors and practices in those hot spots that may trigger a spillover event. And knowing what those behaviors and practices are allows us to actually modulate those human activities, to lower the risk, and prevent the next spillover.” Still, when pushed, he puts bounds on his optimism. “I think it’s a fool’s errand to say which virus will be the cause of the next pandemic,” he allowed. “There are a lot of candidates out there.” The ideal world—in which Zimmerman would find a new virus in a baboon, researchers would recognize its imminent risk, and we’d develop a vaccine or isolate the baboon population,

recognize its imminent risk, and we'd develop a vaccine or isolate the baboon population before anyone gets sick—is almost surely out of reach. Zimmerman proposed an alternative to the avalanche metaphor. “I grew up in Southern California, by the San Andreas Fault,” she said. “My mom’s trunk was filled with water and food, because we knew the big one was coming. You’re prepared for it, and you’re training for it. It’s just a matter of time before it comes. But you don’t know when.” ♦

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